ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

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ABSTRACT

BACKGROUND

Many patients with severe asthma rely on oral glucocorticoids to manage their disease. We investigated whether benralizumab, a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor that significantly reduces the incidence of asthma exacerbations, was also effective as an oral glucocorticoid–sparing therapy in patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia.

METHODS

In a 28-week randomized, controlled trial, we assessed the effects of benralizumab (at a dose of 30 mg administered subcutaneously either every 4 weeks or every 8 weeks [with the first three doses administered every 4 weeks]) versus placebo on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients with severe asthma. The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Annual asthma exacerbation rates, lung function, symptoms, and safety were assessed.

RESULTS

Of 369 patients enrolled, 220 underwent randomization and started receiving benralizumab or placebo. The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ($P<0.001$ for both comparisons). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab as with placebo. Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs. 1.83, $P=0.003$), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83, $P<0.001$). At 28 weeks, there was no significant effect of either benralizumab regimen on the forced expiratory volume in 1 second (FEV_1), as compared with placebo. The effects on various measures of asthma symptoms were mixed, with some showing significant changes in favor of benralizumab and others not showing significant changes. Frequencies of adverse events were similar between each benralizumab group and the placebo group.

CONCLUSIONS

Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on the FEV_1. (Funded by AstraZeneca; ZONDA ClinicalTrials.gov number, NCT02075255.)

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*A complete list of the investigators in the ZONDA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Asthma is a common chronic inflammatory disease of the airways that affects an estimated 315 million persons worldwide.[1] Approximately 5 to 10% of persons with asthma have a severe form of disease that is usually managed with high-dose inhaled glucocorticoids and bronchodilators.[2,3] Within this group, 32 to 45% of persons rely on frequent or maintenance use of oral glucocorticoid therapy.[4,5] Oral glucocorticoid therapy adversely affects health-related quality of life,[6] and effective alternative therapies without severe adverse effects are needed.

Eosinophilic inflammation is a key part of asthma, and increased numbers of circulating and airway eosinophils are accompanied by more frequent asthma exacerbations and declines in lung function.[7-9] Glucocorticoids are thought to act by reducing the number of inflammatory cells, including eosinophils, in airways.[10] Mepolizumab and reslizumab are monoclonal antibodies that are directed against interleukin-5, a cytokine involved in the eosinophil life cycle.[11] Mepolizumab and reslizumab have both been approved as add-on therapies to treat asthma exacerbations and control symptoms in patients who have severe asthma with an eosinophilic phenotype.[12,13] Treatment with mepolizumab also provides a glucocorticoid-sparing effect.[14,15]

Benralizumab is a humanized, afucosylated (engineered to eliminate fucose sugars from the oligosaccharides in the Fc region) monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor that induces direct, rapid, and nearly complete depletion of eosinophils by means of natural killer cell–mediated antibody-dependent cellular cytotoxic effects.[16] In the ZONDA trial, we assessed the effect of benralizumab, as compared with that of placebo, on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients who had severe asthma with persistent blood eosinophilia despite receipt of treatment with high-dose inhaled glucocorticoids, long-acting β_2-agonists (LABAs), and oral glucocorticoids.

Methods

Trial Design

This randomized, double-blind, parallel-group, placebo-controlled trial comprised an enrollment visit, a run-in phase that included stabilization of the oral glucocorticoid dose, a randomized intervention period, and a follow-up visit (Fig. 1). The intervention period consisted of the following: an induction phase, during which patients continued receiving their oral glucocorticoid dose as established during the run-in phase; a dose-reduction phase, during which the oral glucocorticoid dose was reduced at regular intervals; and a dose-maintenance phase, during which the reduced oral glucocorticoid dose was maintained or, in patients in whom oral glucocorticoid therapy was discontinued, no further oral glucocorticoids were received.

All the patients had been treated continuously with oral glucocorticoids for 6 months or more before enrollment and were receiving oral prednisone or prednisolone at trial entry. Patients who were receiving any other oral glucocorticoid at enrollment were switched to an equivalent dose of oral prednisone or prednisolone. During the run-in phase, the oral glucocorticoid dose was adjusted to the minimum dose that could be received without loss of asthma control (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). No additional asthma-controller medication was initiated unless it was used for the treatment of exacerbations (medication was provided by the trial investigators).

After the run-in phase, patients underwent randomization at week 0 (baseline) to receive benralizumab or placebo and then entered the 4-week induction phase, during which the oral glucocorticoid dose established in the run-in phase was maintained. In the subsequent dose-reduction phase (weeks 4 to 24), the daily oral glucocorticoid dose was reduced every 4 weeks by 2.5 to 5.0 mg (Table S2 in the Supplementary Appendix). Only patients who had an oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase (baseline) were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy). If the criteria for dose reduction were not met, the oral glucocorticoid dose was returned to a previous level, which was maintained until the end of the trial. If a patient's asthma worsened during the maintenance phase (weeks 24 to 28), the final dose was deemed to be one adjustment increment greater than the dose at which the worsening started.

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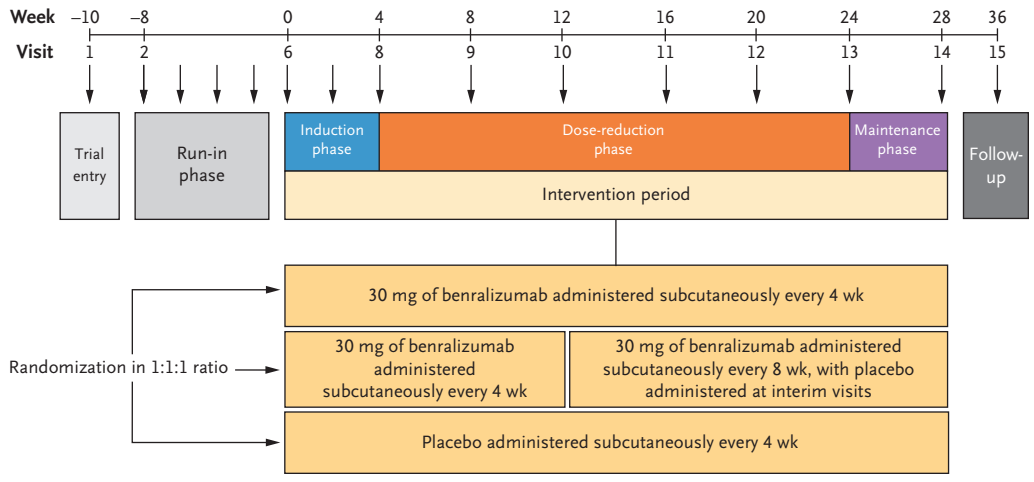


Figure 1. Trial Design.

Patients entering the run-in phase had their oral glucocorticoid dose reduced until the minimum effective dose without loss of asthma control was reached. All the patients then underwent randomization and entered the induction phase, during which the dose established in the run-in phase was maintained. The oral glucocorticoid dose was further reduced, every 4 weeks, in the intervention period from weeks 4 to 24. The oral glucocorticoid dose that was reached at week 24, or the complete discontinuation of oral glucocorticoid therapy, was maintained until week 28. The last dose of benralizumab or placebo was administered at the week 24 visit.

TRIAL OVERSIGHT

The trial was designed by AstraZeneca in collaboration with the first author. Trial data were collected by the clinical investigators and analyzed by employees of AstraZeneca. The first author and two of the authors who are employees of the sponsor vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (available at NEJM.org). All the authors reviewed the data. Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, incorporation of author feedback, and manuscript submission, was provided by Endpoint Medical Communications (funded by the sponsor) and the sponsor. The independent ethics committees of the trial centers or the central institutional review boards approved the trial protocol. The statistical analysis plan is available with the protocol. The trial was conducted in accordance with the principles of the Declaration of Helsinki, and all the patients provided written informed consent.

PATIENTS

Adults were eligible to participate in the trial if they had a blood eosinophil count of 150 cells or more per cubic millimeter and had asthma that had been treated with medium-dose to high-dose inhaled glucocorticoid and LABA therapy for at least 12 months before enrollment and treated with high-dose inhaled glucocorticoid and LABA therapy for at least 6 months before enrollment. Patients had been receiving oral glucocorticoid therapy for at least 6 continuous months directly before enrollment (equivalent to a prednisolone or prednisone dose of 7.5 to 40.0 mg per day). The full eligibility criteria are provided in Section 2 in the Supplementary Appendix.

INTERVENTIONS

Patients received subcutaneous injections of benralizumab at a dose of 30 mg every 4 weeks, benralizumab at a dose of 30 mg administered every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; hereafter referred to as the group that received benralizumab every 8 weeks), or placebo administered every 4 weeks. All the trial agents were provided by AstraZeneca. Patients underwent randomization in a 1:1:1 ratio, with the use of an interactive Web- or voice-response system, and were stratified according to eosinophil count (≥150 to <300 cells per cubic

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millimeter vs. ≥300 cells per cubic millimeter) and country. Investigators and patients were unaware of the trial-group assignments. Patients continued their prescribed high-dose inhaled glucocorticoid and LABA therapies, as well as any other asthma-controller medications aside from oral glucocorticoid therapy (including leukotriene modifiers, long-acting muscarinic antagonists, and theophylline), in an unchanged fashion throughout the trial. Short-acting β_2-agonists were permitted as rescue medications.

ASSESSMENTS AND PROCEDURES

Worsening of asthma was defined as new or increased asthma symptoms or clinical signs that were troubling to the patient or were related to an electronic Asthma Daily Diary alert (see the Supplementary Appendix). An asthma exacerbation was defined as worsening of asthma that led to a temporary increase in the systemic glucocorticoid dose for at least 3 days to treat the symptoms, an emergency department visit resulting from asthma that led to treatment with a systemic glucocorticoid in addition to the patient's regular maintenance medications, or an inpatient hospitalization because of asthma.

Patients recorded their lung-function measurements (using an electronic handheld spirometer) and asthma symptoms in the Asthma Daily Diary. Patients used the diary to complete the Asthma Control Questionnaire 6 (ACQ-6)[17] and the Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12).[18] The total asthma symptom score (a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment) is assessed on a scale from 0 to 6, with higher scores indicating a greater symptom burden. The ACQ-6 is scored on a scale from 0 to 6, with lower numbers indicating better control of asthma), and the AQLQ(S)+12 is scored on a scale from 1 to 7, with higher scores indicating better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful for the ACQ-6 and AQLQ(S)+12. Blood and induced sputum (from a subgroup of patients) were obtained for the analysis of eosinophils.[19] Adverse events were monitored throughout the trial. These procedures are described fully in Section 3 in the Supplementary Appendix.

END POINTS

The primary end point was the percentage reduction in the oral glucocorticoid dose from baseline (randomization at week 0) to the final dose at the end of the maintenance phase (week 28) while asthma control was maintained. Secondary end points included the percentages of patients who had a reduction in the average daily oral glucocorticoid dose of 25% or more, of 50% or more, or of 100% (discontinuation of oral glucocorticoid therapy) from baseline to end of the maintenance phase and the percentage of patients with an average final oral glucocorticoid dose of 5.0 mg or less per day while asthma control was maintained.

Additional end points included the annual asthma exacerbation rate, the time to the first asthma exacerbation, the percentage of patients with at least one asthma exacerbation (including exacerbations associated with emergency department visits or hospitalization), the forced expiratory volume in 1 second (FEV_1) before bronchodilation, the total asthma symptom score, the ACQ-6 score, and the AQLQ(S)+12 score. Exploratory end points were used to investigate the effect of blood and sputum eosinophilia on the efficacy of the trial drug. Safety end points included frequencies of adverse events.

STATISTICAL ANALYSIS

We estimated that 70 patients per group would be required for the trial to detect a difference in the primary end point between each benralizumab group and the placebo group with 86% power by means of a Wilcoxon rank-sum test with a two-sided level of 5%. Our estimation was based on simulations that used data from the Steroid Reduction with Mepolizumab Study (SIRIUS), which yielded a median percentage reduction from baseline of 50% in the glucocorticoid dose in the active-treatment group, as compared with no reduction in the placebo group.[14] We aimed for approximately 60 patients with a blood eosinophil count of at least 150 cells to less than 300 cells per cubic millimeter and 150 patients with a blood eosinophil count of 300 cells or more per cubic millimeter to undergo randomization. Efficacy analyses were conducted with an intention-to-treat approach in the full analysis set.

For the primary end point, benralizumab was compared with placebo by means of a Wilcoxon

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rank-sum test. To control the overall type I error rate, we accounted for multiple comparisons by means of the Hochberg procedure. A sensitivity analysis for the assessment of the primary end point was conducted with a proportional-odds model, with controls for trial group, geographic region (Asia, Central Europe and Eastern Europe, Western Europe and Turkey, North America, and the rest of world), and baseline oral glucocorticoid dose.

We used a Cochran–Mantel–Haenszel test, with adjustment for geographic region, to analyze secondary end points regarding reductions in the oral glucocorticoid dose. A negative binomial model, with adjustment for trial group, geographic region, and number of exacerbations in the previous year, with an offset term of the logarithm of the follow-up time was used to calculate annual exacerbation rates in the trial groups. Treatment effects were described with the use of rate ratios. Details of the models that were used to analyze other secondary end points are described in Section 5 in the Supplementary Appendix. The trial was not powered to assess secondary end points. The analyses of the secondary end points were not controlled for multiple comparisons and are presented with nominal P values. Results for exploratory variables were analyzed with the use of descriptive statistics according to trial group, unless otherwise indicated. Data were analyzed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

From April 2014 through November 2015, a total of 369 patients were recruited and entered screening (Fig. S1 in the Supplementary Appendix). Of these, 98 patients did not enter the run-in phase for the adjustment of the oral glucocorticoid dose, most commonly because they did not fulfill the eligibility criteria (84 patients). An additional 51 patients did not complete the run-in phase, most commonly because they did not meet the eligibility criteria (35 patients). A total of 220 patients underwent randomization and started the intervention phase. A total of 11 patients did not complete the trial, including 5 who withdrew of their own decision. All the patients who underwent randomization were included in the full analysis set. Table 1 provides details about the characteristics of the patients at baseline (additional information is provided in Table S3 in the Supplementary Appendix).

PRIMARY OUTCOME

With respect to the prespecified primary outcome, the median reduction from baseline in the final oral glucocorticoid dose was 75% in patients who received either of the benralizumab regimens, as compared with a reduction of 25% in the patients who received placebo (P<0.001 for both comparisons) (Table 2 and Fig. 2A). A total of 24 patients (33%) who received benralizumab every 4 weeks and 27 patients (37%) who received benralizumab every 8 weeks had a reduction of 90% or more from baseline in their final oral glucocorticoid dose, as compared with 9 patients (12%) who received placebo (Table 2). More patients in the group that received benralizumab every 4 weeks and in the group that received benralizumab every 8 weeks than in the group that received placebo had a reduction of 75% or more from baseline (38 patients [53%] and 37 patients [51%], respectively, vs. 15 patients [20%]); similar results were observed with respect to a reduction of 50% or more (48 patients [67%] and 48 patients [66%], respectively, vs. 28 patients [37%]). The odds of a reduction in the oral glucocorticoid dose were 4.09 times (95% confidence interval [CI], 2.22 to 7.57) as high with benralizumab administered every 4 weeks as with placebo (P<0.001) and 4.12 times (95% CI, 2.22 to 7.63) as high with benralizumab administered every 8 weeks as with placebo (P<0.001) (Table 2).

SECONDARY AND EXPLORATORY OUTCOMES

In patients who received benralizumab, all the secondary end points related to reduction in the oral glucocorticoid dose were met. These end points included cessation of oral glucocorticoid therapy: 56% of the eligible patients who received benralizumab every 4 weeks and 52% of those who received benralizumab every 8 weeks had a 100% reduction from baseline in the final oral glucocorticoid dose, as compared with 19% of those who received placebo. The odds of cessation of oral glucocorticoid therapy were 5.23 times (95% CI, 1.92 to 14.21) as high with benralizumab administered every 4 weeks as with placebo (P<0.001) and 4.19 times (95% CI, 1.58 to 11.12) as high with benralizumab administered every 8 weeks as with placebo (P=0.002) (Table 2).

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (–5.4 to 93.4)	18.2 (–3.0 to 126.0)	22.6 (–3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive benralizumab either every 4 weeks or every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; referred to as the group that received benralizumab every 8 weeks), or placebo. Data on the demographic characteristics of the patients, lung-function variables after bronchodilation, asthma (including smoking) history, and local blood eosinophil counts were collected at visit 1, which occurred 10 weeks before the induction phase began. Data on other clinical characteristics were collected at multiple time points from visit 1 to visit 6 (the start of the induction phase). The last recorded value before randomization served as the baseline measurement. Details about the characteristics at baseline are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.

§ The percentage reversibility of the FEV_1 was calculated with the use of FEV_1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV_1 – prebronchodilation FEV_1] ÷ prebronchodilation FEV_1) × 100.

¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.

‖ The Asthma Control Questionnaire 6 (ACQ-6)[17] is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β_2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.

** The Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12)[18] is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.

†† Patients were stratified at randomization according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.

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Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Primary outcome			
Median oral glucocorticoid dose (range) — mg/day*			
At baseline	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At final visit	10.0 (0.0 to 40.0)	5.0 (0.0 to 45.0)	5.0 (0.0 to 30.0)
Median reduction from baseline (range) — % of baseline value†	25.0 (–150 to 100)	75.0 (–100 to 100)	75.0 (–50 to 100)
P value†	—	<0.001	<0.001
Reduction from baseline in final oral glucocorticoid dose — no. (%)			
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
Any increase or no change in dose	35 (47)	17 (24)	15 (21)
Analysis of percentage reduction from baseline in oral glucocorticoid dose			
Odds ratio (95% CI)	—	4.09 (2.22 to 7.57)	4.12 (2.22 to 7.63)
P value	—	<0.001	<0.001
Secondary outcomes			
Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction			
100% Reduction — no./total no. (%)‡	8/42 (19)	22/39 (56)	22/42 (52)
Odds ratio (95% CI)	—	5.23 (1.92 to 14.21)	4.19 (1.58 to 11.12)
P value	—	<0.001	0.002
≥50% Reduction — no. (%)	28 (37)	48 (67)	48 (66)
Odds ratio (95% CI)	—	3.59 (1.79 to 7.22)	3.03 (1.57 to 5.86)
P value	—	<0.001	<0.001
≥25% Reduction — no. (%)	38 (51)	54 (75)	57 (78)
Odds ratio (95% CI)	—	2.89 (1.45 to 5.79)	3.25 (1.62 to 6.52)
P value	—	0.002	<0.001
Final oral glucocorticoid dose of ≤5.0 mg/day — no. (%)§	25 (33)	44 (61)	43 (59)
Odds ratio (95% CI)	—	3.16 (1.60 to 6.23)	2.74 (1.41 to 5.31)
P value	—	<0.001	0.002

* The baseline oral glucocorticoid dose was the daily dose at which the patient's asthma was stabilized at randomization (after the run-in phase), and the final oral glucocorticoid dose was the final daily dose at week 28.
† Negative values indicate an increase in the final oral glucocorticoid dose from baseline. The P values were calculated with the use of a Wilcoxon rank-sum test.
‡ Patients with a baseline oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy).
§ All the patients with a final oral glucocorticoid dose of 5.0 mg or less per day also had a reduction of at least 25% from baseline in the final oral glucocorticoid dose.

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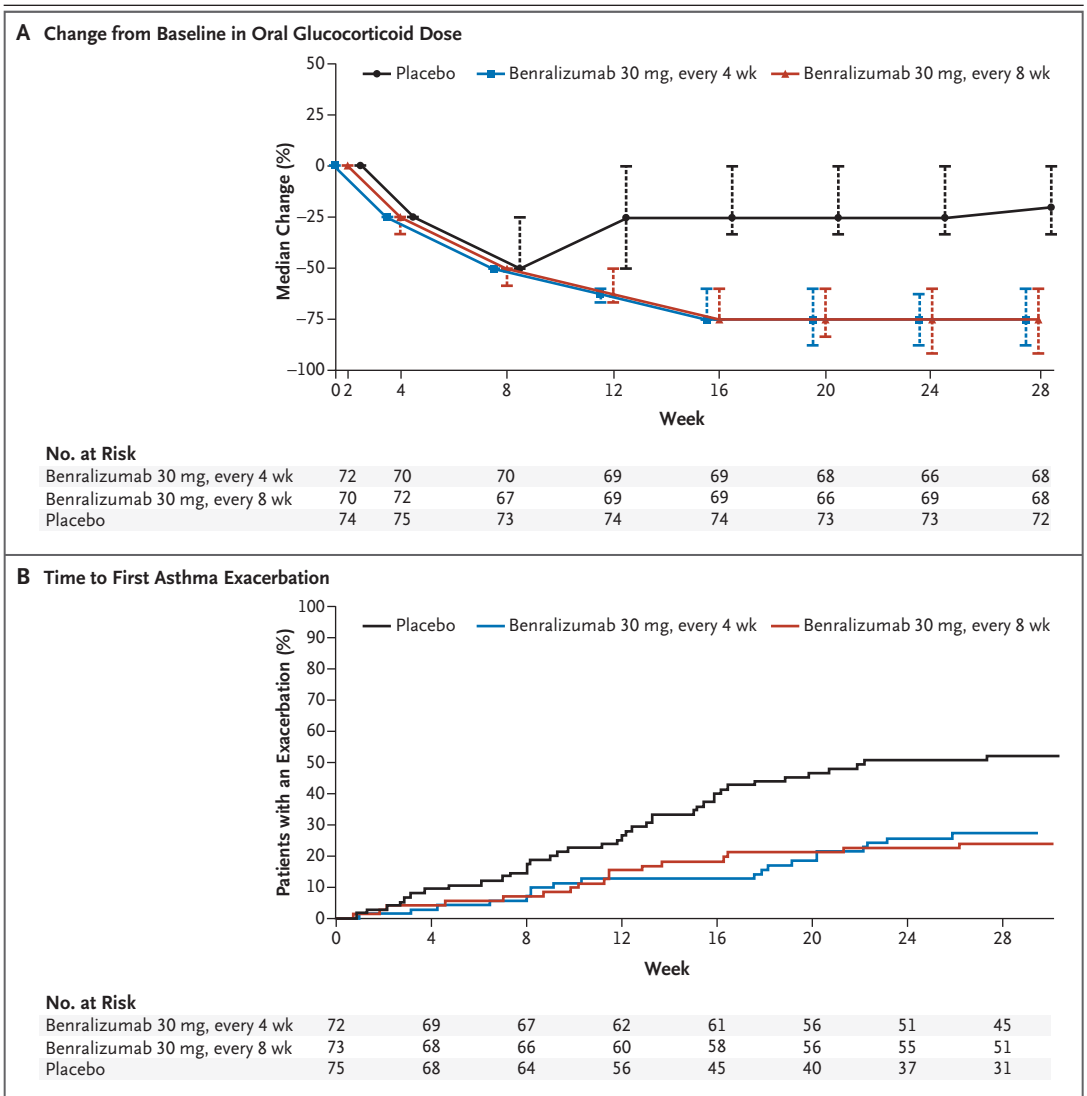


Figure 2. Change from Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations.

Panel A shows the median percentage change from baseline to week 28 in the oral glucocorticoid dose in patients who received benralizumab or placebo. Error bars represent 95% confidence intervals. Values are slightly offset from each other at each time point for clarity. Panel B is a Kaplan–Meier cumulative incidence curve for the time to the first exacerbation in patients who received benralizumab as compared with those who received placebo. Benralizumab administered every 4 weeks was associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.39; 95% confidence interval [CI], 0.22 to 0.66; P<0.001), and benralizumab administered every 8 weeks was also associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.32; 95% CI, 0.17 to 0.57; P<0.001).

Reductions in the oral glucocorticoid dose were observed regardless of the baseline oral glucocorticoid dose (Table S4 of the Supplementary Appendix).

For secondary end points related to asthma exacerbations, benralizumab administered every 4 weeks resulted in an annual asthma exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs. 1.83; rate ratio, 0.45; 95% CI, 0.27 to 0.76; P=0.003), and benralizumab administered every 8 weeks resulted in an annual asthma exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83; rate ratio, 0.30; 95% CI, 0.17

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to 0.53; P<0.001). The two benralizumab regimens were associated with lower odds of having at least one exacerbation than was placebo (odds ratio for benralizumab administered every 4 weeks vs. placebo, 0.32; 95% CI, 0.16 to 0.65; P=0.001; odds ratio for benralizumab administered every 8 weeks vs. placebo, 0.28; 95% CI, 0.14 to 0.56; P<0.001) and resulted in a longer time to the first exacerbation than placebo (Fig. 2B, and Fig. S2 in the Supplementary Appendix). Benralizumab that was administered every 8 weeks resulted in a marginal rate estimate of annual exacerbations associated with an emergency department visit or a hospitalization of 0.02 (95 CI, 0.00 to 0.18), as compared with a marginal rate estimate of annual exacerbations of 0.32 (95% CI, 0.16 to 0.65) in the placebo group. The rate with benralizumab was 93% lower than the rate with placebo (rate ratio, 0.07; 95% CI, 0.01 to 0.63; P=0.02). The differences between the group that received benralizumab every 4 weeks and the placebo group did not reach nominal significance for this end point (Table S5 in the Supplementary Appendix).

For secondary end points related to lung function, the FEV_1 before bronchodilation at week 20 was higher than that in the placebo group by 256 ml (95% CI, 109 to 403) in the group that received benralizumab every 4 weeks and by 222 ml (95% CI, 75 to 370) in the group that received benralizumab every 8 weeks; at this time the increase in each group was significantly larger than that with placebo. By 28 weeks, there was no longer a significant difference between either benralizumab group and the placebo group in the FEV_1 before bronchodilation (Fig. S3 in the Supplementary Appendix).

For secondary end points related to asthma control, symptoms, and asthma-related quality of life, the use of benralizumab every 8 weeks was associated with a decrease in the ACQ-6 score (indicating better asthma control) from baseline to the end of the maintenance phase that was 0.55 points (95% CI, 0.23 to 0.86) greater than the decrease with placebo (P=0.001) and with an increase in the AQLQ(S)+12 score (indicating better asthma-related quality of life) from baseline to the end of the maintenance phase that was 0.45 points (95% CI, 0.14 to 0.76) higher than the increase with placebo (P=0.004) (Figs. S4, S5, and S6 in the Supplementary Appendix). By contrast, the differences at week 28 between the group of patients who received benralizumab every 4 weeks and the placebo group with regard to the end points of the ACQ-6 score (least-squares mean difference, −0.24 points; 95% CI, −0.55 to 0.08; P=0.14) and the AQLQ(S)+12 score (least-squares mean difference, 0.23; 95% CI, −0.08 to 0.53; P=0.15) did not reach nominal significance. In addition, no significant differences were found between either benralizumab group and the placebo group with regard to changes from baseline to the end of the maintenance phase in total asthma symptoms. The results of exploratory analyses that were conducted to assess blood and sputum eosinophil counts and their potential associations with efficacy outcomes are described in Tables S6 and S7 and in Figures S7 through S10 in the Supplementary Appendix.

SAFETY AND ADVERSE EVENTS

A total of 166 patients (75%) had at least one adverse event during the intervention phase (Table 3). The most frequently reported adverse events were nasopharyngitis (in 17% of patients), worsening asthma (in 13%), and bronchitis (in 10%) (Table S8 in the Supplementary Appendix).

A total of 28 patients (13%) had at least one serious adverse event (Table 3). Worsening asthma was the most common serious adverse event (in 7 patients). A total of 3 patients discontinued their assigned regimen because of serious adverse events. Two patients in the group that received benralizumab every 8 weeks discontinued benralizumab: 1 because of pneumonia and 1 because of cardiac failure. One patient in the placebo group discontinued placebo because of pericarditis.

Two patients in the group that received benralizumab every 8 weeks died during the trial (Table 3). The causes of death were acute cardiac failure (the patient had hypertension and coronary artery disease at trial entry) and pneumonia (atrial fibrillation while the patient was in the hospital; this patient had concurrent hypercholesterolemia, hypertension, angina pectoris, congestive heart failure, dyslipidemia, and a history of atrial fibrillation at trial entry). Details are provided in Section 6 in the Supplementary Appendix.

Antidrug antibodies were positive in 12 of 145 patients (8%) who received benralizumab, 10 of whom had neutralizing antibody–positive

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Table 3. Summary of Adverse Events.*

Event	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
		number of patients (percent)	
Adverse event	62 (83)	49 (68)	55 (75)
Adverse event leading to discontinuation of trial regimen	2 (3)	0	3 (4)
Serious adverse event	14 (19)	7 (10)	7 (10)
Serious adverse event unrelated to asthma exacerbation†	11 (15)	6 (8)	6 (8)
Death	0	0	2 (3)
Injection-site reaction	2 (3)	2 (3)	0
Hypersensitivity	1 (1)	1 (1)	2 (3)
Urticaria	1 (1)	0	1 (1)

* Data on adverse events that occurred during the period from the receipt of the first dose of the trial regimen (week 0) to the visit at the end of the trial (week 28) are provided. Complete details of adverse events are provided in Table S8 in the Supplementary Appendix.
† Patients who had only the serious adverse events of worsening asthma or status asthmaticus were excluded from these totals.

status (Table S9 in the Supplementary Appendix). Among patients with a positive antidrug-antibody response, 1 of 5 patients in the group that received benralizumab every 4 weeks and 3 of 7 patients in the group that received benralizumab every 8 weeks had an increase from baseline in the blood eosinophil count (Table S10 in the Supplementary Appendix).

DISCUSSION

In this trial involving patients who relied on oral glucocorticoid therapy to control their asthma, benralizumab significantly reduced the oral glucocorticoid dose, while asthma control was maintained, in patients who had severe asthma, were receiving high-dose inhaled glucocorticoid and LABA, and had an elevated blood eosinophil count. The likelihood of a reduction in the oral glucocorticoid dose was more than 4 times as high with benralizumab as with placebo, and one half the eligible patients (those receiving a baseline prednisone dose of ≤12.5 mg per day) who were receiving benralizumab stopped the oral glucocorticoid therapy completely. In addition to clinically relevant dose reductions or the discontinuation of oral glucocorticoid therapy, patients receiving benralizumab had substantially lower rates of asthma exacerbations than did patients receiving placebo, as well as lower rates of exacerbation-related hospital visits.

The FEV_1 did not significantly increase over the entire 28-week trial period with benralizumab versus placebo. However, it did not decline, either, despite a reduction of 75% in the prednisone dose in each benralizumab group.

Targeting of the alpha subunit of the interleukin-5 receptor with benralizumab has potential advantages over existing anti–interleukin-5 therapies. By targeting the interleukin receptor rather than the cytokine, luminal depletion of eosinophils can occur,[16] which may be related to greater clinical efficacy. In addition, this approach avoids the potential for autoimmune-mediated worsening of asthma, which has been reported with low-dose anti–interleukin-5 therapy.[20]

This trial has limitations. Although we computed annualized exacerbation rates, benralizumab or placebo was administered only for 28 weeks, and longer-term studies involving patients with oral glucocorticoid–dependent asthma would be necessary before definitive conclusions could be drawn about the long-term efficacy and safety of benralizumab in this group of patients, who had undergone a reduction in the oral glucocorticoid dose.

It was unclear why approximately 20% of patients did not have any reduction in the oral

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glucocorticoid dose with benralizumab. In a preliminary analysis (data not shown), the baseline blood eosinophil counts in patients who did not have a response were similar to those in patients who had the greatest reductions in their final oral glucocorticoid doses. Perhaps the presence of blood eosinophilia may not identify the eosinophil as a key effector cell in some patients. Future studies may aim to investigate the characteristics of patients that are indicative of a response to benralizumab, to assess the long-term safety and efficacy of eosinophil depletion (as opposed to normalization of eosinophil counts), and to determine the effects of benralizumab on other cells that may express the interleukin-5 receptor.

In conclusion, in patients with severe eosinophilic asthma who received benralizumab subcutaneously every 8 weeks, the use of maintenance oral glucocorticoid therapy could be reduced while asthma control was maintained. No significant effect on FEV_1 was observed at the end of the trial.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. DOI: 10.1056/NEJMoa1703501

This supplement contains the following items:

ZONDA CSP Edition 1

ZONDA CSP Edition 3

ZONDA CSP Amendment 1

ZONDA CSP Amendment 2

ZONDA SAP Edition 1

ZONDA SAP Edition 2

ZONDA SAP Edition 3

AstraZeneca

Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
Edition Number	1.0
Date	*10 January 2014*

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

International Co-ordinating Investigator: Parameswaran Nair

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**	**Local Amendment No:**	**Date of Local Amendment**

Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures.

PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

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Study centre(s) and number of patients planned

This study will be conducted worldwide in approximately 72 study centers. Target is to randomize 120 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2014	Phase 3
Estimated date of last patient completed	Q1 2016	

(a) Primary Objective

Objective	Endpoint
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of OCS dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Time to the first asthma exacerbation after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator FEV_1 • Change from baseline in pre-bronchodilator Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)

To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening PEF) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in ACQ-6
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in AQLQ(S)+12
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • ADA

(c) Safety Objective

Objective	Endpoint
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• AE/SAE • Laboratory variables • ECG • Physical Examination

(d) Exploratory Objectives

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	• Assessment of eosinophil progenitor cells
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells

To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	• TLC/RV/VC/IC/FRC

Please note: Baseline for all endpoints will be Visit 6.

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in 2 dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter) in patients with uncontrolled asthma receiving high-dose ICS-LABA and OCS with or without additional asthma controller(s).

The study will recruit approximately 120 patients (randomized 1:1:1) and stratified by country/region.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit on Week 28. The treatment period is divided into 3 phases:

- Induction (from Week 0 till Week 4; patients will remain on the optimized OCS dose)
- Reduction (from Week 4 till Week 24, inclusively; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week interval)
- Maintenance (after Week 24 till Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate long-term safety extension study; all patients who complete Week 28 (Visit 14) in the current study will be eligible to enrol in the safety extension study.

The investigational product (IP) will be administered at the study centre every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS-LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Target patient population

Male and female patients aged from 18 to 75 years with diagnosed asthma, willing to provide informed consent and requiring continuous treatment with high-dose inhaled corticosteroids (>500 mcg fluticasone dry powder formulation equivalents total daily dose) plus long-acting β2 agonists and Chronic Oral Corticosteroid Therapy.

Investigational product, dosage and mode of administration

Benralizumab 30mg/mL solution for injection in an accessorized pre-filled syringe (PFS) will be administered at the study centre subcutaneously every 4 weeks for the first 3 doses and then every 4 or 8 weeks thereafter.

Comparator, dosage and mode of administration

Matching placebo solution for injection in an accessorized PFS will be administered at study site subcutaneously every 4 weeks.

Duration of treatment

Following initial enrolment at Week -10 the patient will enter a 10-week enrolment, run-in/optimization phase which is followed by a 28-week double-blind, randomized treatment period, with last dose of benralizumab/placebo administrated at week 24 and end of treatment (EOT) visit on week 28. A follow-up visit will be conducted at Week 36.

The total planned study duration is 46 weeks.

Patients who complete Week 28 visit will be allowed to enrol in a follow-on long-term safety extension study (these patients will not attend the visit at Week 36).

Statistical methods

The primary efficacy variable is the percentage change in OCS dose from the patient's dose at baseline to the patient's final dose at Visit 14. The percentage change in OCS in each of the two benralizumab dose regimen groups will be compared to the percentage reduction in OCS in the placebo group using an analysis of covariance (ANCOVA) model. The response variable in the model is the percentage reduction in OCS dose from baseline to the final dose at Visit 14. The model will include covariates of treatment group, country/region, and baseline OCS dose.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization pre-dose/pre-bronchodilator FEV_1. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline pre-bronchodilator FEV1 will be used as covariates. Visit will be used as a categorical variable. The following variables will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score and total rescue medication use, change

from baseline in post-bronchodilator FEV_1, change from baseline in morning and evening PEF and the change from baseline in ACQ-6 and AQLQ(s)+12.

For categorical or binary variables, the proportion in each of the two benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region.

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The number of nights with awakening due to asthma and requiring rescue medication will be analyzed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country/region and baseline value will be fit as covariates.

Multiplicity will be adjusted for the primary endpoint using Hochberg procedure (Hochberg 1988).

For sample size estimation, a Type I error rate of 5% and 90% power, were used. For the primary endpoint of percentage change in OCS dose, targeting a difference of 60% between groups and assuming an estimate of 70%, the sample size required is 35 patients per treatment group.

Results for exploratory variables will be summarized using descriptive statistics by treatment group.

All safety parameters will be analyzed descriptively. Safety analyses will be based on the safety analysis set, defined as all patients who received at least 1 dose of investigational product.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
CO_2	Carbon dioxide
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EOT	End of treatment
ERV	Expiratory Reserve Volume
ePRO	Electronic patient reported outcome
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HCP	Health care provider
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
IC	Inspiratory capacity
ICI	International Coordinating Investigator
IP	Investigational product
IRV	Inspiratory Reserve Volume
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
RBC	Red blood cell
RV	Residual volume

Abbreviation or special term	Explanation
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
TLC	Total lung capacity
ULN	Upper limit of normal
UNS	Unscheduled
VC	Vital capacity
VCEX	Expiratory Vital Capacity
VCIN	Inspiratory Vital Capacity
VCMAX	Maximum Vital Capacity
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough and chest tightness. Asthma is a leading cause of morbidity with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 - 450 million people worldwide by 2025 (Masoli et al 2004).

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centred around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting β_2 agonists (LABA) in patients with more severe asthma (GINA 2012, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990; Louis et al 2000; Di Franco et al 2003; Scott and Wardlaw 2006, Simpson et al 2006; Zhang and Wenzel 2007). Adjusting conventional ICS-based asthma therapy according to the degree of elevated sputum eosinophils as a marker of disease activity resulted in a reduction in the frequency of asthma exacerbations in prospective trials (Green et al 2002; Jayaram et al 2006). Interleukin-5 (IL-5) is a cytokine factor essential for eosinophil trafficking and survival (Molfino et al 2011). Clinical trials of neutralizing anti-IL-5 antibodies (mepolizumab and reslizumab) in patients with uncontrolled eosinophilic asthma resulted in an improvement in key asthma control metrics, including asthma exacerbations (Castro et al 2011 and Pavord et al 2012). These promising results support continued development of therapies targeting the IL-5 pathway in eosinophilic asthmatics unresponsive to standard therapies.

In contrast to anti-IL-5 therapies, benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994; Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) to benralizumab which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients during Phase 2 development resulted in depletion of blood and airway eosinophils, and improvement in multiple metrics of asthma control including asthma exacerbations, lung function, and Asthma Control Questionnaire (ACQ-6)

scores (Busse et al 2010, Gossage et al 2012, Molfino et al 2012, and Phase 2b MI-CP220 study). For further details please refer to the Investigator's Brochure.

1.2 Rationale for conducting this study

The treatment options for patients who remain uncontrolled on high-dose ICS-LABA are extremely limited; one of the treatment options is addition of the oral corticosteroids (OCS) to the current treatment (GINA 2012). However, regular intake of OCS leads to a number of adverse events (AEs) and as a result decreases quality of life of these patients (Kwong et al 1987).

In previous clinical studies, benralizumab administration resulted in rapid and prolonged depletion of eosinophils in the peripheral blood and in the asthmatic airway with associated improvements in multiple metrics of asthma control. The magnitude of clinical improvement was positively correlated with baseline blood eosinophil counts and was most consistently observed in patients with absolute blood eosinophil counts ≥300/μL. Nair, et al. have demonstrated the steroid-sparing effects of anti-interleukin-5 therapy in OCS-dependent eosinophilic asthmatics, which serves as further support for the proposed mechanism of action of benralizumab in this difficult to treat population (Nair et al 2009).

The purpose of this trial is to confirm if benralizumab can reduce OCS dependence (after dose optimisation) in patients who are uncontrolled on high-dose ICS-LABA, and chronically dependent on OCS as part of their regular asthma controller regimen. In addition, this trial will further confirm the safety and clinical benefit of benralizumab administration.

1.3 Rationale for study design, doses and control groups

This is a global study designed to investigate the safety and efficacy of 2 dosing regimens of benralizumab (at a 30 mg fixed dose) administered subcutaneously (SC) in asthma patients who remain uncontrolled on chronic OCS and high-dose ICS-LABA therapy, with or without additional asthma controller(s). Patients on the first regimen will be dosed every 4 weeks throughout the treatment period, while patients on the second regimen will be dosed every 4 weeks for the first 3 doses and then every 8 weeks thereafter. Primary efficacy will be determined based on the percentage reduction in OCS dose over 24 weeks of benralizumab treatment versus placebo, following OCS dose optimization. In order to avoid biasing the results, the study will be randomized and double-blinded, with stratification by country/region.

The study will recruit patients with blood eosinophils ≥300/μL.

The benralizumab dose (30 mg SC, fixed) and the maintenance regimens are based on all available safety, efficacy and immunogenicity data, as well as population exposure-response modeling, and stochastic trial simulations from earlier phase benralizumab trials. In particular, Phase 2b MI-CP220 study showed that fixed doses of benralizumab ≥20 mg administered every 8 weeks were clinically effective. Analyses of efficacy endpoints (asthma exacerbations, forced expiratory volume in 1 second (FEV_1) and ACQ) suggest 30 mg every 8 weeks (with the first 3 doses administered every 4 weeks) is an effective and tolerable dose for further testing in patients with severe asthma. This dose corresponds to the ED_{90} for asthma exacerbation

reduction and ACQ, and maintains a steady-state PK exposure close to EC_{90} levels for FEV_1 and ACQ. Because the development of anti-drug antibodies (ADA) to biologic products appears to be related to the consistency of exposure, a second, more frequent (every 4 weeks) dosing regimen will also be tested.

Other stable asthma therapies on top of OCS and ICS-LABA that are within expert guidance and that are not restricted per protocol (see Section 3.5.2) are allowed in order to accommodate local standards of care.

1.4 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS-LABA (GINA 2012). The evidence base for oral add-on therapies (ie, OCS, leukotriene inhibitors, and xanthenes) is extremely limited. Anti-IgE therapy (ie, omalizumab) may improve control in patients with severe asthma and IgE-mediated allergy to a perennial allergen. Tiotropium is a long-acting bronchodilator that has recently been shown to produce improvement in lung function and exacerbation risk (pooled data) in patients with severe asthma, with inconsistent effects on other measures of asthma control (Kerstjens et al 2012). As such, new therapies are needed for asthma management in patients who remain uncontrolled on standard of care.

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA, benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/µL.

Development of ADA to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease).

Blood eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The efficacy and safety data obtained to date support the continued clinical development of benralizumab in asthma.

A detailed assessment of the overall risk/benefit of benralizumab in patients with asthma is given in the Investigator's Brochure.

1.5 Overall study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in 2 dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter) in patients with uncontrolled asthma receiving high-dose ICS-LABA and OCS with or without additional asthma controller(s).

The study will recruit approximately 120 patients (randomized 1:1:1) and stratified by country/region.

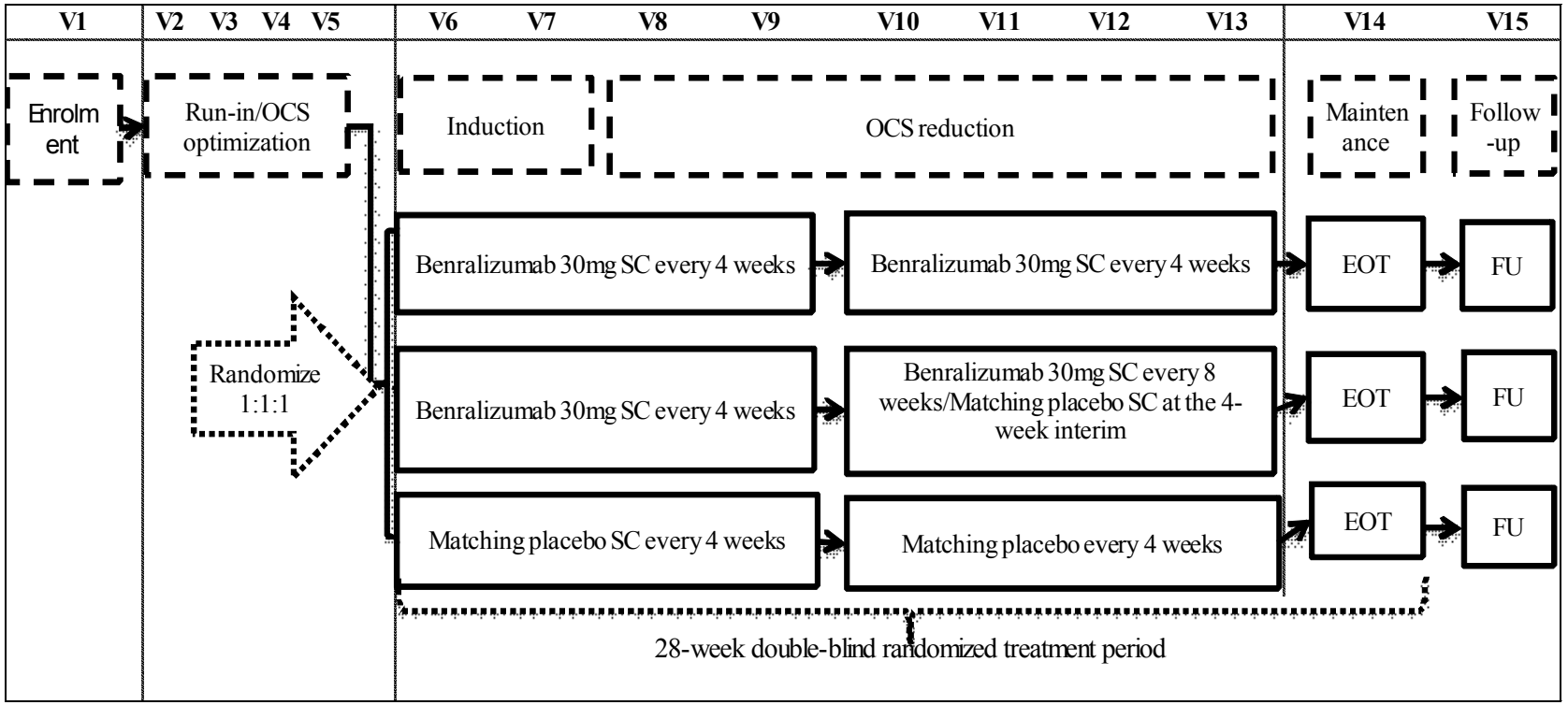
After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit on Week 28. The treatment period is divided into 3 phases:

- Induction (from Week 0 till Week 4; patients will remain on the optimized OCS dose)
- Reduction (from Week 4 till Week 24, inclusively; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week interval)
- Maintenance (after Week 24 till Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate long-term safety extension study; all patients who complete Week 28 (Visit 14) in the current study will be eligible to enrol in the safety extension study.

The investigational product (IP) will be administered at the study centre every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS-LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of OCS dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Time to the first asthma exacerbation after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator FEV_1 • Change from baseline in pre-bronchodilator Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)

To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening PEF) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in ACQ-6
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in AQLQ(S)+12
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • ADA

(c) Safety Objective

Objective	**Endpoint**
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• AE/SAE • Laboratory variables • ECG • Physical Examination

(d) Exploratory Objectives

Objective	**Endpoint**
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	• Assessment of eosinophil progenitor cells
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells

To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	• TLC/RV/VC/IC/FRC

Please note: Baseline for all endpoints will be Visit 6.

3. PATIENT SELECTION CRITERIA AND WITHDRAWAL CRITERIA

3.1 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female and male aged from 18 to 75 years, inclusively

3. Women of childbearing potential (WOCBP) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomised sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. WOCBP must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration and within 16 weeks after last dose of IP, and have negative serum pregnancy test result on Visit 1.

   Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postemenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

   – Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone (FSH) levels in the postmenopausal range

   – Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment

4. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose

5. Weight of ≥40 kg

6. Peripheral blood eosinophil count of ≥300 cells/μL assessed by local lab at visit 1

7. History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250μg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to Visit 1. Equivalents for fluticasone dry powder can be found in appendix E

8. Documented treatment with high-dose ICS (>500μg fluticasone propionate dry powder formulation equivalents total daily dose) and LABA for at least 6 months prior to Visit 1. The ICS and LABA can be contained within a combination product, or given by separate inhalers:

   – In order to aid the dose assessment, ICS equivalents for high-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma (GINA) guidelines, are presented in appendix E.

   – The ICS high-dose criterion can also be considered to be met by the highest locally approved maintenance dose for patients whose ICS-LABA dose, however maximal by local labelling, does not reach the GINA ICS high-dose level

9. Chronic oral prednisone or prednisolone therapy for at least 6 continuous months directly preceding Visit 1, and on a stable dose for at least one month prior to Visit 1

   – 7.5mg – 40mg daily

10. Patients with documented failures of OCS reduction within 6 months prior to Visit 1 will not be required to proceed through the dose optimization phase during run-in. Failed attempts at OCS dose reduction are those, which resulted in documented clinical deterioration or reduced lung function attributed to asthma, defined as:

    – Pre-BD FEV1 < 80% of personal baseline

    – Morning PEF < 80% of personal baseline

    – Night time awakenings increase of > 50% of mean personal baseline

    – Albuterol, salbutamol use > 4 puffs/day above mean personal baseline

    – Requirement for a prednisone or prednisolone burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction

11. Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline), that have been stable for at least 30 days prior to Visit 1, are allowed. Five- lipoxygenase inhibitors (eg, Zileuton) are prohibited

12. Morning pre-bronchodilator (Pre-BD) FEV_1 of <80% predicted at Visit 2 (Week -8)

13. Either documented post bronchodilator (post-BD) reversibility of ≥ 12% and ≥ 200 mL in FEV_1 or PC_{20} FEV1 methacholine concentration ≤ 8mg/mL within 60 months prior to planned date of randomization

14. At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained (please refer to Section 4.1.1)

Inclusion criteria at randomization

15. For WOCBP only: have a negative urine pregnancy test at Visit 6

16. Optimized OCS dose reached at least 2 weeks prior to randomization

17. Additional asthma controller medication must not have been initiated during run-in period

18. At least 70% compliance with OCS use from Visit 1 to Visit 6 based on the Asthma Daily Diary

19. At least 70% compliance with usual asthma controller ICS-LABA from Visit 1 to Visit 6 based on Asthma Daily Diary

20. Minimum 70% (i.e. 10 of 14 days) compliance with asthma daily diary (morning and evening diary) for the period between each study visit from Visit 1 to Visit 6

21. No documented asthma exacerbations during the screening/dose optimization period

3.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)

2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological,

psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

- Affect the safety of the patient throughout the study
- Influence the findings of the studies or their interpretations
- Impede the patient's ability to complete the entire duration of study

3. Known history of allergy or reaction to the IP formulation

4. History of anaphylaxis to any biologic therapy

5. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to standard of care therapy

6. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization period

7. Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during run-in/optimization period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study

8. Any clinically significant cardiac disease or any ECG abnormality obtained during the run-in/optimization period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments

9. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained

10. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol

11. A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test

12. Current smokers or former smokers with a smoking history of $\geq$ 10 pack-years

13. History of cancer:

- Patients who have had basal cell carcinoma, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained

- Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained

14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent is obtained. Chronic maintenance OCS for the treatment of asthma is allowed.

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids, or an increase in maintenance dose of OCS 30 days prior to the date of informed consent.

16. History of life-threatening asthma

17. Asthma control reached at an OCS dose of ≤5mg during run-in/OCS optimization phase (Visit 2 to Visit 6)

18. Qualifies for 3 consecutive dose reductions at Visits 2-4 and continues to meet OCS dose reduction criteria at Visit 5

19. Receipt of oral dexamethasone as the maintenance oral steroid controller for asthma symptoms

20. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained

21. Receipt of any marketed (eg, omalizumab) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer

22. Receipt of live attenuated vaccines 30 days prior to the date of randomization

    - Receipt of inactive/killed vaccinations (eg, inactive influenza) are allowed provided they are not administered within 1 week before/after any study visit

23. Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to the date informed consent is obtained, whichever is longer

24. Patients previously randomized and dosed in any benralizumab clinical trial

25. Change to allergen immunotherapy or new allergen immunotherapy within 30 days prior to the date of informed consent and anticipated changes in immunotherapy throughout the study

26. Current use of any oral or ophthalmic β-adrenergic antagonist (eg, propranolol)

27. Planned surgical procedures during the conduct of the study

28. Currently breastfeeding or lactating women

29. Previous randomization in the present study

30. Concurrent enrolment in another clinical trial

31. AstraZeneca staff involved in the planning and/or conduct of the study

32. Employees of the study centre or any other individuals involved with the conduct of the study, or immediate family members of such individuals

For procedures for withdrawal of incorrectly enrolled or randomized patients see Section 3.4.

3.3 Patient enrolment and randomization

Investigator(s) should keep a record of patients considered for, and included in the study. This pre-screening/screening log will be evaluated periodically by AstraZeneca or its delegates during routine monitoring visits.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

The Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign each potential patient a unique enrolment number, beginning with ‘E# via interactive web/voice response system (IWRS/IVRS)

3. Determine patient eligibility.

4. Assign eligible patient unique randomization code via IWRS/IVRS

Patients will be allocated to 1 of 3 treatment arms in a 1:1:1 ratio. The randomization will be stratified by country/region and the randomization numbers will be grouped in blocks.

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from the IP administration will not be replaced.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found to not meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

If a patient that does not meet all the eligibility criteria is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

3.5 Concomitant medications, restrictions during and after the study

3.5.1 Concomitant medication

Information about any treatment in the 3 months prior to the date of the informed consent and all the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the Electronic Case Report Form (eCRF).

Note: to satisfy inclusion criteria 8 and 9 the history of continuous treatment with high-dose ICS-LABA for at least 6 months prior to Visit 1 and use of OCS for at least 6 months prior to Visit 1 should be documented in source and recorded in the eCRF (see Section 4.1.1).

3.5.1.1 Background medication

Oral corticosteroids

For eligibility purposes all patients are required to be treated with prednisone or prednisolone for at least 6 months prior to Visit 1 and be on the stable maintenance dose for at least 1 month prior to Visit 1.

The dose of OCS will be titrated during optimization and reduction phases of the study (OCS optimization and Reduction phases, for details see Sections 4.1.2 and 4.2.2). Patients who have one or more documented OCS reduction failures as outlined in section 3.1 which define the optimized dose prior to Visit 1 are not required to proceed through the pre-randomization optimization phase.

OCS medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

ICS-LABA and other asthma controllers

All patients are required to be treated with a stable, high-dose ICS (>500 µg fluticasone dry powder formulation equivalents) and LABA for at least 6 months prior to Visit 1 and during the course of the study.

The aim of this study is to establish the treatment effect of benralizumab as add-on therapy. Therefore the background asthma controller medications should be maintained at a stable dose from Visit 1 until the end of the study. If changing the ICS-LABA dose is judged as necessary by the Investigator, the justification should be documented in the source and the change in the doses should be reflected in the eCRF.

ICS-LABA medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Additional controllers that are labeled for asthma and allowed per protocol (see 3.1, criterion 11) will be provided by AstraZeneca.

3.5.1.2 Rescue medication

Salbutamol, albuterol, and recemic preparations of albuterol (i.e levalbuterol) will be used as rescue medication during the study in the event of a worsening of asthma symptoms. As with background ICS-LABA medication, rescue medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to ensure access to essential rescue therapy.

3.5.2 Restrictions

3.5.2.1 Asthma medication restrictions

(a) **Use of short-acting ß$_2$ agonists (SABA)**

Prophylactic use of SABA in the absence of symptoms (e.g., prior to planned exercise), if deemed necessary by the patient and Investigator, can be used, but prophylactic inhalations should not be recorded in the Asthma Daily Diary, such use should be documented in medical notes and recorded in the eCRF.

SABA via a metered dose device is permitted as needed for worsening asthma symptoms (ie, rescue use) and will be recorded in the Asthma Daily Diary as number of inhalations.

Rescue use of SABA administered via jet or ultrasonic nebulisation, outside of managing an acute asthma exacerbation event, is discouraged unless the Investigator deems access to nebulised SABA essential for that patient. Occasions where SABA was administered via nebulisation will be recorded separately from metered dose inhaler (MDI) inhalations in the Asthma Daily Diary.

(b) **Use of short acting anticholinergics** (eg, ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event is not allowed from enrolment and throughout the study duration

(c) **Use of long-acting beta-agonists as a reliever** (eg, Symbicort Maintenance and Reliever Treatment) is not allowed from enrolment and throughout the study duration

(d) Maintenance of asthma controller medications

The patient's usual pre-study ICS-LABA formulation, dose and regimen, and any other additional allowed asthma controllers that they may have been taking prior to enrolment, should be continued unchanged throughout the run-in and treatment period. Please refer to Section 3.1, inclusion criterion 11 for examples of allowed additional controller therapies for this study.

Changes to the patient's background controller regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator; ideally such changes should be discussed with the AstraZeneca Study Team Physician. All changes in the patient's background medication should be documented in medical notes along with rational for change and recorded in eCRF. Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

(e) Asthma medication restrictions on the days of scheduled spirometry visit

Pre- and/or post-dose spirometry assessments will be performed at the study centre at scheduled visits (see Table 1 and Table 2): restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 5.1.3):

Visit 2-5: Patients will be asked to withhold their usual bronchodilator medications on the morning of scheduled spirometry measurements. ICS-LABA medications should be withold for 12 hours. In addition, SABA should not be used within 6 hours of these spirometry assessments. The patient's usual asthma medications may be administered following completion of the screening lung function procedures.

Treatment Visits 6-14: Patients will be asked to withhold their usual ICS-LABA medications on the mornings of scheduled spirometry visits for at least 12 hours prior to the spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in Section 5.1.3.

If the patient has taken their usual ICS-LABA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day, within the allowed window. If rescheduling is absolutely not feasible for the patient, spirometry may be performed

with a notation indicating that pre-BD spirometry was performed after usual ICS-LABA was administered.

If the patient has taken rescue SABA within 6 hours of the planned spirometry assessment, they should ideally 1) remain at the centre until such time that the 6-hour withholding time has been reached if it does not exceed the 1.5-hour spirometry window or 2) return on another day, within the visit window. If neither of options is feasible for the patient, spirometry may be performed with a notation indicating that the pre-BD spirometry was conducted within 6 hours of SABA use.

(f) Asthma medication restrictions prior to home lung function testing

Patients should avoid taking their morning asthma controllers prior to the morning home lung function testing, and should conduct the evening home lung function testing before taking evening asthma controllers. When possible, home lung function testing, should be taken at least 6 hours after the last dose of SABA rescue medication.

(g) Asthma medication restrictions on unscheduled visits

Asthma medication restrictions on unscheduled (UNS) visits may not be feasible, and may be applied at the discretion of the Investigator. Timing of recent controller and rescue SABA use relative to the UNS spirometry should be noted in the record

(h) Asthma medication restrictions at centre visits with scheduled ECG assessment

The patients should be instructed not to take their usual asthma controller medication (ie, LABA) prior to scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restriction is waived for the screening ECG at Visit 1.

3.5.2.2 Other medication restrictions

(a) Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines is not allowed. Please see Section 3.2 exclusion criteria 14 and 22 for examples and further details.

(b) Receipt of live attenuated vaccines within 30 days prior to randomization, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the IP is not allowed

(c) Patient should not receive allergen immunotherapy injections on the same day as the IP administration

(d) Patients should not take any other excluded medications:

- Five-lipoxygenase inhibitors (eg, Zileuton)

– Oral or ophthalmic β-adrenergic antagonist (eg, propranolol)

A table with medication-related restrictions presented in the Appendix G.

3.5.2.3 Other restrictions

(a) Fertile and sexually active patients or their partners should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP (see Section 3.1, inclusion criteria 3 and 4; Section 7.3).

(b) Patients must abstain from donating blood, plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP.

3.6 Discontinuation from investigational product

Patients will be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
2. AE that, in the opinion of the Investigator, contraindicates further dosing
3. Risk to patient as judged by the Investigator or AstraZeneca
4. Severe non-compliance to Clinical Study Protocol (CSP)
5. Eligibility requirement found not to be fulfilled
6. Pregnancy
7. Lost to follow-up[1]
8. Development of any study specific criteria for discontinuation:
   (a) Anaphylactic reaction to the IP requiring administration of epinephrine
   (b) Development of helminth parasitic infestations requiring hospitalization
   (c) If 2 consecutive doses of IP missed or more than 2 scheduled doses of IP are missed during course of the study
   (d) Intensive care unit admission for asthma-related event

[1] Patient is considered lost to follow up when any of the following attempts of contact are failed: -3 attempts of either phone calls, faxes or emails; - having sent 1 registered letter/certified mail; one unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.

When feasible, compliant patients who are discontinued from the IP should be encouraged to continue to undergo all study related visits/procedures for the full 28-week double-blind treatment period, including follow-up, in order to support the final efficacy and safety analyses for benralizumab. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

Patients who prematurely discontinued IP and are not willing to continue participation in the study should return to the study centre and complete procedures described for the EOT (4±1 weeks after last dose of IP) and Follow up visit 12±1 weeks after last dose of IP).

3.7 Withdrawal from the study

3.7.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.7.2 Withdrawal of the Informed Consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study. The patient will return electronic patient reported outcome (ePRO) devices. The enrolment/randomization code of the withdrawn patient cannot be reused.

If patient agrees, he/she will be asked to return to the study centre and complete procedures described for the EOT (4±1 weeks after last dose of IP) and Follow up visit 12±1 weeks after last dose of IP).

3.8 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent for the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study centre.

4. STUDY PLAN AND PROCEDURES

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
Informed consent[a]	10.4	X				
Inclusion/exclusion criteria	3.1/3.2	X	X	X	X	X
Medical and asthma history	4.1.1	X				
Complete physical examination	5.2.1.1	X				
Brief physical examination	5.2.1.2		X	X	X	X
Weight, Height	5.3.1	X				
Vital Signs	5.2.2	X	X	X	X	X
ECG	5.2.3	X				
Local laboratory eosinophil test	5.3.3.1	X				
Serum chemistry	5.2.4	X				
Haematology	5.2.4	X				
Urinalysis	5.2.4	X				
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.3.2	X				
Serum pregnancy test	5.2.4.1	X				
FSH[b]	5.2.4.1	X				
Sputum collection [c]	5.3.5					

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
PEF adherence check	5.1.4		X	X	X	X
Asthma Daily Diary adherence check	5.3.2.1		X	X	X	X
ACQ-6 adherence check	5.3.2.2		X	X	X	X
AQLQ(S)+12 adherence check	5.3.2.3		X	X	X	X
Screening pre-BD spirometry	5.1.3		X	X	X	X
Screening post-BD spirometry[d]	5.1.3		X			
Assessment of asthma exacerbations	5.1.2		X	X	X	X
OCS dose reduction [e]	5.1.1.1		X	X	X	
OCS dose increase, if indicated [f]	5.1.1.1					X
Adverse events	7.1	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X

a ICF can be signed 3 days prior to Visit 1
b FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
c The assessment is applicable for designated sites only
d The screening post-BD FEV1 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in section 3.1. The post-BD FEV1 should be performed using the guidance in section 5.1.3.
e If the patient's OCS dose was optimized prior to Visit 5, the patient must be maintained on the optimized dose for at least 2 weeks and then can be randomized
f If the patient fails to meet titration criteria at Visits 2-4, the OCS dose should be returned to one level higher and Visit 5 can be activated on the same day

D Days; EOT End-of-treatment; FU Follow-up; R Randomization; V Visit; UNS Unscheduled; W Week.

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	UNS[f]
		V6 (w0) R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)	
		Visit window (days)[a]										
		±0	±3	±3	±3	±3	±3	±3	±3	±7	±7	
Inclusion/exclusion criteria	3.1/3.2	X										
Complete physical examination	5.2.1.1	X								X		X
Brief physical examination	5.2.1.2		X	X	X	X	X	X	X			
Weight	5.3.1	X								X		
Vital Signs	5.2.2	X	X	X	X	X	X	X	X	X		X
ECG	5.2.3	X								X		
Serum chemistry[b]	5.2.4	X				X				X		
Haematology	5.2.4	X				X			X	X	X	
Urinalysis	5.2.4	X				X				X		
Urine pregnancy test (dipstick)[c]	5.2.4.1	X	X	X	X	X	X	X	X	X		
Total IgE	5.3.4	X										
Phadiatop	5.3.4	X										
PK	5.3.7	X		X	X	X	X		X	X	X	

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	UNS[f]
		V6 (w0) R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)	
		Visit window (days)[a]										
		±0	±3	±3	±3	±3	±3	±3	±3	±7	±7	
ADA	5.3.9	X			X	X	X		X	X	X	
Serum biomarkers	5.3.8.1	X		X		X				X	X	
Sputum collection[d]	5.3.5	X				X				X	X	X
Blood for flow cytometry[d]	5.3.8.1	X				X				X	X	X
PEF adherence check	5.1.4	X	X	X	X	X	X	X	X	X		
Asthma Daily Diary adherence check	5.3.2.1	X	X	X	X	X	X	X	X	X		
ACQ-6 adherence check	5.3.2.2	X	X	X	X	X	X	X	X	X		
AQLQ(S)+12 adherence check	5.3.2.3	X	X	X	X	X	X	X	X	X		
Assessment of asthma exacerbations	5.1.2	X	X	X	X	X	X	X	X	X		X

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	UNS[f]
		V6 (w0) R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)	
		Visit window (days)[a]										
		±0	±3	±3	±3	±3	±3	±3	±3	±7	±7	
OCS dose titration	5.1.1.1			X	X	X	X	X	X			X[h]
Pre-BD spirometry	5.1.3	X[g]		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[d]	X
Post-BD spirometry for Sputum collection[d]	5.1.3	X				X				X	X	X
Body plethysmography[d]	5.3.6	X				X				X		
Randomization	4.2/6.5	X										
Administration of IP[e]	6.8	X		X	X	X	X	X	X			
Adverse events	7	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X	X	X

a All visits are to be scheduled from the date of randomization but not from the date of previous visit
b Detailed schedule for serum chemistry tests provided in Section 5.2.4, Table 5
c For WOCBP only, urine HCG test to be done at centre on each treatment visit before any invasive procedures and IP administration
d The assessment is applicable for designated sites only

e In case of anaphylaxis additional samples to be taken (see Section 6.9)
f Unscheduled visits may be initiated as needed, and additional assessments performed at these visits
g Slow spirometry included in the pre-BD assessment
h Up titration only

D Days; **EOT** End-of-treatment; **FU** Follow-up; **R** Randomization; **V** Visit; **UNS** Unscheduled; **W** Week.

4.1 Enrolment and run-in/optimization period

4.1.1 Enrolment (Visit 1)

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1).

In cases where patient signs the informed consent form (ICF) prior to Visit 1, Visit 1 procedures must be initiated within 3 working days from the date of ICF. Registration of patient's enrolment via IWRS/IVRS should occur on day of Visit 1.

Visit 1 assessments are primarily concerned with confirmation of the asthma disease state, the requisite level of severity based on background medications and exacerbation history. From Visit 1 till Visit 2, the baseline for the ePRO parameters will be established.

A record of physician-diagnosed asthma, ICS-LABA and OCS use (Section 3.1, criteria 7, 8 and 9) and asthma exacerbations over the prior 12 months (Section 3.1, criterion 14) is required source documentation. A patient verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

Examples of acceptable documentation of the asthma disease state and prior asthma exacerbations include clinic visit (primary or specialist HCP), emergency room or hospital records listing asthma as a current problem, plus documentation of at least 1 asthma exacerbations during the 12 months prior to ICF:

A qualifying historical asthma exacerbation is a symptomatic worsening requiring use of systemic corticosteroid (ie, oral, intravenous (IV) or intramuscular (IM); in any healthcare setting) or temporary increase from a stable maintenance dose of oral corticosteroid, or that resulted in hospitalization.

Current, regular use of a high-dose ICS and LABA for at least 6 months prior to enrolment and OCS use for at least 6 continuous months prior to enrolment must be documented in the source. ICS and LABA may have been administered as either as fixed dose or 2 separate inhalers, and consistent with dose limits set by inclusion criterion 8. Stable dose of OCS must have been maintained for at least 1 month prior to Visit 1. This documentation may be in the form of a recent, active medication list as per an HCP note, or filled prescriptions based on a pharmacy record.

After confirmation of initial entry criteria the patient will be supplied with an electronic hand-held spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.3.2 for further details).

Patients will continue on their current ICS-LABA and other controller(s) (if applicable) treatment with no changes.

Following registration of enrolment, screening procedures may begin to assess study eligibility (inclusion/exclusion) criteria (see Table 1).

4.1.2 Run-in/OCS optimization phase (Visit 2-Visit 5)

The run-in/OCS optimization phase will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0). The patient should remain on their current ICS-LABA treatment with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

During the OCS optimization phase, a patient's OCS dose will be titrated (see Section 5.1.1.1) to ensure the patient is taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration will be initiated at Visit 2. Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture period is not yet complete. The decision to initiate OCS dose reduction at Visit 2 is under the discretion of the investigator and can include consideration of Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months. Patients who do not have historic evidence of dose optimization and who are judged not to be candidates for OCS dose reduction, based upon asthma symptoms or other clinical reasons in the opinion of the investigator, should be screen-failed.

From Visit 3 onwards, the dose of OCS may be reduced only if criteria listed in Section 5.1.1.1 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). The optimized dose of OCS is defined as a lowest dose of OCS at which patient meets criteria listed in section 5.1.1.1. In cases when the patient is optimized on their OCS dose prior to Visit 5 (Week-2), he/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized. The optimized dose reached during the OCS optimization phase becomes the patient's baseline OCS dose for analysis purposes.

If a patient does not meet down titration criteria, the OCS dose should be returned to the previous effective dose (i.e., the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until randomization (Visit 6).

If the patient experiences an asthma exacerbation requiring evaluation in an Urgent Care Centre, in Emergency Department (ED), Hospitalization, or temporary increase (bolus/burst) of systemic steroids, they will be screen failed.

If a patient reaches asthma control at an OCS dose of ≤5mg during this phase, the patient will be a screen failure and will not be randomized. If the patient does not reach optimized dose of the OCS by the end of the run-in/optimization phase the patient should be screen failed and cannot be randomized. An asthma exacerbation during dose optimization will result in screen-failure with possibility of re-screening.

The screening post-BD FEV1 performed at Visit 2 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine

sensitivity, as outlined in section 3.1. The post-BD FEV1 should be performed using the guidance in section 5.1.3

Patient's eligibility should be evaluated at each visit during the run-in/OCS optimization phase with the relevant documentation entered in the source and eCRF.

Patients whose compliance with the electronic diary is <70% will be given the option, one time during screening, to reschedule a study visit (with the exception of Visit 6) within 72 hours. Compliance <70% on more than one visit during screening will result in screen failure.

4.1.3 Re-screening

Patients who experience an asthma exacerbation within 30 days prior to ICF date or during the run-in/optimization phase should be screen failed (exclusion criterion 15). They may be re-screened no sooner than 30 days after their last dose of systemic steroids, or for those patients on chronic oral steroid controller therapy, 30 days after their dose has returned to their regular maintenance levels.

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization phase may also be re-screened (exclusion criterion 6). They may be re-screened 30 days after recovery, e.g., completion of the therapy.

Re-screening for the above mentioned reasons is allowed only once for the patient.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

4.2 Randomized treatment period

The randomized treatment period is divided into 3 phases based on the OCS dose adjustment: induction phase (Section 4.2.1), reduction phase (Section 4.2.2), and maintenance phase (Section 4.2.3).

Inclusion criteria at randomization will be confirmed at Visit 6. Before randomization the patient's compliance with usual asthma controller ICS-LABA, OCS, and ePRO completion must be confirmed (see Section 3.1, inclusion criteria 18, 19 and 20).

Patients confirmed to be eligible will be randomized at Visit 6 (Week 0) in a 1:1:1 ratio to receive benralizumab 30 mg either every 4 weeks throughout the treatment period, or every 4 weeks for the first 3 doses and then every 8 weeks thereafter, or placebo every 4 weeks.

The first dose of the IP will be administered at Visit 6 after the patient's randomization via IWRS/IVRS.

Following randomization the patient will receive 28-week double-blind treatment, with the last dose of benralizumab/placebo administered at Visit 13 (Week 24).

At Week 2 (Visit 7) patient will be seen at the site to for health check; IP will not be administered at this visit. Procedures specific for this visit are listed in Table 2.

Patients will have scheduled visits at 4-week interval to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see Section 5.1.2), patients should be evaluated at the study centre, when feasible, at UNS visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using ePRO device throughout the 28-week treatment period (see Section 5.3.2 for details).

At Week 28 patients will come to the centre for the EOT visit.

Patients who prematurely discontinued IP (see Section 3.6) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for Visits 14 (EOT), 15 (FU) within 4 weeks (±7 days) and 12 weeks (±7 days) after the last dose of IP, respectively.

Patients will return the ePRO device at EOT visit.

Completion or early termination of the treatment will be registered via IWRS/IVRS for each patient.

4.2.1 Induction phase

The induction phase will start at Week 0 (Visit 6) and will continue up till Week 4 (Visit 8). During this time, patients will remain on all of their regular asthma controller medications. No dose adjustments to OCS will be made during this period; patients will continue the optimized OCS dose that was achieved during OCS optimization phase.

4.2.2 Reduction phase

The reduction phase will start at Week 4 (Visit 8) and will be completed at Week 24 (Visit 13). The first reduction of OCS dose can occur at the Week 4 (Visit 8). Subsequent OCS dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4 The presence of exacerbation, changes in symptoms, and rescue medication use will be assessed.

Patients who experience an asthma exacerbation requiring evaluation in an Urgent Care Centre, in ED, Hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) should be returned to the previous effective OCS dose (i.e., the higher dose level prior to the titration

criterion not being met) after they have returned to their baseline level of asthma control. This dose should be maintained until the EOT (Visit 14).

NOTE: OCS dose reduction may take place only when criteria for OCS dose reduction are met (see Section 5.1.1.1).

4.2.3 Maintenance phase

Patients will be maintained for the 4-week period after Week 24 to Week 28 on the stable dose of OCS achieved during the reduction phase, or if requirement for OCS was eliminated then maintained without OCS. Patients will be maintained without further OCS dose adjustments until their last visit within the study to assess symptoms, ACQ-6 and exacerbations.

4.3 Follow-up period

Patients that complete 28-week double blind randomized treatment period may be enrolled into a separate long-term safety extension study.

Patients who complete Week 28 (Visit 14) and do not enter the safety extension study will be requested to return to the study centre at Week 36 for the follow-up assessments. During these visits patients will be assessed for any ongoing safety issues and any potential prospective AEs; serum biomarker, PK and immunogenicity samples will be collected (see Table 2).

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of OCS dose

During run-in/OCS optimization phase the minimum OCS dose while maintaining asthma control will be reached for each patient. The optimized dose will be considered as the baseline OCS dose.

The baseline OCS dose will be maintained at the same level from Visit 6 to Visit 8 (induction phase).

If dose reduction criteria are met (see below), the dose reduction of the OCS will commence at Visit 8 and will continue at 4-weekly intervals till Visit 13 in accordance with OCS dose titration schedule provided in Table 4 (reduction phase). During reduction phase a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each patient.

If a patient does not meet titration criteria, the OCS dose should be returned to the previous effective dose (i.e., the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until EOT (Visit 14).

No adjustments will be made to OCS dose after Visit 13 and the patient will enter the maintenance phase.

The OCS dose changes will be documented in the source documentation and recorded in the appropriate eCRF form.

Patient should have a minimum of 70% compliance with ePRO completion between each study visit (from Visit 6 to Visit 14) based on Asthma Daily Diary for OCS dose titration. If compliance falls under 70%, OCS dose titration may be performed at the Investigator's discretion according to the protocol-specified titration criteria.

5.1.1.1 OCS dose titration

For the optimization phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 1 and Visit 2. Dose titration begins at Visit 2. Baseline FEV1 for the optimization phase will be collected at Visit 2.

For the dose reduction phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between visit 5 and visit 6. Dose titration begins at Visit 8. Baseline FEV1 for dose reduction phase will be collected at Visit 6.

Patients who meet all of the following criteria are eligible for OCS dose titration:

- Pre-BD FEV_1 ≥80% of baseline
- Morning PEF ≥80% of mean morning measures over the 14 days period prior to the scheduled study visit as compared to baseline
- Mean night time awakenings ≤50% increase over the 14 days period prior to the scheduled study visit, as compared to baseline
- SABA rescue medication use of not more than 4 inhalations/day above the mean value over 14 days period prior to the scheduled study visit, as compared to baseline, or above 12 inhalations/day
- No requirement to increase the dose of OCS for asthma symptoms since the last visit

When a patient doesn't meet the above criteria, further reduction of the OCS dose will be stopped for the duration of the study and the patient will be returned to the dose one level higher.

During the post-randomization phase, not all patients will be allowed to reduce their OCS dose to 0. A minimum maintenance dose will be required for patients whose dose at Visit 6 is 15 – 40 mg/day (Table 4); these patients may not be reduced to doses lower than that which is specified.

If, in the opinion of the investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect patient safety), titration may be stopped. The patient should be returned to a dose one level higher (unless a temporary bolus/burst of steroid is warranted) and no further reductions may take place.

For statistical analysis purposes in the event that titration is terminated prior to Visit 13, a patient's final OCS dose will be recorded as one dose level higher than that, which directly preceded termination.

The titration schedule of OCS dose reductions is presented in Table 3 and Table 4.

Table 3 OCS dose titration schedule during the optimization phase (V2 – V4)

Regimen	Dose of OCS at the beginning of optimization phase	Reduction by [a]
Daily	12.5-40 mg	5 mg
	7.5-10 mg	2.5 mg

[a] – During Run-in/optimization phase the reductions should occur at 2-week intervals.

Table 4 OCS dose titration schedule during the reduction phase (V8-V13) a,b

Optimized dose at V6	V 8	V9	V10	V11	V12	V13
40	35	30	25	20	15	10
37.5	32.5	27.5	22.5	17.5	12.5	7.5
35	30	25	20	15	10	7.5
32.5	27.5	22.5	17.5	12.5	7.5	5
30	25	20	15	10	7.5	5
27.5	22.5	17.5	12.5	7.5	5	5
25	20	15	10	7.5	5	5
22.5	17.5	12.5	7.5	5	5	5
20	15	10	7.5	5	5	5
17.5	12.5	7.5	5	5	5	2.5
15	10	7.5	5	5	2.5	1.25
12.5	7.5	5	2.5	1.25	0	0
10	7.5	5	2.5	1.25	0	0

Table 4 OCS dose titration schedule during the reduction phase (V8-V13) a,b

Optimized dose at V6	V 8	V9	V10	V11	V12	V13
7.5	5	2.5	1.25	0	0	0

[a] – All doses expressed in mg/day

[b] – A daily dose of 1.25 mg may be administered as 2.5 mg every other day

5.1.2 Assessment of asthma exacerbations

The treatment, including changes in the OCS dose and duration and the use of additional, potentially emergent therapies is at the discretion of the treating physician. For the purpose of the CSP, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose above one level higher than the current titration step) for at least 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
    - Discontinuation due to exacerbation after V6 is not mandatory. Patients who experience an exacerbation during screening (between Visits 1 and 6) should be screen failed. Those who experience an exacerbation after randomization may remain on investigative product at the PI's discretion. However, they will not be eligible for additional OCS dose titration steps. After the bolus/burst is complete, they should be returned to one dose level higher than the dose that preceded their exacerbation
    - Up titration of OCS dose during optimization to one level higher is not considered an exacerbation
- An emergency room visit due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization due to asthma

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven).

For the optimization phase, the baseline will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected on each day between visit 5 and visit 6.

The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of one new or additional nebulized β2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7 day period compared with the average during baseline, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An asthma exacerbation that occurs ≤7 days of the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so.

Reasonable attempts should be made by the Investigator to bring the patient into the study centre for evaluation of a diary alert or patient initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study centre evaluations for asthma worsening may occur as an UNS visit or as part of an ordinary centre visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (eg, by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.3 Spirometry

General requirements

Lung function (FEV_1 and FVC) at the study centre will be measured by spirometry using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study centre personnel who will be performing the testing are

properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Patients should be instructed not to use their usual ICS-LABA medication within 12 hours of scheduled centre visit spirometry as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the centre. **For the same reason patients should not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled centre visit spirometry.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening FEV_1 and reversibility eligibility criteria.

Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.5.2.

Time of day for scheduled centre visit spirometry

Spirometry testing should be initiated in the morning between 6:00 AM and 11:00 AM according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the centre. Slow spirometry will be conducted prior to the forced manoeuvres. Both slow and forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each slow spirometry and forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

Instruct the patient to inhale and exhale slowly (at least 10 breaths).

From normal breathing, the patient should slowly exhale to a maximum (ERV manoeuvre).

For reaching the end-expiratory level the following two criteria must be complied with according to ATS/ERS.

- Duration of expiration
  - Patients must exhale for at least 6 seconds.
- End of Test Criteria

- Towards the end of the expiration it is important to motivate the patient to try hard. Within the last second of expiration the exhaled volume must not exceed 25 mL.

Next, the patient should slowly inhale to a maximum (VCIN) and then slowly exhale to tidal breathing. According to ATS/ERS criteria at least three trials should be performed.

If the difference between the best and second VCIN and/or VCmax is greater than 0.150 L further trials should be performed.

For IC only: If the coefficient of variation is greater than 6% further trials should be performed.

The forced expiratory manoeuvre (FEV_1 and FVC) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each centre spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal (PN) value (Quanjer et al 2012) will be recorded. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

Post-bronchodilator spirometry

Post-bronchodilator (Post-BD) spirometry will be performed at Visit 2 to assess the degree of airway reversibility and, in a subset of patients who participate in the sputum assessment, as part of the sputum induction procedure. The post BD spirometry procedures should commence within 30±15 after pre- bronchodilator (Pre-BD) spirometry and up to 4 SABA inhalations are allowed.

Order of administration of usual asthma controller medication and IP relative to scheduled pre- and post-bronchodilator spirograms

The patient's usual asthma morning asthma controller therapy must not be given until after the initial pre-medication, pre-bronchodilator spirograms are complete for the reasons discussed above; usual asthma controller may be given after final post-bronchodilator spirograms. IP dosing should also be withheld until pre-bronchodilator spirometry is complete.

The screening post-BD FEV1 performed at Visit 2 is not part of the eligibility criteria for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in section 3.1.

Detailed sputum collection procedures, including related pre and post-BD spirometry measurements are available in a separate sputum manual provided to the designated study centres.

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at study centre for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patients predicted normal (PN) values and are pre-programmed into your spirometer (Quanjer et al 2012).

FEV_1 expressed as percent of the PN value will be calculated as follows:

$$FEV_1\% \text{ of PN} = FEV_1 \text{ measured}/FEV_{1PN} \times 100$$

5.1.4 Home lung function testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the patient on Visit 1.

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 1 (Week-9) until the morning of Visit 14 (Week 28) using the provided ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Patients should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres.

Investigator/authorized delegate will check patient's adherence to correct use of the peak flow meter at each visit as shown in Table 1 and Table 2 (or on EOT Visit if prematurely discontinued from the study).

5.2 Safety assessments

5.2.1 Physical examination

Physical examination will be done in accordance with schedule provided in Table 1 and Table 2.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 7.1.

5.2.1.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

5.2.1.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

5.2.2 Vital signs

Pre-dose vital signs (pulse, blood pressure (BP), respiration rate and body temperature) will be obtained in accordance with schedule provided in Table 1 and Table 2.

The vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. Vital signs should also be taken prior to per protocol BD administration if applicable for that visit.

Pulse rate and BP should be measured after the patient has been resting for at least 5 minutes. The measurement will be taken in sitting position. Pulse rate will be obtained before BP.

Respiration rate will be obtained after patient has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

Body temperature will be measured in Celsius before IP administration in accordance with local standards.

5.2.3 ECG

ECG will be performed in accordance with schedule provided in Table 1 and Table 2.

The assessments will be performed prior to blood drawing, spirometry, IP administration and BD administration.

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry and administration of asthma-related medications and IP).

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigators interpretation and that provided by the ECG machine (if applicable), the Investigators interpretation take precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the ECG will be produced and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine is used for assessment throughout the patient's participation in the study.

ECG data and evaluation will be recorded in the eCRF.

In all patients, the printouts of the ECG will be collected and signed, dated and stored at the study centre along with a signed and dated copy (if the printouts are not on archive-quality paper).

5.2.4 Safety laboratory tests

Safety laboratory tests (list provided in Table 5) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples please refer to the separate Laboratory Manual. Safety samples will be collected in accordance with the schedules provided in Table 1 and Table 2.

The blood eosinophil count from the sample drawn at Visit 1 will be used to inform primary and secondary efficacy of benralizumab.

Haematology and urinalysis will be assessed in line with the schedules provided in the in Table 1 and Table 2; a detailed schedule of the chemistry tests is presented in Table 6.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the Investigators'/authorized delegate's judgement should be reported as AE as described in Section 7.1.3.

The copy of laboratory result report should be signed and data by Investigator and retained at the study centre.

Table 5 List of safety laboratory tests

Serum chemistry		**Haematology**	**Urinalysis**
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Colour
BUN (blood urea nitrogen)	Potassium	Platelet count	Glucose
Calcium	Sodium	Red blood cell (RBC) count	Ketones
Chloride	Total bilirubin	WBC count with differential[a]	Microscopy including WBC/high power field (HPF), RBC/HPF
CO2 (carbon dioxide)	Total cholesterol		pH
Creatinine	Uric acid		Specific gravity

a eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except Visit 1 laboratory report (see Section 6.6).

Table 6 Schedule of serum chemistry tests

VISIT	V1	V6	V10	V14
Alkaline phosphatase	X	X	X	X
ALT	X	X	X	X
AST	X	X	X	X
BUN	X	X	X	X
Calcium, serum	X			
Chloride, serum	X			
CO2 (carbon dioxide)	X			
Creatinine	X	X	X	X
Gamma-GT	X	X	X	X
Glucose	X			
Phosphorus, serum	X			
Potassium, serum	X			
Sodium, serum	X			
Total bilirubin	X	X	X	X
Total cholesterol	X			
Uric acid	X			

5.2.4.1 Pregnancy Test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in Table 1 and Table 2.

- Serum beta-HCG (Beta- human chorionic gonadotropin): To be done at screening Visit 1 only, for WOCBP (analysed at central laboratory)
- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
- Urine HCG: To be performed at the study centre for WOCBP at each treatment visit before any invasive study procedures (eg, blood sampling, spirometry) and IP administration using a dipstick. Positive urine test result must be confirmed with serum beta HCG.

5.3 Other assessments and procedures

5.3.1 Weight and height

Weight and height will be measured in accordance with the schedules provided in Table 1 and Table 2. **Note**: Height will be taken on screening Visit 1 only.

The patient's weight will be recorded in kilograms; height will be recorded in centimetres.

Weight and height measurements will be performed in light clothing and with shoes off.

5.3.2 Patient reported outcomes

Patients will be supplied with an ePRO device and hand-held spirometer at Visit 1. The study centre staff will be trained on how to use both devices and will be responsible for instructing patients on how to use both devices. Patients will have an opportunity to practice using the devices through a pre-programmed training module. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur.

5.3.2.1 Asthma daily diary

The Asthma Daily Diary will be completed each day from the evening of Visit 1 to the morning of Visit 14. The Asthma Daily Diary will include the following daily recordings: morning and evening home lung function data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, background medication compliance (ICS-LABA and OCS). There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician, please refer to Section 5.1.2.

The patient should contact the study physician for evaluation in the event of a diary alert.

Investigator/authorized delegate will check patient's adherence to the Asthma Daily Diary at each visit as shown in Table 1 and Table 2.

Home lung function measurement

For details regarding home lung function measurement please refer to Section 5.1.4.

Asthma symptoms

Asthma symptoms during night time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary, from Visit 1 to Visit 14.

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Rescue medication

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Background medication

Background medication (ICS-LABA) will be recorded in the Asthma Daily Diary in the morning and evening as "yes" or "no", whereas OCS will be recorded in the evening as "yes", "no, dose was missed", not scheduled today" or "not applicable, dose reduced to 0".

5.3.2.2 Asthma control questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β2 agonist use) omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma, and a score >1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device.

The ACQ-6 will be completed by the patient on the ePRO device at Visit 1 and will be given the device to take home.

After V1, the patient will complete the ACQ-6 at home every 7 days (±1 day) until Visit 6 or Randomization (week 0). The patient will bring the device to the randomization visit and complete the ACQ-6 on site during the randomization visit (Week 0).

After randomization the patient will complete the ACQ-6 at home every 2 weeks (±1 day) until Visit 14 (Week 28) where the ACQ-6 will be completed by the patient during study visit at site.

The Investigator/authorized delegate will check patient's adherence to the ACQ-6 at each visit as shown in Table 1 and Table 2.

5.3.2.3 Standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma patients.

The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change, with score changes of >1.5 identified as large meaningful changes

The questionnaire will be completed using the ePRO device.

The AQLQ(s)+12 will be completed by the patient on the ePRO device at Visit 1 and will be given the device to take home.

After Visit 1, the patient will complete the AQLQ(s)+12 at home every 2 weeks (±1 day) until Visit 6 or Randomization (week 0). The patient will bring the device to the randomization visit and complete the AQLQ(s)+12 on site during the randomization visit (Week 0).

After randomization the patient will complete the AQLQ(s)+12 at home every 4 weeks (±1 day) until Visit 14 (Week 28) where the AQLQ(s)+12 will be completed by the patient during study visit at site.

The Investigator/authorized delegate will check patient adherence to the AQLQ(S)+12 at each visit as shown in Table 1 and Table 2.

5.3.3 Other assessments

5.3.3.1 Local laboratory eosinophil test

Only patients with an absolute blood eosinophil count of ≥ 300 cells/µL at visit 1, as assessed at the local laboratory, will be eligible for randomisation (see inclusion criterion 6).

The expectation is that there should be **no more than 36 hours between documented time of blood draw and the local analysis of the sample.** If this window is exceeded, the test must be repeated prior to randomization.

5.3.3.2 Serology

Hepatitis B surface antigen, hepatitis C antibody: To be done only at Visit 1; test to be performed at central laboratory.

HIV-1 and HIV-2 antibodies: To be done only at Visit 1; test to be performed at central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.3.4 Total IgE and Phadiatop

The test will be performed at Visit 6 (Week 0, see Table 2). Analysis will be performed by the central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.3.5 Sputum collection

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, eosinophil progenitor cells by flow cytometry, the pharmacology of benralizumab, and eosinophils recruitment, activation and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients; in addition, in a sub-set of approximately 20 patients flow cytometry will be performed to assess eosinophil progenitor cells in sputum.

Details related to sputum induction, collection, and processing are available in separate manual provided to the designated study centres.

The sputum will be induced by inhaling hypertonic saline.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centres.

The samples will be analyzed by a central laboratory on behalf of AstraZeneca.

5.3.6 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed in approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the investigator or qualified designee according to ATS/ERS guidelines (Wanger et al, 2005) according to the study schedule. Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is

< 0.05) should be obtained and the mean value reported. Measurements using the body plethysmography will be conducted at visit 6, 10 and 14. Prior to the assessment, certain restrictions need to be adhered to. Patients should be instructed not to use their usual ICS-LABA medication within 12 hours of scheduled assessment. Patients should also not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled assessment. This assessment is to be performed on all subjects enrolled for sputum collection. Each site will be allowed to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centres.

5.3.7 Pharmacokinetics

For the PK analysis it is important that the date and time of each SC injection is recorded for each patient.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

Serum will be collected pre-dose according to the schedule of study procedures (Table 2).

Samples for determination of benralizumab concentration in serum will be analyzed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report.

The PK samples will be retained for future use at AstraZeneca or designee for a maximum of 15 years following Last Patient's Last Visit.

A summary of PK analysis results will be reported in the Clinical Study Report (CSR).

5.3.8 Pharmacodynamics

5.3.8.1 Blood biomarkers

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including IL-5, Eosinophil-derived neurotoxin EDN, and eotaxin), and eosinophil- and inflammation-related biomarkers of asthma.

Blood samples will be collected according to the schedule in Table 2 to evaluate the eosinophil progenitor cells by flow cytometry (subset of patients).

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

AstraZeneca or a designee will retain serum biomarker samples for investigation of the pharmacology of benralizumab for a maximum of 15 years following the Last Patient's Last Visit.

The results from the investigation of such samples will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.3.9 Immunogenicity

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

The immunogenicity samples will be retained at AstraZeneca or a designee for a maximum of 15 years following the Last Patient's Last Visit.

A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

Anti-benralizumab antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see Table 2).

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

5.3.10 Handling of biological samples

5.3.10.1 Labelling and shipment of biological samples

The Principal Investigator is to ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not to be shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.3.10.2 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator at each study centre is to keep full traceability of collected biological samples from the patients while in storage at the study centre until shipment or disposal (where appropriate) and is to keep documentation of receipt of arrival.

The sample receiver is to keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and is to keep documentation of receipt of arrival.

AstraZeneca will maintain oversight of the entire life cycle through internal procedures, monitoring of study centres and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle.

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

All investigational products will be manufactured in accordance with Good Manufacturing Practice (GMP).

Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution.

Table 7 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	30mg/mL solution for injection in accessorized pre-filled syringe, 1mL fill volume	MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 1mL fill volume	MedImmune

6.2 Labelling

Labelling of the IP will be carried out by AstraZeneca or designee in accordance with current GMP and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable.

6.3 Storage

Benralizumab/placebo is to be stored at the study centre in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label (between 2–8°C (36–46°F), protected from the light).

In the following cases:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged syringe/cartridge

the centre staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

6.4 Accountability

The study drug provided for this study will be used only as directed in the CSP.

The study personnel will account for all study drugs dispensed to the patient.

The monitor will account for all study drugs received at the centre, unused study drugs, and for appropriate destruction according to local procedures. Certificates of delivery, destruction, and/or return should be signed.

In case of malfunctioning accessorized pre-filled syringe (APFS), the site should contact the study monitor to initiate return of the APFS according to the procedure as described in the separate Shipment and Handling of Product Complaint Returns for IP.

6.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum (country/region) as patients become eligible for randomization.

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

6.6 Methods for ensuring blinding

The study will be conducted in double-blind, double-dummy fashion

All packaging and labelling will be done in such way as to ensure blinding. The following personnel will have access to the randomization list:

- the personnel carrying out the packaging and labelling of IMP
- the personnel generating the randomization list

The information in the randomization list will be kept from other personnel involved in the conduct of the study, and in a secure location until the end of the study.

AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation.

Placebo solution will be visually matched with benralizumab solution. Both benralizumab and placebo will be provided in an accessorized pre-filled syringe.

Maintaining the blind to the patient's blood eosinophil counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. Procedures to mitigate unblinding on this basis include:

- Except for the Visit 1 screening eosinophil count (local laboratory), per protocol hematology will be run by the central laboratory with eosinophil and basophil counts redacted from the laboratory report (other than the Visit 1 laboratory report). Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil+basophil' compartment, monocyte counts will also be redacted from the report
- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a haemoglobin is desired the Investigator should avoid ordering a complete blood cell count with differential
- **Handling of labs obtained during the treatment period but ordered outside of the clinical trial.** Centre staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports. To help ensure this, each investigational centre will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the centre staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

6.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists at the study centre from the IWRS/IVRS. Further detail on how to unblind a patient's treatment allocation will be described in the IWRS/IVRS user manual provided to each study centre

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator is to document and report the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.8 IP administration and treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

The IP will be administered via subcutaneous injection at the study centre on treatment visits and within visit windows as specified in Table 2. In cases when a treatment visit cannot be scheduled within the specified window, the IP administration should be skipped. If 2 consecutive doses of the IP or more than 2 of the scheduled doses of IP are missed during course of the study the patient should be discontinued; please refer to Section 3.6.

Before IP administration

Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For WOCBP urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.2.4.1)

IP administration

The IP will be administered at the study centre on treatment visits and within visit windows as specified in the CSP. In case when treatment visit cannot be scheduled within specified window the IP administration should be skipped. If 2 consecutive doses of the IP or more than 2 of the scheduled doses of IP are missed during course of the study the patient should be discontinued.

Further details on IP administration are provided in the IP Handling Instruction. IP administration must be carried out in line with the Instruction.

After IP administration

After IP administration the patient should be observed for a minimum of 2 hours for the appearance of any acute drug reactions.

Conditions requiring IP administration rescheduling

If any of the following should occur, the Investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The patient has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the patient in the study (eg, viral illnesses)
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration

6.9 Management of IP-related reactions

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available. Study

personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Simpson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least one of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms, and/or persistent gastrointestinal symptoms

3. Reduced BP after exposure

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration) and should be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

7. SAFETY REPORTING

7.1 Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

7.1.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram (ECG)). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.1.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the CSP.

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent throughout the treatment period and including the follow-up period (Visit 15, Week 36).

7.1.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at follow-up in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The requirement to follow-up AEs is not intended to delay database lock or production of the CSR. These activities should proceed as planned with ongoing AEs if necessary.

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca.

7.1.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP

- AE caused patient's withdrawal from study (yes or no)
- Outcome

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

7.1.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

7.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.1.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator will use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases in which a patient shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs (please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions).

7.1.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other centre personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other centre personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 h** from when he or she becomes aware of it.

Once the Investigators or other centre personnel indicate an AE is serious in the WBDC system, an automated email alert will be sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study centre personnel is to report the SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study centre personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

7.2 Overdose

- An overdose with associated AEs will be recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module
- An overdose without associated symptoms will be reported on the Overdose CRF module only

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other centre personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 7.1.4. For other overdoses, reporting should be done within 30 days.

7.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

7.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other centre personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 7.1.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy (PREGREP) module in the CRF will be used to report the pregnancy and the pregnancy outcome (PREGOUT) module will be used to report the outcome of the pregnancy.

7.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose.

Pregnancy of the patient's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

8. EVALUATION AND CALCULATION OF VARIABLES

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

For sample size estimation purposes, the targeted difference in the percentage reduction of the OCS dose between the active drug regimens and placebo is 60%. That is, the final OCS reduction from baseline in benralizumab group is targeted to be 60% greater than the final OCS reduction from baseline in the placebo group. Based on previous studies of OCS reduction an estimate of 70% was used for the standard deviation. Assuming a Type I error rate of 5% and 90% power, the sample size required is 35 patients per treatment group.

8.3 Definitions of analysis sets

All efficacy analyzes will be performed using an Intent-to-Treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

8.3.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

8.3.2 Full analysis set

All patients randomized and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

8.3.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen. All safety summaries will be based on this analysis set.

8.3.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol deviations (eg, disallowed medication) will be included in the PK analysis set. All PK summaries will be based on this analysis set.

8.3.5 Anti-drug antibodies (ADA) analysis set

All patients in the safety analysis set who received at least 1 dose of benralizumab will be included in the ADA analysis set. Patients will be classified the same way as in the safety analysis set. All ADA summaries will be based on this analysis set. Both treatment induced and non-treatment induced (baseline) ADA responses will be summarized.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomized IP at Visit 6 and the conclusion of Visit 14, inclusive.

8.4.2 Percentage reduction from baseline in oral corticosteroid dose

The primary variable is the percentage reduction from baseline in the final OCS dose. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

8.4.3 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation above results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

8.4.4 Proportion of patients with ≤5 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

8.4.5 Proportion of patients with average final OCS dose ≤5.0 mg daily

For each treatment group, the number of patients with average final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with average final OCS dose ≤5 mg daily at final visit / number of patients in treatment group

8.4.6 Forced expiratory volume in one second (FEV_1)

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-bronchodilator measurements recorded at Visit 6 will be used as baseline FEV_1.

8.4.7 Inspiratory capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-bronchodilator measurements recorded at Visit 6 will be used as baseline IC, ERV, IRV, VCIN, VCEX, and VCMAX.

8.4.8 Rate of exacerbations

An asthma exacerbation is defined in Section 5.1.2. Refer to the SAP for exacerbation calculation rules.

Additional bolus/burst of systemic corticosteroid, emergency room visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted for as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. Maximum follow-up time for a patient is approximately 28 weeks; defined as the time from randomization to the date of Visit 14. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

In the statistical analysis, the number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. For the production of summary statistics, the annual exacerbation rate per patient is calculated.

8.4.9 Proportion of patients with at least one exacerbation during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment will also be analyzed. The proportion of such patients will be calculated for each treatment group as:

Number of patients with at least on exacerbation/number of patients in treatment group

8.4.10 Time to first exacerbation

Time from randomization to the first asthma exacerbation will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation −Date of Randomization+1.

The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.11 Calculation or derivation of patient reported outcome variables

8.4.11.1 Asthma symptom score

The outcome variable for asthma symptom score will be the change in mean asthma symptom scores from baseline to each of the post-randomization periods. Asthma symptom daytime scores, night time scores, and total scores will be calculated separately.

8.4.11.2 Asthma Control Questionnaire (ACQ-6)

The outcome variable for ACQ-6 will be the change in mean score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (EOT – baseline) ≤-0.5 → Improvement
- -0.5 < ACQ-6 (EOT – baseline) <0.5 → No change
- ACQ-6 (EOT – baseline) ≥0.5 → Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ-6 responder variable takes value 1 if change from baseline to EOT in ACQ-6 ≤-0.5 and 0 otherwise. Furthermore, patients will be categorized according to their ACQ-6 EOT score as follows (Juniper et al 2006):

- ACQ-6 (EOT) ≤0.75 → Well controlled
- 0.75< ACQ-6 (EOT) < 1.5 → Partly controlled
- ACQ-6 (EOT) ≥ 1.5 → not well controlled

8.4.11.3 Asthma Quality of Life Questionnaire for patients 12 years or older (AQLQ(S)+12)

The AQLQ(S)+12 score will be summarized by domain (4 domains) and for overall. The outcome variable for the AQLQ(S)+12 will be the change in score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits:

- AQLQ(S)+12 (EOT – baseline) ≥0.5 → Improvement

- -0.5 < AQLQ(S)+12 (EOT – baseline) <0.5 → No change
- AQLQ(S)+12 (EOT – baseline) ≤-0.5 → Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to EOT in AQLQ(S)+12 ≥0.5 and 0 otherwise.

8.4.11.4 Electronic diary variables

Asthma PROs (ACQ-6, AQLQ(S)+12), and daily metrics (rescue medication, awakenings and peak flow and asthma symptom scores) derived from the Asthma Daily Diary will be summarized as the mean for baseline period and each of the post randomization periods.

Baseline is defined as the last non-missing value before randomization for the asthma PROs and as the mean of the last 14 days before randomization for the daily metrics. Each post-randomization period is defined as the period between two consecutive scheduled visits (until the Week 28 Visit 14). The change from baseline to each post-randomization period will be used as secondary efficacy variables.

8.4.12 Calculation or derivation of safety variables

8.4.12.1 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (Visit 6) to each post-treatment time point where scheduled assessments are made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

8.4.12.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant Advers Events (OAEs) and reported as such in the CSR.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

8.4.13 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at (or under the guidance of) AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarized using descriptive statistics at each visit by treatment group. Due to the sparse sampling schedule, if data allows population modeling will be performed to further characterize the PK of benralizumab. The potential influence of demographic covariates such as body weight, race, gender and age will be explored. Impact of ADA on PK will also be assessed. The PK results will be provided in a clinical PK report (as an addendum to the CSR). The population modeling results will be presented in a separate pharmacometrics report.

8.4.14 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). Evaluations will be made at baseline (prior to benralizumab administration), and at routine time points during the treatment and follow up phases of the study or discontinuation. ADA titers by treatment group and visit will be summarized. The association of ADA status (positive or negative) with treatment-emergent adverse events (TEAEs)/ treatment-emergent serious adverse events (TESAEs), benralizumab concentration, blood eosinophil levels, and asthma exacerbation rate will be evaluated. In addition, the association of ADA titers (≤ median titer vs > median titer) with TEAEs/ TESAEs, benralizumab concentration, blood eosinophil levels, and asthma exacerbation rate will be evaluated for ADA positive patients only. The neutralizing activity of the ADA response will be assessed at EOT and also during the study follow up period.

8.4.15 Exploratory variables

8.4.15.1 Blood eosinophil levels

The blood eosinophil level change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline.

The eosinophil progenitor change from baseline to each of the post-randomization visits (post Visit 6) at which it is measured up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables (subset of patients). The level recorded at Visit 6 will be used as baseline.

8.4.15.2 Sputum differential cell counts and biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. These variables include sputum cell differential counts, quantification of sputum cytokines and biomarkers, and assessment of eosinophil progenitor cells in sputum.

8.4.15.3 Serum biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline.

8.4.15.4 Lung function as assessed through body plethysmography

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. Variables include TLC, RV, VC, IC and FRC.

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 28-week treatment period, including follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence. To emphasize the importance of collecting complete primary and secondary outcome data in all patients, the ICF form will ask that patients continue study assessments for the whole 28-week double-blind treatment period, including follow-up, even if they discontinue study treatment prematurely.

8.5.1 Testing strategy to account for multiplicity considerations

To account for multiplicity to test the primary endpoint, the percentage reduction from baseline in oral corticosteroid dose, for the two dosing regimens a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Hochberg 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the two p-values is less than 0.05 then reject both null hypotheses. If the larger of the two p-values is greater than 0.05 then proceed to Step 2.

Step 2: If the smaller of the two p-values is less than 0.025 then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (ie, unadjusted).

8.5.2 Primary analysis method(s)

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose. Each benralizumab dose regimen will be compared with placebo.

For each of the two benralizumab dose regimens, the null hypothesis is that the percentage reduction in OCS on benralizumab is equal to the percentage reduction in OCS on placebo. The alternative hypothesis is that the percentage reduction in OCS on benralizumab is not equal to the percentage reduction in OCS on placebo, ie:

H0: % reduction OCS (benralizumab vs Placebo)=0

Ha: % reduction OCS (benralizumab vs Placebo)≠0

The percentage reduction in OCS in each of the two benralizumab dose regimen groups will be compared to the percentage reduction in OCS in the placebo group using an analysis of covariance (ANCOVA) model.

The response variable in the model is the percentage reduction in OCS dose from baseline to the final dose that the patient is receiving at Visit 14. The model will include covariates of treatment group, country/region, and baseline OCS dose.

The estimated treatment effect (ie, difference in mean percentage reduction of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the difference will be presented. In addition, the percentage reduction in OCS and the corresponding 95% CI within each treatment group will be presented.

In addition, the percentage reduction in OCS will also be summarized in patients with baseline blood eosinophil counts 300-450/μL, and >450/μL separately for descriptive purposes only.

8.5.3 Secondary analysis methods

8.5.3.1 Analysis methods for secondary efficacy variables

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- PK and immunogenicity variables
- Proportion of patients with ≥1 asthma exacerbation
- Time to the first asthma exacerbation
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- Change from baseline in pre-bronchodilator FEV1
- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom daytime/night time scores
- Change from baseline in rescue medication use

- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- PK parameters
- ADA

The secondary efficacy endpoints will be analyzed in patients with baseline blood eosinophil counts 300-450/μL and >450/μL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV1 will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-dose/pre-bronchodilator FEV1 and at least one post-randomization pre-dose/pre-bronchodilator FEV1. The dependent variable will be the change from baseline in pre-bronchodilator FEV1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline pre-bronchodilator FEV1 will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in FEV_1=Treatment group+baseline FEV_1+country/region+visit +treatment*visit

The following variables will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score and total rescue medication use, change from baseline in post-bronchodilator FEV_1 and change from baseline in morning and evening PEF.

For the following variables, the proportion in each of the two benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The number of nights with awakening due to asthma and requiring rescue medication will be analyzed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country/region and baseline value will be fit as covariates.

The change from baseline in ACQ-6 and AQLQ(s)+12 will be analyzed using a similar repeated measures model as described for the change from baseline in pre-dose/pre-bronchodilator FEV1.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analyzed using a logistic regression model with factors of treatment, country/region and the baseline value as a covariate.

8.5.3.2 Analysis of methods for exploratory variables

Exploratory endpoints in this study will be obtained from sputum collection and body plethysmography and include (subset of patients):

- sputum cell differential counts
- quantification of sputum cytokines and biomarkers
- assessment of eosinophil progenitor cells
- TLC, RV, VC, IC, FRC

Other exploratory endpoints will be obtained from blood and include:

- blood eosinophils
- assessment of eosinophil progenitor cells (subset of patients)
- serum biomarkers

Raw values and change from baseline for the above indicated sputum, blood endpoints and lung volume measurements will be summarized by treatment group and study visit. Measurements may also be plotted over time.

8.5.3.3 Analysis methods for safety variables

Adverse events (AEs) will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each patient and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA.

Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate.

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis. Changes in vital signs and ECGs will be examined at each visit and at endpoint. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

8.5.4 Subgroup analysis (if applicable)

No subgroup analyses are planned.

8.5.5 Interim analysis and Data Monitoring Committee (if applicable)

No interim analyses are planned.

8.5.6 Sensitivity analysis

No sensitivity analyses are planned but may be conducted as suggested by the data.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study centre personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and WBDC, IWRS/IVRS, ePROs, and other systems to be utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study centre, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Please refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Recording of data

A Web-based Data Capture (WBDC) system will be used for data collection and query handling. Trained study centre personnel will be responsible for entering data on the observations, tests, and assessments specified in the CSP into the WBDC system and according to eCRF instructions. The eCRF instructions will also guide the study centre in performing data entry.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be source data verified, reviewed/queried and updated as needed. The data will be validated as defined in the Data Management Plan. The Investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study centre.

9.2.3 Study agreements

The Principal Investigator at each/the study centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.

The study is expected to start in Q2 2014 and to end by Q1 2016.

The study may be terminated at individual study centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on eCRF as specified in the CSP and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study centre.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) /Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study centre staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the ECs/IRB (Institutional Review Board) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each study centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File and kept for a period that is complaint with GCP/local regulatory requirements, whichever is longer
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a study centre's ICF, AstraZeneca and the study centre's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study centre.

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AstraZeneca

Revised Clinical Study Protocol 2

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
Edition Number	3.0
Date	10 February 2016

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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Date

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	10 April 2015		
2	10 February 2016		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	26 August 2015		

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures.

PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

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Study center(s) and number of patients planned

This study will be conducted worldwide in approximately 100 study centers. Target is to randomize approximately 210 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2014	Phase 3
Estimated date of last patient completed	Q3 2016	

(a) Primary Objective

Objective	Endpoint [a]
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Annual rate of asthma exacerbations after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization • Time to first asthma exacerbation after randomization • Time to first exacerbation requiring hospitalization • Time to first exacerbation requiring hospitalization or emergency department [ED] visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator forced expiratory flow in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

(c) **Safety Objective**

Objective	Endpoint [a]
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

(d) **Exploratory Objectives**

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on eosinophil progenitor cells (subset of patients)	• Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers

[a] Please note: Baseline for all endpoints will be Visit 6.

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in 2 dosing regimens (every 4 weeks [Q4W] throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks [Q8W] thereafter) in patients with uncontrolled asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting β_2 agonist(LABA) and OCS with or without additional asthma controller(s).

The study will recruit approximately 210 patients (randomized 1:1:1), stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region. **Approximately 60 patients will be randomized into the lower eosinophil stratum (≥150 to <300/μL). Approximately 150 patients will randomize into the higher eosinophil stratum (≥300 cells/μL).**

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with the last dose of benralizumab/placebo administered at Week 24, and an end-of-treatment (EOT) visit at Week 28. The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimized OCS dose)
- Reduction (from Week 4 to Week 24, inclusive; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)
- Maintenance (after Week 24 until Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on investigational product (IP) for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in

the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

The IP will be administered at the study center every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS/LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Target patient population

Male and female patients aged from 18 to 75 years with diagnosed asthma, willing to provide informed consent, and requiring continuous treatment with high-dose ICS (>500 mcg fluticasone dry powder formulation equivalents total daily dose) plus LABA and chronic OCS therapy.

Investigational product, dosage and mode of administration

Benralizumab 30mg/mL solution for injection in an accessorized pre-filled syringe (APFS) will be administered at the study center SC every 4 weeks for the first 3 doses and then every 4 or 8 weeks thereafter.

Comparator, dosage and mode of administration

Matching placebo solution for injection in an APFS will be administered at the study center SC every 4 weeks.

Duration of treatment

Following initial enrolment at Week -10, the patient will enter a 10-week enrolment, run-in/optimization phase which is followed by a 28-week double-blind, randomized treatment period, with the last dose of benralizumab/placebo administered at Week 24 and an EOT visit at Week 28. A follow-up visit will be conducted at Week 36.

The total planned study duration is up to 46 weeks.

Patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

Statistical methods

The primary efficacy variable is the percentage change in OCS dose from the patient's dose at baseline to the patient's final dose at Visit 14, while maintaining asthma control. The percentage change in OCS in each of the 2 benralizumab dose regimen groups will be compared with the percentage reduction in OCS in the placebo group using a Wilcoxon rank sum test. Multiplicity will be adjusted using Hochberg procedure (Hochberg 1988).

For the following variables, the proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with 100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Annual exacerbation rates will be analyzed using a negative binomial model with a log-link function. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. Annual exacerbation rates that are associated with an emergency room visit or a hospitalization will be analyzed similarly to annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analyzed using a Cox proportional hazard model with the covariates of treatment, country/region and number of exacerbations in the year before the study. Time to first asthma exacerbation requiring hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit will be analyzed similarly to time to first asthma exacerbation.

Change from baseline in pre-bronchodilator (pre-BD) FEV_1 will be analyzed using a repeated measures analysis model which will include treatment group country/region and baseline pre-BD FEV_1 as covariates. Visit will be fitted as a categorical variable. The following variables will be analyzed similarly to change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score, total rescue medication use, change from baseline in number of nights awakening due to asthma requiring rescue medication use, change from baseline in morning and evening PEF, and the change from baseline in ACQ-6 and AQLQ(s)+12.

The study will recruit a total of 210 patients with blood eosinophils ≥150 to <300 and ≥300/μL. As the targeted patient population for the pivotal studies is ≥300 eosinophils/μL, this study will be stratified by ≥300 and ≥150 to <300 cells/μL. The eosinophil ≥150 to <300/μL stratum will randomize approximately 60 patients and the ≥300 cells/μL stratum will randomize approximately 150 patients. For sample size estimation, 70 patients per treatment arm are required to detect a difference in percent reduction of OCS dose each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

Results for exploratory variables will be summarized using descriptive statistics by treatment group.

All safety parameters will be analyzed descriptively. Safety analyses will be based on the safety analysis set, defined as all patients who received at least 1 dose of IP.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)+12	Standardized Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CO_2	Carbon dioxide
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EOT	End of treatment
ePRO	Electronic patient reported outcome
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HCP	Health care provider
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IC	Inspiratory capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICI	International Coordinating Investigator
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
IP	Investigational product
IPD	Premature investigational product discontinuation
IRV	Inspiratory Reserve Volume
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator

Abbreviation or special term	Explanation
RBC	Red blood cell
RV	Residual volume
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
TLC	Total lung capacity
ULN	Upper limit of normal
UNS	Unscheduled
VC	Vital capacity
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction and airway hyper responsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough and chest tightness. Asthma is a leading cause of morbidity with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 - 450 million people worldwide by 2025 (Masoli et al 2004).

The current approach to anti-inflammatory controller therapy in asthma is based on a step–wise intensification of a daily maintenance regimen primarily centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long–acting β_2 agonists (LABA) in patients with more severe asthma (GINA 2014, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Barnes 1998, Barnes and Adcock 2003, Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990; Louis et al 2000; Di Franco et al 2003; Scott and Wardlaw 2006, Simpson et al 2006; Zhang and Wenzel 2007). Adjusting conventional ICS-based asthma therapy according to the degree of elevated sputum eosinophils as a marker of disease activity resulted in a reduction in the frequency of asthma exacerbations in prospective trials (Green et al 2002; Jayaram et al 2006). Interleukin-5 (IL-5) is a cytokine factor essential for eosinophil trafficking and survival (Molfino et al 2011). Clinical trials of neutralizing anti-IL-5 antibodies (mepolizumab and reslizumab) in patients with uncontrolled eosinophilic asthma resulted in an improvement in key asthma control metrics, including asthma exacerbations (Castro et al 2011 and Pavord et al 2012). These promising results support continued development of therapies targeting the IL-5 pathway in eosinophilic asthmatics unresponsive to standard therapies.

In contrast to anti-IL-5 therapies, benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994; Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) to benralizumab which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients during Phase 2 development resulted in depletion of blood and airway eosinophils, and improvement in multiple metrics of

asthma control including asthma exacerbations, lung function, and Asthma Control Questionnaire (ACQ-6) scores (Busse et al 2010, Gossage et al 2012, Molfino et al 2012, and Phase 2b MI-CP220 study). For further details please refer to the Investigator's Brochure.

1.2 Rationale for conducting this study

The treatment options for patients who remain uncontrolled on high-dose ICS-LABA are extremely limited; one of the treatment options is addition of the oral corticosteroids (OCS) to the current treatment (GINA 2014). However, regular intake of OCS leads to a number of adverse events (AEs) and as a result decreases quality of life for these patients (Kwong et al 1987).

In previous clinical studies, benralizumab administration resulted in rapid and prolonged depletion of eosinophils in the peripheral blood and in the asthmatic airway with associated improvements in multiple metrics of asthma control. The magnitude of clinical improvement was positively correlated with baseline blood eosinophil counts and was most consistently observed in patients with absolute blood eosinophil counts ≥300/μL. Nair et al have demonstrated the steroid-sparing effects of anti-interleukin-5 therapy in OCS-dependent eosinophilic asthmatics, which serves as further support for the proposed mechanism of action of benralizumab in this difficult to treat population (Nair et al 2009).

The purpose of this trial is to confirm if benralizumab can reduce the use of maintenance OCS in systemic corticosteroid dependent patients with severe refractory asthma with elevated eosinophils.

In addition, this trial will further confirm the safety and clinical benefit of benralizumab compared with placebo on markers of asthma impairment and risk including exacerbation rate, pulmonary function, asthma symptoms, and asthma-related quality of life.

1.3 Rationale for study design, doses, and control groups

This is a global study designed to investigate the safety and efficacy of 2 dosing regimens of benralizumab (at a 30 mg fixed dose) administered subcutaneously (SC) in asthma patients who remain uncontrolled on chronic OCS and high-dose ICS-LABA therapy, with or without additional asthma controller(s). Patients on the first regimen will be dosed every 4 weeks (Q4W) throughout the treatment period, while patients on the second regimen will be dosed every 4 weeks for the first 3 doses and then every 8 weeks (Q8W) thereafter. Primary efficacy will be determined based on the percentage reduction in OCS dose over 24 weeks of benralizumab treatment versus placebo, following OCS dose optimization.

The study will recruit approximately 210 patients with blood eosinophils ≥150/μL. It is well established that corticosteroid administration can dramatically suppress blood eosinophil counts (Schleimer and Bochner 1994, Barnes 1998, Barnes and Adcock 2003), and some level of efficacy was seen in patients with peripheral blood eosinophil counts <300/μL from the 100 mg treatment arm Phase 2b study MI-CP220 (see Section 1.4); thus, the target population in this study will be patients with blood eosinophils ≥150/μL. In order to avoid biasing the

results, the study will be randomized and double-blinded, with additional stratification by country/region.

All patients are required to be treated with oral corticosteroids for at least 6 months prior to Visit 1 and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization.

The benralizumab dose (30 mg SC, fixed) and the maintenance regimens are based on all available efficacy and safety data, as well as population exposure-response modeling and stochastic trial simulations from earlier phase benralizumab trials. In particular, Phase 2b MI-CP220 study showed that fixed doses of benralizumab ≥20 mg administered Q8W were clinically effective. Analyses of efficacy endpoints (asthma exacerbations, forced expiratory volume in 1 second [FEV_1] and Asthma Control Questionnaire [ACQ]) suggest 30 mg Q8W (with the first 3 doses administered every 4 weeks) is an effective and tolerable dose for further testing in patients with severe asthma. This dose corresponds to the ED_{90} for asthma exacerbation reduction and ACQ, and maintains a steady-state pharmacokinetic (PK) exposure close to EC_{90} levels for FEV_1 and ACQ.

Other stable asthma therapies on top of OCS and ICS-LABA that are within expert guidance and that are not restricted per protocol (see Section 3.5.2) are allowed in order to accommodate local standards of care.

1.4 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS-LABA (GINA 2014). The evidence base for oral add-on therapies (ie, OCS, leukotriene inhibitors, and xanthenes) is extremely limited. Anti-IgE therapy (ie, omalizumab) may improve control in patients with severe asthma and IgE-mediated allergy to a perennial allergen. Tiotropium is a long-acting bronchodilator that has recently been shown to produce improvement in lung function and exacerbation risk (pooled data) in patients with severe asthma, with inconsistent effects on other measures of asthma control (Kerstjens et al 2012). As such, new therapies are needed for asthma management in patients who remain uncontrolled on standard of care.

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA, benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/μL; however, some level of efficacy (a 16% reduction in annual rate of asthma exacerbations) was seen in patients with peripheral blood eosinophil counts <300/μL from the 100 mg treatment arm of Study CP220 and should support a positive benefit/risk balance in this population. Furthermore, Bel et al saw a significant reduction in oral glucocorticoid dose with mepolizumab treatment in patients with blood eosinophil counts of 150/μL and above (Bel et al 2014).

Development of ADA to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease).

Blood eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The efficacy and safety data obtained to date support the continued clinical development of benralizumab in asthma.

A detailed assessment of the overall risk/benefit of benralizumab in patients with asthma is given in the Investigator's Brochure.

1.5 Overall study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in 2 dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter) in patients with uncontrolled asthma receiving high-dose ICS-LABA and OCS with or without additional asthma controller(s).

The study will recruit approximately 210 patients (randomized 1:1:1) with eosinophils ≥150 cells/μL, stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control. If the patient meets all of the criteria listed for OCS titration in Section 5.1.1.1, his/her asthma will be considered stable and the patient will be eligible for further OCS dose reduction. All patients must be on either oral prednisone or prednisolone as their OCS. Patients who are on any other oral corticosteroid must switch over to an equivalent dose of either oral prednisone or prednisolone at Visit 1. Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit at Week 28.

The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimized OCS dose)

- Reduction (from Week 4 to Week 24, inclusive; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)

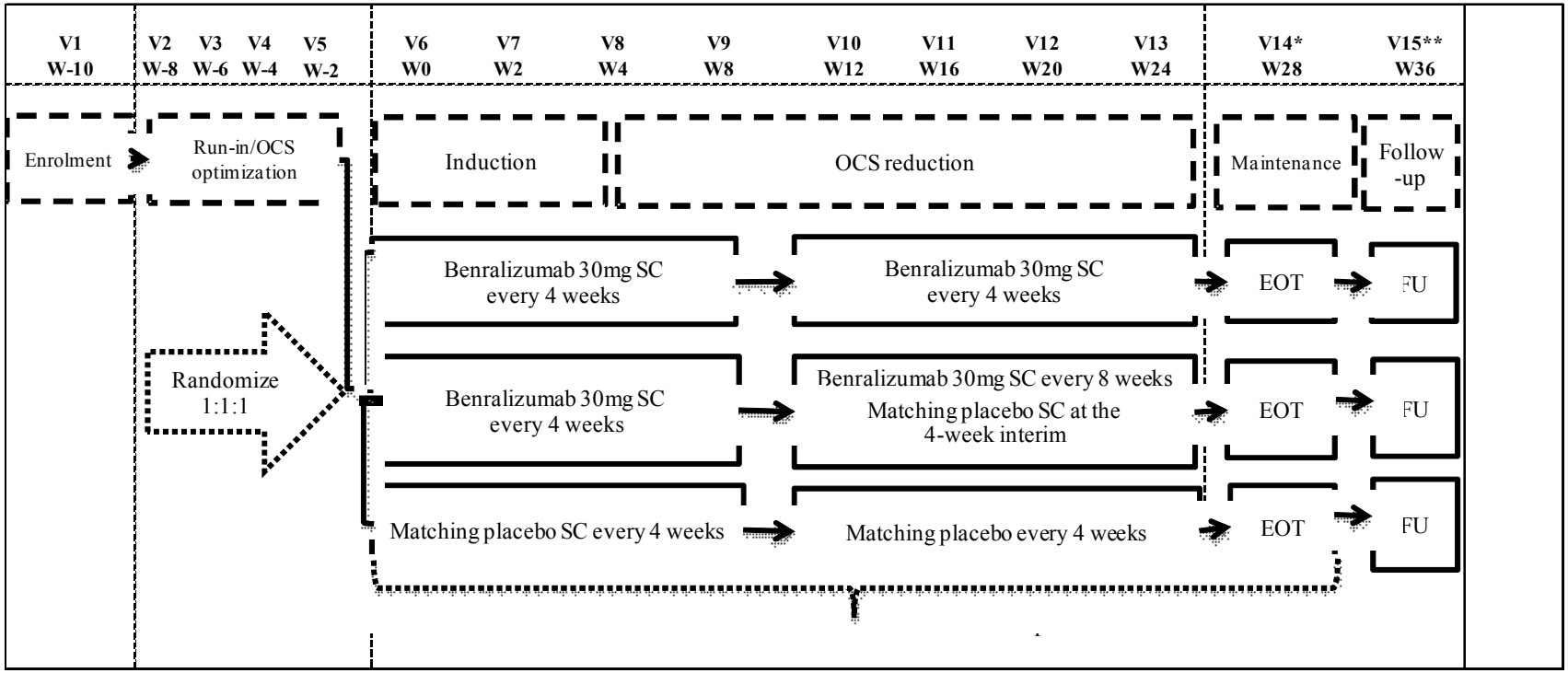
- Maintenance (after Week 24 to Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained).

A Follow-up visit will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

The investigational product (IP) will be administered at the study center every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS-LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Figure 1 Study flow chart



*Patients entering the extension study (D3250C00021) will receive their first dose of benralizumab at Visit 1 in that study, which must occur on the same day as Visit 14 (EOT) for this study (D3250C00020).

**Only those patients not entering the extension study will complete this Follow-up visit.

2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint [a]
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Annual rate of asthma exacerbations after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization • Time to the first asthma exacerbation after randomization • Time to first exacerbation requiring hospitalization • Time to first exacerbation requiring hospitalization or emergency department (ED) visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

(c) **Safety Objective**

Objective	Endpoint [a]
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

(d) **Exploratory Objectives**

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	• Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers

[a] Please note: Baseline for all endpoints will be Visit 6.

3. PATIENT SELECTION CRITERIA AND WITHDRAWAL CRITERIA

3.1 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female and male aged from 18 to 75 years, inclusively

3. Women of childbearing potential (WOCBP) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. Women of childbearing potential must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration, and to within 16 weeks after last dose of IP, and have a negative serum pregnancy test result on Visit 1.

   Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

   - Women <50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone (FSH) levels in the postmenopausal range

   - Women ≥50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment

4. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose

5. Weight of ≥40 kg

6. Peripheral blood eosinophil count of ≥150 cells/μL assessed by local lab at Visit 1

7. History of physician diagnosed asthma requiring treatment with medium-to-high dose ICS (>250μg fluticasone dry powder formulation equivalents total daily dose) and a LABA for at least 12 months prior to Visit 1. Equivalents for fluticasone dry powder can be found in Appendix E

8. Documented treatment with high-dose ICS (>500μg fluticasone propionate dry powder formulation equivalents total daily dose) and LABA for at least 6 months prior to Visit 1. The ICS and LABA can be contained within a combination product or given by separate inhalers:

- In order to aid the dose assessment, ICS equivalents for high-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma (GINA) guidelines, are presented in Appendix E

- For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion

9. Chronic oral corticosteroid therapy for at least 6 continuous months directly preceding Visit 1. Subjects must be on doses equivalent to 7.5 – 40 mg/day of prednisolone/prednisone at Visit 1 and be on a stable dose for at least 2 weeks prior to randomization. In order to aid the dose assessment, a guide for OCS dose equivalence is presented in Appendix H. Patients must agree to switch to study-required prednisone/prednisolone as their oral corticosteroid for the duration of the study.

10. Patients with documented failures of OCS reduction within 6 months prior to Visit 1 will not be required to proceed through the dose optimization phase during run-in. Failed attempts at OCS dose reduction are those which resulted in documented clinical deterioration or reduced lung function attributed to asthma, defined as:

    - Pre-BD FEV_1 < 80% of personal baseline

    - Morning PEF < 80% of personal baseline

    - Night time awakenings increase of > 50% of mean personal baseline

    - Albuterol, salbutamol use > 4 puffs/day above mean personal baseline

    - Requirement for a prednisone or prednisolone burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction

11. Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline), are allowed. Five-lipoxygenase inhibitors (eg, zileuton and roflumilast) are prohibited

12. Morning pre-BD FEV_1 of <80% predicted at Visit 2 (Week -8)

13. Evidence of asthma as documented by either:

    - Airway reversibility (FEV_1 ≥12% and 200 mL) demonstrated at Visit 1, Visit 2, or Visit 3 using the Maximum Post-bronchodilator Procedure OR

    - Documented reversibility in the previous 24 months prior to Visit 1 OR

- Airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/mL) documented in the previous 12 months prior to planned date of randomization OR

- Airflow variability in clinic FEV1 ≥20% between 2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV_1 recorded during an exacerbation should not be considered for this criterion).

Note: **All patients must have reversibility testing performed before randomization to establish a baseline characteristic.**

If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomization, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

14. At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained (please refer to Section 4.1.1)

Inclusion criteria at randomization

15. For WOCBP only: have a negative urine pregnancy test at Visit 6

16. Optimized OCS dose reached at least 2 weeks prior to randomization

17. Additional asthma controller medication must not have been initiated during run in/optimization period (not applicable for management of exacerbations during screening/ run in optimization phase)

18. At least 70% compliance with OCS use from Visit 1 to Visit 6 based on the Asthma Daily Diary

19. At least 70% compliance with usual asthma controller ICS-LABA from Visit 1 to Visit 6 based on Asthma Daily Diary

20. Minimum 70% (ie, 10 of 14 days) compliance with Asthma Daily Diary (morning and evening diary) for the period between each study visit from Visit 1 to Visit 6

3.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are

associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)

2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

   – Affect the safety of the patient throughout the study

   – Influence the findings of the studies or their interpretations

   – Impede the patient's ability to complete the entire duration of study

3. Known history of allergy or reaction to the IP formulation

4. History of anaphylaxis to any biologic therapy

5. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy

6. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization period

7. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during run-in/optimization period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study

8. Any clinically significant cardiac disease or any ECG abnormality obtained during the run-in/optimization period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments

9. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained

10. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol

11. A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test

12. Current smokers or former smokers with a smoking history of ≥10 pack-years

13. History of cancer:

    – Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained

    – Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained

14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent is obtained. Chronic maintenance OCS for the treatment of asthma is allowed.

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids, or an increase in maintenance dose of OCS 2 weeks prior to the date of informed consent.

16. History of life-threatening asthma

17. Asthma control reached at an OCS dose of ≤5mg during run-in/OCS optimization phase (Visit 2 to Visit 6)

18. Qualifies for 3 consecutive dose reductions at Visits 2-4 and continues to meet OCS dose reduction criteria at Visit 5

19. Receipt of oral corticosteroids, other than prednisone or prednisolone, as the maintenance oral steroid controller for asthma symptoms from Visit 1 and throughout the study.

20. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained

21. Receipt of any marketed (eg, omalizumab) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer

22. Receipt of live attenuated vaccines 30 days prior to Visit 1

    – Receipt of inactive/killed vaccinations (eg, inactive influenza) are allowed provided they are not administered within 1 week before/after any study visit

23. Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to Visit 1 is obtained, whichever is longer

24. Patients previously randomized and dosed in any benralizumab clinical trial

25. Initiation of new allergen immunotherapy is not allowed within 30 days prior to Visit 1. Immunotherapy initiated prior to this period, or as a routine part of the patient's seasonal treatment, is allowed. If the immunotherapy is delivered as an injection, there should be a gap of 7 days between the immunotherapy and IP administration

26. Current use of any oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)

27. Planned surgical procedures during the conduct of the study

28. Currently breastfeeding or lactating women

29. Previous randomization in the present study

30. Concurrent enrolment in another clinical trial

31. AstraZeneca staff involved in the planning and/or conduct of the study

32. Employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals

33. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) confirmed during screening period

For procedures for withdrawal of incorrectly enrolled or randomized patients see Section 3.4.

3.3 Patient enrolment and randomization

Investigator(s) should keep a record of patients considered for and included in the study. This pre-screening/screening log will be evaluated periodically by AstraZeneca or its delegates during routine monitoring visits.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

The Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign each potential patient a unique enrolment number, beginning with 'E# via interactive web/voice response system (IWRS/IVRS)

3. Determine patient eligibility.

4. Assign eligible patient unique randomization code via IWRS/IVRS

Patients will be allocated to 1 of 3 treatment arms in a 1:1:1 ratio. The randomization will be stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region and the randomization numbers will be grouped in blocks.

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from IP administration will not be replaced. When a stratum is full, patients who fall within that stratum will not be randomized and will be screen failed from the study (see Section 3.7.2).

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found to not meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

If a patient that does not meet all the eligibility criteria is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

3.5 Concomitant medications, restrictions during and after the study

3.5.1 Concomitant medication

Information about any treatment in the 3 months prior to the date of the informed consent and all the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the Electronic Case Report Form (eCRF).

Note: to satisfy inclusion criteria 8 and 9 the history of continuous treatment with high-dose ICS-LABA for at least 6 months prior to Visit 1 and use of OCS for at least 6 months prior to Visit 1 should be documented in source and recorded in the eCRF (see Section 4.1.1).

3.5.1.1 Background medication

Oral corticosteroids

For eligibility purposes, all patients are required to be treated with oral corticosteroids for at least 6 months prior to Visit 1 and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization. To aid the dose assessment, a guide for OCS dose equivalents is presented in Appendix H.

The dose of OCS will be titrated during optimization and reduction phases of the study (OCS optimization and reduction phases, for details see Sections 4.1.2 and 4.2.2). Patients who have 1 or more documented OCS reduction failures as outlined in Section 3.1, which defines the optimized dose prior to Visit 1, are not required to proceed through the pre-randomization optimization phase.

Oral corticosteroid medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Inhaled corticosteroid/long-acting β_2 agonist and other asthma controllers

All patients are required to be treated with high-dose ICS (>500 µg fluticasone dry powder formulation equivalents) and LABA for at least 6 months prior to Visit 1 and during the course of the study.

The aim of this study is to establish the treatment effect of benralizumab as add-on therapy. Therefore, the background asthma controller medications should be maintained at a stable dose from Visit 1 until the end of the study. If changing the ICS/LABA dose is judged as necessary by the Investigator, the justification should be documented in the source and the change in the doses should be reflected in the electronic case report form (eCRF).

Inhaled corticosteroid/long-acting β_2 agonist medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Additional controllers that are labeled for asthma and allowed per protocol (see 3.1, criterion 11) will be provided by AstraZeneca.

3.5.1.2 Rescue medication

Salbutamol, albuterol, and racemic preparations of albuterol (ie, levalbuterol) will be used as rescue medication during the study in the event of a worsening of asthma symptoms. As with background ICS/LABA medication, rescue medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to ensure access to essential rescue therapy.

3.5.2 Restrictions

3.5.2.1 Asthma medication restrictions

(a) **Use of short-acting ß$_2$ agonists (SABA)**

Prophylactic use of SABA in the absence of symptoms (eg, prior to planned exercise), if deemed necessary by the patient and Investigator, can be used, but prophylactic inhalations should not be recorded in the Asthma Daily Diary. Such use should be documented in medical notes and recorded in the eCRF.

Short-acting ß$_2$ agonist medication via a metered dose device is permitted as needed for worsening asthma symptoms (ie, rescue use) and will be recorded in the Asthma Daily Diary as number of inhalations.

Rescue use of SABA administered via jet or ultrasonic nebulization, outside of managing an acute asthma exacerbation event, is discouraged unless the Investigator deems access to nebulized SABA essential for that patient. Occasions where SABA was administered via nebulization will be recorded separately from metered dose inhaler (MDI) inhalations in the Asthma Daily Diary.

(b) **Use of short acting anticholinergics** (eg, ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event is not allowed from enrolment and throughout the study duration

(c) **Use of long-acting beta-agonists as a reliever** (eg, Symbicort Maintenance and Reliever Treatment) is not allowed from enrolment and throughout the study duration

(d) **Maintenance of asthma controller medications**

The patient's usual pre-study ICS/LABA formulation, dose and regimen, and any other additional allowed asthma controllers that they may have been taking prior to enrolment aside from oral corticosteroids, should be continued unchanged throughout the run-in and treatment period. Please refer to Section 3.1, inclusion criterion 11 for examples of allowed additional controller therapies for this study.

Changes to the patient's background controller regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator; ideally such changes should be discussed with the AstraZeneca Study Team Physician. All changes in the patient's background medication should be documented in medical notes along with rationale for change and recorded in eCRF. Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

(e) **Asthma medication restrictions on the days of scheduled spirometry visit**

Pre- and/or post-dose spirometry assessments will be performed at the study center at scheduled visits (see Table 1 and Table 2); restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 5.1.3):

Visits 2-14: Patients will be asked to withhold their usual ICS/LABA medications on the mornings of scheduled spirometry visits. Twice daily ICS and LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments.

For Visits 2-5, the patient's usual asthma medications may be administered following completion of the screening lung function procedures. For Visits 6-14, the patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in Section 5.1.3.

If the patient has taken their usual ICS/LABA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day, within the allowed window.

If the patient has taken rescue SABA within 6 hours of the planned spirometry assessment, they should ideally either

- remain at the center until such time that the 6-hour withholding time has been reached if it does not exceed the 1.5-hour spirometry window or
- return on another day, within the visit window.

(f) **Asthma medication restrictions prior to home peak expiratory flow testing**

Patients should avoid taking their morning asthma controllers prior to the morning home peak expiratory flow (PEF) testing and should conduct the evening home PEF testing before taking evening asthma controllers. When possible, home PEF testing should be performed at least 6 hours after the last dose of SABA rescue medication.

(g) **Asthma medication restrictions on unscheduled visits**

Asthma medication restrictions on unscheduled (UNS) visits may not be feasible, and may be applied at the discretion of the Investigator. Timing of recent controller and rescue SABA use relative to the UNS spirometry should be noted in the patient's record

(h) **Asthma medication restrictions at center visits with scheduled ECG assessment**

The patients should be instructed not to take their usual asthma controller medication (ie, LABA) prior to a scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restriction is waived for the screening ECG at Visit 1.

3.5.2.2 Other medication restrictions

(a) Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca study physician. Please see Section 3.2 exclusion criteria 14 and 22 for examples and further details.

(b) Receipt of live attenuated vaccines within 30 days prior to randomization, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the IP is not allowed

(c) Patient should not receive allergen immunotherapy injections on the same day as the IP administration

(d) When enrolling a patient who is on theophylline or digoxin, the Investigator should ensure the levels of each of these medications must not exceed the upper limit of therapeutic range. The Investigator will also be responsible for ensuring that these levels are regularly checked, assessed and documented as per local practice (see Table 1)

(e) Patients should not take any other excluded medications:

- Five-lipoxygenase inhibitors (eg, zileuton)
- roflumilast
- Oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)

A table with medication-related restrictions presented in the Appendix G.

3.5.2.3 Other restrictions

(a) Fertile and sexually active patients or their partners should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives)

after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP (see Section 3.1, inclusion criteria 3 and 4; Section 7.3).

(b) Patients must abstain from donating blood and plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP.

3.6 Discontinuation from investigational product

Patients will be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment without prejudice to further treatment

2. AE that, in the opinion of the Investigator, contraindicates further dosing

3. Risk to patient as judged by the Investigator or AstraZeneca

4. Severe noncompliance to Clinical Study Protocol (CSP)

5. Eligibility requirement found not to be fulfilled

6. Pregnancy

7. Lost to follow-up[1]

8. Development of any study specific criteria for discontinuation:

   (a) Anaphylactic reaction to the IP requiring administration of epinephrine

   (b) Development of helminth parasitic infestations requiring hospitalization

   (c) If 2 consecutive doses of IP are missed or more than 2 scheduled doses of IP are missed during course of the study,

   (d) An asthma-related event requiring mechanical ventilation.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7days) after last IP administration. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments or alternatively agree to be contacted by phone calls

[1] Patient is considered lost to follow up when any of the following attempts of contact are failed: -3 attempts of either phone calls, faxes or emails; - having sent 1 registered letter/certified mail; one unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.

at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

3.7 Withdrawal from the study

3.7.1 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.7.2 Withdrawal due to recruitment completion in a randomization stratum

When a specific stratum is full, patients in completed stratum will not be randomized and will be withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF as a development of study specific criteria for discontinuation. As with screen failures, no further study related follow-up of these patients is required.

Strata closure process:

1. The eosinophil ≥150 to <300/μL stratum will be closed to patients when the total number of adult patients in the stratum reaches approximately 60

2. The eosinophil ≥300/μL stratum will be closed to patients when the total number of patients in the stratum reaches approximately 150

The whole study will be closed for recruitment when the total number of patients reaches approximately 210.

3.7.3 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study. The patient will return electronic patient reported outcome (ePRO) devices. The enrolment/randomization code of the withdrawn patient cannot be reused.

If patient agrees, he/she will be asked to return to the study center and complete procedures described for the IPD within 4 weeks (+7 days) after last dose of IP and Follow-up visit 12 weeks ±3 days after last dose of IP for final study-related assessments.

3.8 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As use of the biological samples is an integral part of the study, withdrawal of informed consent for the use of donated samples by the patient will result in the patient being withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent for the use of donated samples is sent immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study center, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study center.

4. STUDY PLAN AND PROCEDURES

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
Informed consent[a]	10.4	X				
Inclusion/exclusion criteria	3.1/3.2	X	X	X	X	X
Medical and asthma history	4.1.1	X				
Complete physical examination	5.2.1.1	X				
Brief physical examination	5.2.1.2		X	X	X	X
Weight, Height	5.3.1	X				
Vital Signs	5.2.2	X	X	X	X	X
ECG	5.2.3	X				
Local laboratory eosinophil test	5.3.3.1	X				
Blood concentration for theophylline and digoxin [b]	5.2.4	X				
Serum chemistry	5.2.4	X				
Hematology	5.2.4	X				
Urinalysis	5.2.4	X				
Serology (hepatitis B, C; HIV-1; HIV-2)	5.3.3.2	X				
Serum pregnancy test	5.2.4.1	X				

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
FSH[c]	5.2.4.1	X				
PEF adherence check	5.1.4		X	X	X	X
Asthma Daily Diary adherence check	5.3.2.1		X	X	X	X
ACQ-6 completion on site	5.3.2.2	X				
ACQ-6 adherence check	5.3.2.2		X	X	X	X
AQLQ(S)+12 completion on site	5.3.2.3	X				
AQLQ(S)+12 adherence check	5.3.2.3		X	X	X	X
Screening pre-BD spirometry[d]	5.1.3	X	X	X	X	X
Screening post-BD spirometry[d,e]	5.1.3	X	X	X		
Assessment of asthma exacerbations	5.1.2		X	X	X	X
OCS dose reduction [f]	5.1.1.1		X	X	X	
OCS dose increase, if indicated [g]	5.1.1.1					X
Adverse events	7.1	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X

a ICF can be signed 3 days prior to Visit 1
b If and when appropriate prior to randomization; for patients who are on theophylline or digoxin, (see Section 3.5.2.2 [d])
c FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
d If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomization, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

e The screening post-BD FEV_1 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in Section 3.1. The post-BD FEV_1; however, still needs to be completed as a baseline characteristic and should be performed using the guidance in Section 5.1.3.

f If the patient's OCS dose was optimized prior to Visit 5, the patient must be maintained on the optimized dose for at least 2 weeks and then can be randomized

g If the patient fails to meet titration criteria at Visits 3-4, the OCS dose should be returned to 1 level higher and Visit 5 can be activated on the same day.

ACQ-6 Asthma Control Questionnaire 6; AQLQ(S)+12 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BD Bronchodilator; D Days; ECG Electrocardiogram; FEV_1 Forced expiratory volume in 1 second; FSH Follicle stimulating hormone; HIV Human immunodeficiency virus; ICF Informed consent form; OCS Oral corticosteroid; PEF Peak expiratory flow; V Visit; UNS Unscheduled; W Week.

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
Inclusion/exclusion criteria	3.1/3.2	X											
Complete physical examination	5.2.1.1	X								X		X	X
Brief physical examination	5.2.1.2		X	X	X	X	X	X	X				
Vital Signs	5.2.2	X	X	X	X	X	X	X	X	X		X	X
ECG	5.2.3	X								X		X	
Serum chemistry[b]	5.2.4	X				X				X		X	
Hematology	5.2.4	X				X			X	X	X	X	
Urinalysis	5.2.4	X				X				X		X	

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
Urine pregnancy test (dipstick)[c]	5.2.4.1	X	X	X	X	X	X	X	X	X		X	
Total IgE	5.3.4	X											
Phadiatop	5.3.4	X											
PK	5.3.7	X		X	X	X	X		X	X	X	X	
ADA	5.3.9	X			X	X	X		X	X	X	X	
Serum biomarkers	5.3.8.1	X		X		X				X	X	X	
Sputum collection[d]	5.3.5	X				X				X	X	X	X
PEF adherence check	5.1.4	X	X	X	X	X	X	X	X	X		X	
Asthma Daily Diary adherence check	5.3.2.1	X	X	X	X	X	X	X	X	X		X	
ACQ-6 adherence check	5.3.2.2	X	X	X	X	X	X	X	X	X		X	
AQLQ(S)+12 adherence check	5.3.2.3	X	X	X	X	X	X	X	X	X		X	
Assessment of asthma exacerbations	5.1.2	X	X	X	X	X	X	X	X	X		X	X
OCS dose titration	5.1.1.1			X	X	X	X	X	X				X[g]

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
Pre-BD spirometry	5.1.3	X		X	X	X	X	X	X	X	X[d]	X	X
Post-BD spirometry for Sputum collection[d]	5.1.3	X				X				X	X	X	X
Body plethysmography[d]	5.3.6	X				X				X		X	
Randomization	4.2/6.5	X											
Administration of IP[e]	6.8	X		X	X	X	X	X	X				
Adverse events	7	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X	X	X	X

a All visits are to be scheduled from the date of randomization but not from the date of previous visit
b Detailed schedule for serum chemistry tests provided in Section 5.2.4, Table 5
c For WOCBP only, urine HCG test to be done at center on each treatment visit before any invasive procedures and IP administration
d The assessment is applicable for designated sites only. Post-BD spirometry as part of sputum induction procedure must be performed on site-owned devices.
e In case of anaphylaxis additional samples to be taken (see Section 6.9)
f Unscheduled visits may be initiated as needed, and additional assessments performed at these visits
g If unscheduled visit caused by exacerbation or infection (if applicable). Up titration only

ACQ-6 Asthma Control Questionnaire 6; ADA Anti-drug antibodies; AQLQ(S)+12 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BD Bronchodilator; D Days; ECG Electrocardiogram; EOT End-of-treatment; FEV_1 Forced expiratory volume in 1 second; FU Follow-up; IP Investigational product; IPD IP discontinuation; OCS Oral corticosteroid; PEF Peak expiratory flow; PK Pharmacokinetics; R Randomization; V Visit; UNS Unscheduled; W Week.

4.1 Enrolment and run-in/optimization period

4.1.1 Enrolment (Visit 1)

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1).

In cases where the patient signs the informed consent form (ICF) prior to Visit 1, Visit 1 procedures must be initiated within 3 working days from the date of informed consent. Registration of the patient's enrolment via IWRS/IVRS should occur on day of Visit 1.

Visit 1 assessments are primarily concerned with confirmation of the asthma disease state, the requisite level of severity based on background medications, and exacerbation history. From Visit 1 until Visit 2, the baseline for the electronic patient-reported outcome (ePRO) parameters will be established.

A record of physician-diagnosed asthma, ICS-LABA and OCS use (Section 3.1, criteria 7, 8, and 9) and asthma exacerbations over the prior 12 months (Section 3.1, criterion 14) is required in source documentation. A patient verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

Examples of acceptable documentation of physician diagnosed asthma and prior asthma exacerbations can include clinic visit (primary or specialist healthcare provider [HCP]), emergency room or hospital records listing asthma as a current problem, plus documentation of at least 1 asthma exacerbation during the 12 months prior to signing the ICF.

A qualifying historical asthma exacerbation is a symptomatic worsening requiring use of systemic corticosteroids (ie, oral, intravenous [IV] or intramuscular [IM] in any healthcare setting) or a temporary increase from a stable maintenance dose of OCS, or that resulted in hospitalization.

Current, regular use of a high-dose ICS and LABA for at least 6 months prior to enrolment and OCS use for at least 6 continuous months prior to enrolment must be documented in the source. Inhaled corticosteroid and LABA may have been administered as either as fixed dose or 2 separate inhalers, and consistent with dose limits set by inclusion criterion 8. This documentation may be in the form of a recent, active medication list as per an HCP note, or filled prescriptions based on a pharmacy record.

After confirmation of initial entry criteria the patient will be supplied with an electronic hand-held spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.3.2 for further details). ACQ-6 and AQLQ(S)+12 should be completed during this visit.

Patients will continue on their current ICS/LABA and other controller(s) (if applicable) treatment with no changes. All patients must be on either prednisone or prednisolone as their OCS at Visit 1. If patients are on any other oral corticosteroids, they must agree to switch to an equivalent dose of the study-required prednisone/ prednisolone as their OCS for the duration of the study. Please refer to Appendix H for the OCS dose-equivalence guide.

Following registration of enrolment, screening procedures may begin to assess study eligibility (inclusion/exclusion) criteria (see Table 1).

4.1.2 Run-in/oral corticosteroid optimization phase (Visit 2 to Visit 5)

Pulmonary function tests and assessment of reversibility (maximum post-BD value of lung function) may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 and this is needed to qualify the patient for randomization (see Section 5.1.3.1).

The run-in/OCS optimization phase will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0). The patient should remain on their current ICS/LABA treatment with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

Patients with documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criterion 10) will not be required to proceed through the OCS optimization phase during the run-in period. For these patients, Visit 2 must be combined with Visit 5. The patient must be maintained on the same OCS dose until randomization at Visit 6. In such cases, all assessments listed in Table 1 for Visit 2 should be conducted at this visit. All eligibility criteria **mus**t be met prior to randomization at Visit 6.

Patients who do not have documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criteria 10), will enter the OCS optimization phase. Their OCS dose will be titrated (see Section 5.1.1.1) to ensure they are taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration must be initiated at Visit 2. The Investigator should follow the titration schedule list in Table 3. Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture period is not yet complete. The decision to initiate OCS dose reduction at Visit 2 is at the discretion of the Investigator and can include consideration of Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months. If inclusion criterion 13 has not been met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility (as per inclusion criterion 13). The patient must be screen failed if they fail to demonstrate reversibility. All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase

If at Visit 2, the patient is judged not to be a candidate for OCS dose reduction based upon asthma symptoms or other clinical reasons in the opinion of the Investigator, he/she should be screen-failed.

At Visit 3 and Visit 4, the dose of OCS may be reduced only if all criteria listed in Section 5.1.1.1 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). If a patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5. **Once the OCS dose is uptitrated, no further OCS dose reductions should be performed. The patient should be maintained on that OCS dose until randomization (Visit 6).**

At Visit 5, if the patient still meets all of the criteria for OCS dose down-titration, this patient must be screen-failed (refer to exclusion criterion 18). If the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until randomization (Visit 6).

The optimized dose of OCS is defined as a lowest dose of OCS at which patient meets criteria listed in Section 5.1.1.1. In cases when the patient is optimized on their OCS dose prior to Visit 5 (Week-2), that visit should be combined with Visit 5 (eg, Visit 3 would be combined with Visit 5). He/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized at Visit 6. Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. The optimized dose reached during the OCS optimization phase becomes the patient's baseline OCS dose for analysis purposes.

It is possible that the patient's asthma symptoms may worsen (excluding exacerbation and/or infection requiring antiviral or antibiotic therapy), in between visits, during the run in/optimization period, as evidenced through patient history and corroborated through the data collect through eDiary. In this case, the OCS dose can be increased to a previous effective dose without a visit to the clinic. The patient can be assessed in clinic at the earliest opportunity or at the next scheduled visit (at the Investigator's discretion). If the patient is assessed during an unscheduled visit, he/she should still return for the next scheduled visit. This scheduled visit can be combined with Visit 5. The patient should be maintained on this new OCS dose for at least 2 weeks prior to randomization (Visit 6).

If the patient experiences an asthma exacerbation requiring evaluation in an Urgent Care Center, in an Emergency Department (ED), Hospitalization, or temporary increase (bolus/burst) of systemic steroids, they do not need to be screen failed. The exacerbation should be treated according local standard of care. After completing the treatment for the exacerbation, the patient should return back to his/her regular maintenance dose of OCS. He/she must remain on this dose for 2 weeks and then return for Visit 5. The maintenance OCS dose must be at least 1 dose-level higher than the dose at which the exacerbation occurred. The patient should be maintained on this OCS dose for 2 weeks prior to randomization (Visit 6). The patient should continue to complete the eDiary daily during the

asthma exacerbation. This is important as compliance will be assessed as per inclusion criteria 18, 19, and 20.

If a patient reaches asthma control at an OCS dose of ≤5mg during the optimization phase, the patient will be a screen failure and will not be randomized (refer to exclusion criterion 17; at Visit 6, the OCS dose must be >5 mg). If the patient does not reach an optimized dose of the OCS by the end of the run-in/optimization phase, the patient should be screen failed and cannot be randomized.

The post-BD FEV_1 should be performed using the guidance in Section 5.1.3.1, if necessary. If inclusion criterion 13 was not met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility. The patient must be screen failed if they fail to demonstrate reversibility. Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics.

Patient eligibility should be evaluated at each visit during the run-in/OCS optimization phase with the relevant documentation entered in the source and eCRF.

Patients whose compliance with the electronic diary is <70% will be given the option once during screening to reschedule a study visit (with the exception of Visit 6) within 72 hours.

Table 3 Oral corticosteroid titration schedule during the optimization phase (Visit 2 to Visit 5)

Enrolment Visit	**Run in/Optimization Phase (OCS dose in mg)**			
V1/W -10	**V2/W -8**	**V3[a]/W -6**	**V4[a]/W -4**	**V5/W -2**
40	35	30	25	A
37.5	32.5	27.5	22.5	A
35	30	25	20	A
32.5	27.5	22.5	17.5	A
30	25	20	15	A
27.5	22.5	17.5	12.5	A
25	20	15	10	A
22.5	17.5	12.5	7.5	A
20	15	10	7.5	A

Table 3 Oral corticosteroid titration schedule during the optimization phase (Visit 2 to Visit 5)

Enrolment Visit	Run in/Optimization Phase (OCS dose in mg)			
17.5	12.5	7.5	5	A & B
15	10	7.5	5	A & B
12.5	7.5	5	B	
10	7.5	5	B	
7.5	5	B		

[a] Check if the patient meets all the criteria listed in Section 5.1.1.1. If yes, then down titrate as per Table 3. If no, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5 (eg, a patient met the criteria and was down titrated to 20 mg at Visit 3; at Visit 4, the patient does not meet the criteria for down titration; therefore, the patient must be uptitrated to at least 25mg).

A. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 18).

B. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 17).

4.1.3 Re-screening

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization phase may also be re-screened (exclusion criterion 6). They may be re-screened 30 days after recovery, eg, completion of the therapy.

Re-screening for the above mentioned reasons is allowed only once for the patient.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

Rescreening of patients for any other reason will be allowed only upon approval of the medical monitor or AstraZeneca Study Physician.

4.2 Randomized treatment period

The randomized treatment period is divided into 3 phases based on the OCS dose adjustment: induction phase (Section 4.2.1), reduction phase (Section 4.2.2), and maintenance phase (Section 4.2.3).

Inclusion criteria at randomization will be confirmed at Visit 6. Before randomization the patient's compliance with usual asthma controller ICS/LABA, OCS, and ePRO completion must be confirmed (see Section 3.1, inclusion criteria 18, 19, and 20).

Patients confirmed to be eligible will be randomized at Visit 6 (Week 0) in a 1:1:1 ratio to receive benralizumab 30 mg either every 4 weeks (Q4W) throughout the treatment period, or every 4 weeks for the first 3 doses and then every 8 weeks (Q8W) thereafter, or placebo Q4W.

The first dose of the IP will be administered at Visit 6 after the patient's randomization via IWRS/IVRS.

Following randomization, the patient will enter a 28-week double-blind treatment period, with the last dose of benralizumab/placebo administered at Visit 13 (Week 24).

At Week 2 (Visit 7), the patient will be seen at the study center for a health check; IP will not be administered at this visit. Procedures specific for this visit are listed in Table 2.

Starting at Visit 8, patients will have scheduled visits at 4-week intervals to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using the ePRO device throughout the 28-week treatment period (see Section 5.3.2 for details).

At Week 28, patients will come to the center for the EOT visit.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7days). At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments, or alternatively agree to be contacted by phone at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilization, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

Patients will return the ePRO device at the EOT (or IPD, if applicable) visit.

Completion or early termination of the treatment will be registered via IWRS/IVRS for each patient.

4.2.1 Induction phase

The induction phase will start at Week 0 (Visit 6) and will continue until Week 4 (Visit 8). During this time, patients will remain on all of their regular asthma controller medications. No dose adjustments to OCS will be made during this period; patients will continue the optimized OCS dose that was achieved during OCS optimization phase. The pre BD

spirometry of acceptable quality must be performed at Visit 6. The pre-BD spirometry will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent post randomization visits until Visit 13.

4.2.2 Reduction phase

The reduction phase will start at Week 4 (Visit 8) and will be completed at Week 24 (Visit 13). The first reduction of OCS dose should occur at the Week 4 visit (Visit 8). Visit 8 is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose. At all other visits in the reduction phase, the OCS dose reduction must take place only when all the titration criteria are met as per Section 5.1.1.1. If Visits 9, 10, 11, 12, and 13, the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met). Oral corticosteroid dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4. **Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. This dose should be maintained until the EOT (Visit 14).** The occurrence of exacerbations, changes in symptoms, and rescue medication use will be assessed.

Table 4 Oral corticosteroid dose titration schedule during the reduction phase (Visit 8 to Visit 13) [a, b]

Optimized dose at V6	V8/W4	V9/W8	V10/W12	V11/W16	V12/W20	V13/W24
40	35	30	25	20	15	10
37.5	32.5	27.5	22.5	17.5	12.5	7.5
35	30	25	20	15	10	7.5
32.5	27.5	22.5	17.5	12.5	7.5	5
30	25	20	15	10	7.5	5
27.5	22.5	17.5	12.5	7.5	5	5
25	20	15	10	7.5	5	5
22.5	17.5	12.5	7.5	5	5	5
20	15	10	7.5	5	5	5
17.5	12.5	7.5	5	5	5	2.5
15	10	7.5	5	5	2.5	1.25
12.5	7.5	5	2.5	1.25	0	0
10	7.5	5	2.5	1.25	0	0
7.5	5	2.5	1.25	0	0	0

[a] All doses expressed in mg/day
[b] A daily dose of 1.25 mg may be administered as 2.5 mg every other day

Patients who experience an asthma exacerbation requiring evaluation in an Urgent Care Center, in ED, Hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) should be returned to the previous effective OCS dose (ie, the higher dose level prior to the titration criterion not being met) after they have returned to their baseline level of asthma control. This dose should be maintained until the EOT (Visit 14).

NOTE: OCS dose reduction may take place only when criteria for OCS dose reduction are met (not applicable for Visit 8, see Section 5.1.1.1).

4.2.3 Maintenance phase

Patients will be maintained for the 4-week period after Week 24 to Week 28 on the stable dose of OCS achieved during the reduction phase, or if requirement for OCS was eliminated, then maintained without OCS. Patients will be maintained without further OCS dose adjustments until their last visit within the study to assess symptoms, ACQ-6, and exacerbations. Patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

4.3 Follow-up period

Patients who have remained on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study

Patients who complete Week 28 (Visit 14) and do not enter the follow-on extension study will be requested to return to the study center at Week 36 for the follow-up assessments. During these visits, patients will be assessed for any ongoing safety issues, and any potential prospective AEs; serum biomarker, PK, and immunogenicity samples will be collected (see Table 2).

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of oral corticosteroid dose

During run-in/OCS optimization phase, the minimum OCS dose while maintaining asthma control will be reached for each patient. The optimized dose will be considered as the baseline OCS dose.

The baseline OCS dose will be maintained at the same level from Visit 6 to Visit 8 (induction phase).

The reduction of the OCS dose will commence at Visit 8 and will continue at 4-week intervals until Visit 13 in accordance with OCS dose titration schedule provided in Table 4 (reduction phase). During reduction phase, a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each patient.

If a patient does not meet titration criteria, the OCS dose should be returned to the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until EOT (Visit 14).

No adjustments will be made to OCS dose after Visit 13 and the patient will enter the maintenance phase.

The OCS dose changes will be documented in the source documentation and recorded in the appropriate eCRF form.

Patient should have a minimum of 70% compliance with ePRO completion between each study visit (from Visit 6 to Visit 14) based on Asthma Daily Diary for OCS dose titration. If compliance falls under 70%, OCS dose titration may be performed at the Investigator's discretion according to the protocol-specified titration criteria.

5.1.1.1 Oral corticosteroid dose titration

Oral corticosteroid dose titration occurs during the Optimization Phase (Table 3) and again during the Reduction Phase (Table 4).

For the optimization phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 1 and Visit 2. Dose titration begins at Visit 2 at the discretion of the Investigator (refer to Section 4.1.2). Baseline FEV_1 for the optimization phase will be collected at Visit 2.

For the dose reduction phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 5 and Visit 6. Dose titration begins at Visit 8 and it is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose. Baseline FEV_1 for dose reduction phase will be collected at Visit 6.

Patients who meet all of the following criteria are eligible for OCS dose reduction during the optimization phase (Table 3) and during the reduction phase (Table 4):

- Pre-BD FEV_1 ≥80% of baseline
- Morning PEF ≥80% of mean morning measures over the 14 days period prior to the scheduled study visit as compared with baseline
- Mean night time awakenings ≤50% increase over the 14 days period prior to the scheduled study visit, as compared with baseline
- SABA rescue medication use of not more than 4 inhalations/day above the mean value over 14 days period prior to the scheduled study visit, as compared with baseline, or above 12 inhalations/day
- No requirement to increase the dose of OCS for asthma symptoms since the last visit

During the optimization phase, if the patient fails to meet all of the above criteria at Visit 3, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose that is at least 1 dose level higher than the OCS dose at which further titration criteria was not met. If randomized at Visit 6, the patient will then be maintained at this OCS dose until the reduction phase (Visit 8).

At Visit 8, the down titration will be initiated. If, at any subsequent visits during the reduction phase, the patient fails to continue to meet the criteria for down titration, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose that is at least 1 dose level higher than the OCS dose at which the down titration criteria were not met. Once the OCS has been uptitrated, no further OCS dose reduction should be performed.

During the post-randomization phase, not all patients will be allowed to reduce their OCS dose to 0. A minimum maintenance dose will be required for patients whose dose at Visit 6 is 15 – 40 mg/day (Table 4); these patients may not be reduced to doses lower than that which is specified.

If, in the opinion of the Investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect patient safety), titration may be stopped after discussion with the AstraZeneca Study Physician. The patient should be returned to a dose at least 1 level higher (unless a temporary bolus/burst of steroid is warranted) and no further reductions may take place. In these instances, the reason(s) for stopping the OCS dose reductions must be documented in the source notes.

For statistical analysis purposes, in the event that titration is terminated prior to Visit 13, a patient's final OCS dose will be recorded as 1 dose level higher than that which directly preceded termination.

The titration schedule of OCS dose reduction during the reduction phase is presented in Table 4.

5.1.2 Assessment of asthma exacerbations

The treatment, including changes in the OCS dose and duration and the use of additional, potentially emergent therapies is at the discretion of the treating physician. For the purpose of the CSP, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step for at least 3 days to treat symptoms of asthma worsening,
- an emergency room visit due to asthma that required systemic corticosteroids, or
- an inpatient hospitalization due to asthma.

Discontinuation due to exacerbation after Visit 6 (the OCS dose reduction period) is not mandatory. Those who experience an exacerbation after randomization may remain on IP at

the Principal Investigator's discretion. Following resolution of the exacerbation, the patient should be placed on the OCS dose 1 step higher than that which they were on when the exacerbation occurred (see Table 4).

Up titration of OCS dose during optimization to 1 level higher is not considered an exacerbation

Worsening of asthma is defined as new or increased symptoms and/or signs (eg, examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (ie, diary-driven).

The baseline during the optimization phase will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected on each day between visit 5 and visit 6.

The ePRO device will be programmed to alert both the patient and study center when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of 1 new or additional nebulized β_2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7-day period compared with the average during baseline, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the baseline average or the highest possible score [daily score of 6]), on at least 2 consecutive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An asthma exacerbation that occurs within ≤7 days of the last dose of systemic steroids prescribed for a prior exacerbation will be counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centers (eg, by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.3 Spirometry

During the run in /optimization phase, all patients must perform pre-BD and post-BD spirometry. Assessment of reversibility may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 (refer to Section 5.1.3.1)

Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to the planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics. Nevertheless, their historical data will be used to meet eligibility prior to randomization as per inclusion criterion 13.

All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase.

For the reduction phase, pre-BD FEV_1 must be performed at Visit 6 and will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits.

General requirements

Lung function (FEV_1 and forced vital capacity [FVC]) at the study center will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Patients should be instructed to restrict the use of their usual ICS/LABA medication prior to scheduled center visit spirometry as this will affect the pre-BD FEV_1 value that may be taken subsequently at the center. Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment. **For the same reason, patients should not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled center visit spirometry.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening FEV_1 and reversibility eligibility criteria.

Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.5.2.

Time of day for scheduled center visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ±1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the center. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the maneuver. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

For reaching the end-expiratory level, the following 2 criteria must be complied with according to ATS/ERS:

- Duration of expiration
  - Patients must exhale for at least 6 seconds.
- End of Test Criteria
  - Towards the end of the expiration, it is important to motivate the patient to try hard. Within the last second of expiration the exhaled volume must not exceed 25 mL.

The forced expiratory maneuver (FEV_1 and FVC) should start with a maximal inspiration and then be followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the maneuver. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal (PN) value (Quanjer et al 2012) will be recorded. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

Post-bronchodilator spirometry

The post-BD spirometry procedures should commence within 30±15 minutes after pre-bronchodilator (pre-BD) spirometry according to the regimen for reversibility testing outlined in Section 5.1.3.1.

Post-bronchodilator (post-BD) spirometry will also be performed in a subset of patients who participate in the sputum assessment, as part of the sputum induction procedure on site-owned spirometry devices.

Order of administration of usual asthma controller medication and investigational product relative to scheduled pre- and post-bronchodilator spirometry

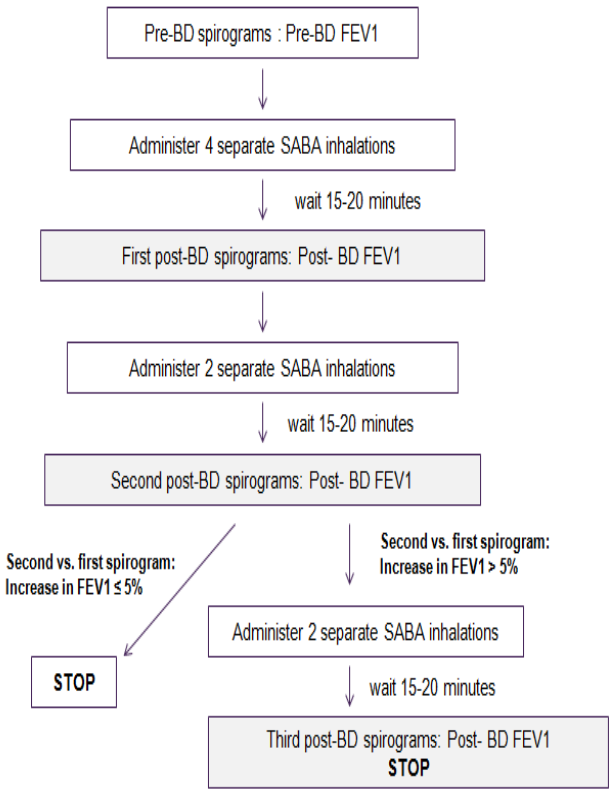
The patient's asthma morning asthma controller therapy must not be given until after the initial pre-BD spirometry is complete; asthma controller medications may be given after final post-BD spirometry assessments. Investigational product dosing should also be withheld until pre-BD spirometry is complete.

Detailed sputum collection procedures, including related pre and post-BD spirometry measurements are available in a separate sputum manual provided to the designated study centers.

5.1.3.1 Reversibility test and post-bronchodilator FEV_1 assessment

The procedure described in this section refers to the reversibility testing at Visit 1 or Visit 2 or Visit 3 (to evaluate inclusion criterion 13, if applicable). Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose) up to a maximum of 8 inhalations). It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 2.

Figure 2 Reversibility testing algorithm



1 Verify with the patient that the medication restrictions to allow the reversibility assessment have been met (Section 3.5.2)

2 After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in 1 breath to total lung capacity (TLC) from a spacer device. The breath is then held for 5–10 seconds before the patient exhales. Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 15-20 minutes later.

3 If the patient has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). A second post-BD spirometry should be performed 15-20 minutes later.

4 If the patient still has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations can be administered (for a total of 8 inhalations). A third post-BD spirometry should be performed 15-20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffs, and/or a total of less than 8 puffs, can be used if there is a concern about any effect on the patient's heart rate, tremor, or safety. For reversibility testing at Visit 1, Visit 2, or Visit 3, it is acceptable to stop the procedure when eligibility criterion is met.

The highest pre- and post-BD FEV_1 should be used to determine reversibility.

Reversibility is calculated as follows:

$$\% \text{ Reversibility} = \frac{(\text{post-BD } FEV_1 - \text{pre BD } FEV_1) \times 100}{\text{pre-BD } FEV_1}$$

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at study center for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patients predicted normal (PN) values and are pre-programmed into your spirometer (GINA 2014).

FEV_1 expressed as percent of the PN value will be calculated as follows:

$$FEV_1\% \text{ of PN} = FEV_1 \text{ measured} / FEV_{1PN} \times 100$$

5.1.4 Home lung function testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the patient on Visit 1.

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 1 (Week -10) until the morning of Visit 14 (Week 28) using the provided ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Patients should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres.

The Investigator/authorized delegate will check the patient's adherence to correct use of the peak flow meter at each visit as shown in Table 1 and Table 2 (or at EOT Visit if prematurely discontinued from the study).

5.2 Safety assessments

5.2.1 Physical examination

Physical examination will be done in accordance with the schedules provided in Table 1 and Table 2.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 7.1.

5.2.1.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

5.2.1.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, and cardiovascular and respiratory systems. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

5.2.2 Vital signs

Pre-dose vital signs (pulse, blood pressure (BP), respiration rate and body temperature) will be obtained in accordance with schedules provided in Table 1 and Table 2.

The vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. Vital signs should also be taken prior to per protocol BD administration if applicable for that visit.

Pulse rate and blood pressure (BP) should be measured after the patient has been resting for at least 5 minutes. The measurement will be taken in sitting position. Pulse rate will be obtained before BP.

Respiration rate will be obtained after the patient has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

Body temperature will be measured in degrees Celsius before IP administration in accordance with local standards.

5.2.3 Electrocardiogram

Electrocardiograms will be performed in accordance with the schedules provided in Table 1 and Table 2.

The assessments will be performed prior to blood drawing, spirometry, IP administration, and BD administration.

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry and administration of asthma-related medications and IP).

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigators interpretation and that provided by the ECG machine (if applicable), the Investigators interpretation take precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the ECG will be produced and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine is used for assessment throughout the patient's participation in the study.

Electrocardiogram data and evaluation will be recorded in the eCRF.

For all patients, the printouts of the ECG will be collected, signed, dated, and stored at the study center along with a signed and dated copy (if the printouts are not on archive-quality paper).

5.2.4 Safety laboratory tests

Safety laboratory tests (list provided in Table 5) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage, and shipment of samples, please refer to the separate Laboratory Manual. Safety samples will be collected in accordance with the schedules provided in Table 1 and Table 2.

Hematology and urinalysis will be assessed in line with the schedules provided in the in Table 1 and Table 2; a detailed schedule of the chemistry tests is presented in Table 6.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the Investigators'/authorized delegate's judgement should be reported as AE as described in Section 7.1.3.

The copy of laboratory result report should be signed and data by Investigator and retained at the study center.

Table 5 List of safety laboratory tests

Serum chemistry		**Hematology**	**Urinalysis**
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Colour
BUN (blood urea nitrogen)	Potassium	Platelet count	Glucose
Calcium	Sodium	Red blood cell (RBC) count	Ketones
Chloride	Total bilirubin	WBC count with differential[a]	Microscopy including WBC/high power field (HPF), RBC/HPF
CO_2 (carbon dioxide)	Total cholesterol		pH
Creatinine	Uric acid		Specific gravity
Serum concentration[b]			

a eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except Visit 1 laboratory report (see Section 6.6).

[b] If and when appropriate prior to randomization; For patients who are on theophylline and digoxin (see Section 3.5.2.2 [d])

Table 6 Schedule of serum chemistry tests

VISIT	V1	V6	V10	V14	IPD
Alkaline phosphatase	X	X	X	X	X
ALT	X	X	X	X	X
AST	X	X	X	X	X
BUN	X	X	X	X	X
Calcium, serum	X			X	X
Chloride, serum	X			X	X
CO_2 (carbon dioxide)	X			X	X
Creatinine	X	X	X	X	X
Gamma-GT	X	X	X	X	X
Glucose	X			X	X
Phosphorus, serum	X			X	X
Potassium, serum	X			X	X
Sodium, serum	X			X	X
Total bilirubin	X	X	X	X	X
Total cholesterol	X			X	X
Uric acid	X			X	X

IPD Premature investigational product discontinuation

5.2.4.1 Pregnancy Test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in Table 1 and Table 2.

- Serum beta-HCG (Beta- human chorionic gonadotropin): To be done at screening Visit 1 only, for WOCBP (analyzed at central laboratory)
- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
- Urine HCG: To be performed at the study center for WOCBP at each treatment visit before any invasive study procedures (eg, blood sampling, spirometry) and IP administration using a dipstick. A positive urine test result must be confirmed with serum beta HCG.

5.3 Other assessments and procedures

5.3.1 Weight and height

Weight and height will be measured in accordance with the schedules provided in Table 1.

Note: Weigh and height will be taken on screening Visit 1 only.

The patient's weight will be recorded in kilograms; height will be recorded in centimetres.

Weight and height measurements will be performed in light clothing and with shoes off.

5.3.2 Patient reported outcomes

Patients will be supplied with an ePRO device and hand-held spirometer at Visit 1. The study center staff will be trained on how to use both devices and will be responsible for instructing patients on how to use both devices. Patients will have an opportunity to practice using the devices through a pre-programmed training module. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur.

5.3.2.1 Asthma daily diary

The Asthma Daily Diary will be completed each day from the evening of Visit 1 to the morning of Visit 14. The Asthma Daily Diary will include the following daily recordings: morning and evening home lung function data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, background medication compliance (ICS/LABA and OCS). There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician (refer to Section 5.1.2).

The patient should contact the study physician for evaluation in the event of a diary alert.

Investigator/authorized delegate will check the patient's adherence to the Asthma Daily Diary at each visit as shown in Table 1 and Table 2.

Home lung function measurement

For details regarding home lung function measurement please refer to Section 5.1.4.

Asthma symptoms

Asthma symptoms during night time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary, from Visit 1 to Visit 14.

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Rescue medication

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Background medication

Background medication (ICS/LABA) will be recorded in the Asthma Daily Diary in the morning and evening as "yes" or "no", whereas OCS will be recorded in the evening as "yes", "no, dose was missed", not scheduled today" or "not applicable, dose reduced to 0".

5.3.2.2 Asthma Control Questionnaire

The Asthma Control Questionnaire (ACQ-6) is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β_2 agonist use), omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of $\leq$0.75 indicate well-controlled asthma, scores between 0.75 and $\leq$1.5 indicate partly controlled asthma, and a score >1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device.

The ACQ-6 will be completed by the patient on the ePRO device at Visit 1 and the patient will be given the device to take home.

After Visit 1, the patient will complete the ACQ-6 at home every 7 days (±1 day) until Visit 6 or Randomization (Week 0). The patient will bring the device to the randomization visit and complete the ACQ-6 on site during the randomization visit (Week 0).

After randomization, the patient will complete the ACQ-6 at home every 2 weeks (±1 day) until Visit 14 (Week 28), where the ACQ-6 will be completed by the patient during study visit at site.

The Investigator/authorized delegate will check patient's adherence to the ACQ-6 at each visit as shown in Table 1 and Table 2.

5.3.2.3 Standardized Asthma Quality of Life Questionnaire for 12 years and older

The Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S]+12) is a questionnaire that measures the health-related quality of life experienced by asthma patients.

The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change, with score changes of >1.5 identified as large meaningful changes

The questionnaire will be completed using the ePRO device.

The AQLQ(s)+12 will be completed by the patient on the ePRO device at Visit 1 and the patient will be given the device to take home.

After Visit 1, the patient will complete the AQLQ(s)+12 at home every 2 weeks (±1 day) until Visit 6 or Randomization (Week 0). The patient will bring the device to the randomization visit and complete the AQLQ(s)+12 on site during the randomization visit (Week 0).

After randomization, the patient will complete the AQLQ(s)+12 at home every 4 weeks (±1 day) until Visit 14 (Week 28) where the AQLQ(s)+12 will be completed by the patient during study visit at site.

The Investigator/authorized delegate will check patient adherence to the AQLQ(S)+12 at each visit as shown in Table 1 and Table 2.

5.3.3 Other assessments

5.3.3.1 Local laboratory eosinophil test

Only patients with an absolute blood eosinophil count of ≥150 cells/μL at Visit 1, as assessed at the local laboratory, will be eligible for randomization (see inclusion criterion 6).

The expectation is that there should be **no more than 36 hours between documented time of blood draw and the local analysis of the sample.** If this window is exceeded, the test must be repeated prior to randomization.

5.3.3.2 Serology

Hepatitis B surface antigen, hepatitis C antibody: To be done only at Visit 1; test to be performed at central laboratory.

HIV-1 and HIV-2 antibodies: To be done only at Visit 1; test to be performed at central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.3.4 Total IgE and Phadiatop

The test will be performed at Visit 6 (Week 0, see Table 2). Analysis will be performed by the central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.3.5 Sputum collection

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, eosinophil progenitor cells by flow cytometry, the pharmacology of benralizumab, and eosinophil recruitment, activation, and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients.

Details related to sputum induction, collection, and processing are available in separate manual provided to the designated study centers.

The sputum will be induced by inhaling hypertonic saline.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

The samples will be analyzed by a central laboratory on behalf of AstraZeneca. AstraZeneca or a designee will retain sputum biomarker samples for investigation of the pharmacology of benralizumab for a maximum of 15 years following the Last Patient's Last Visit.–The results from the investigation of such samples, including sputum biomarkers will not be reported in the CSR, but in separate reports and in scientific publications as appropriate.

5.3.6 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed on approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the Investigator or qualified designee according to ATS/ERS guidelines (Wanger et al 2005) according to the study schedule (see Table 2). Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is <0.05) should be obtained and the mean value reported. Measurements using the body plethysmography will be conducted at visit 6, 10 and 14. Prior to the assessment, certain restrictions need to be adhered to. Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours to scheduled assessment. Patients should also not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled assessment. This assessment is to be performed on all subjects enrolled for sputum collection. Each site will be allowed to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centers.

5.3.7 Pharmacokinetics

For the PK analysis, it is important that the date and time of each SC injection is recorded for each patient.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

Serum will be collected pre-dose according to the schedule of study procedures (Table 2).

Samples for determination of benralizumab concentration in serum will be analyzed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report.

The PK samples will be retained for future use at AstraZeneca or designee for a maximum of 15 years following the Last Patient's Last Visit.

A summary of PK analysis results will be reported in the Clinical Study Report (CSR).

5.3.8 Pharmacodynamics

5.3.8.1 Blood biomarkers

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including IL-5, Eosinophil-derived neurotoxin [EDN], and eotaxin)., Eosinophil-, basophil- and inflammation-related biomarkers of asthma may also be assessed.

Blood samples will be collected according to the schedule in Table 2 to evaluate the eosinophil progenitor cells by flow cytometry (subset of patients).

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

AstraZeneca or a designee will retain serum biomarker samples for investigation of the pharmacology of benralizumab for a maximum of 15 years following the Last Patient's Last Visit.

The results from the investigation of such samples will not be reported in the CSR, but in separate reports and in scientific publications as appropriate.

5.3.9 Immunogenicity

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

The immunogenicity samples will be retained at AstraZeneca or a designee for a maximum of 15 years following the Last Patient's Last Visit.

A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

Anti-benralizumab antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see Table 2).

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

5.3.10 Handling of biological samples

5.3.10.1 Labelling and shipment of biological samples

The Principal Investigator is to ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not to be shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

5.3.10.2 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator at each study center is to keep full traceability of collected biological samples from the patients while in storage at the study center until shipment or disposal (where appropriate) and is to keep documentation of receipt of arrival.

The sample receiver is to keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and is to keep documentation of receipt of arrival.

AstraZeneca will maintain oversight of the entire life cycle through internal procedures, monitoring of study centers, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle.

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

All investigational products will be manufactured in accordance with Good Manufacturing Practice (GMP).

Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution (Table 7).

Table 7 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	30mg/mL solution for injection in accessorized pre-filled syringe, 1mL fill volume	MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 1mL fill volume	MedImmune

6.2 Labelling

Labelling of the IP will be carried out by AstraZeneca or designee in accordance with current Good Manufacturing Practice (GMP) and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable.

6.3 Storage

Benralizumab/placebo is to be stored at the study center in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label (between 2–8°C (36–46°F), protected from the light).

In the following cases:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged syringe/cartridge

The center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

6.4 Accountability

The study drug provided for this study will be used only as directed in the CSP.

The study personnel will account for all study drugs dispensed to the patient.

The monitor will account for all study drugs received at the center, unused study drugs, and for appropriate destruction according to local procedures. Certificates of delivery, destruction, and/or return should be signed.

In case of malfunctioning accessorized pre-filled syringe (APFS), the site should contact the study monitor to initiate return of the APFS according to the procedure as described in the separate Shipment and Handling of Product Complaint Returns for IP.

6.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum (combination of eosinophil level and country/region) as patients become eligible for randomization.

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

6.6 Methods for ensuring blinding

The study will be conducted in double-blind, double-dummy fashion

All packaging and labelling will be done in such way as to ensure blinding. The following personnel will have access to the randomization list:

- the personnel carrying out the packaging and labelling of IMP
- the personnel generating the randomization list

The information in the randomization list will be kept from other personnel involved in the conduct of the study and in a secure location until the end of the study.

AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation.

Placebo solution will be visually matched with benralizumab solution. Both benralizumab and placebo will be provided in an APFS.

Maintaining the blind to the patient's blood eosinophil counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. Procedures to mitigate unblinding on this basis include:

- Except for the Visit 1 screening eosinophil count (local laboratory), per protocol hematology will be run by the central laboratory with eosinophil and basophil counts redacted from the laboratory report (other than the Visit 1 laboratory report). Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil+basophil' compartment, monocyte counts will also be redacted from the report
- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with differential
- **Handling of labs obtained during the treatment period but ordered outside of the clinical trial.** Center staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside lab reports. To help ensure this, each investigational center will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the center staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

6.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists at the study center from the IWRS/IVRS. Further detail on how to unblind a patient's treatment allocation will be described in the IWRS/IVRS user manual provided to each study center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The

Investigator is to document and report the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.8 Investigational product administration and treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the case report form (CRF).

The IP will be administered via SC injection at the study center on treatment visits and within visit windows as specified in Table 2. In cases when a treatment visit cannot be scheduled within the specified window, the IP administration should be skipped. If 2 consecutive doses of the IP or more than 2 of the scheduled doses of IP are missed during course of the study, the patient should be discontinued (refer to Section 3.6).

If an Investigator decides to skip the IP administration due to exacerbations, the above rule does not apply.

Before investigational product administration

Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For WOCBP, a urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.2.4.1)

Investigational product administration

The IP will be administered at the study center on treatment visits and within visit windows as specified in the CSP. In cases when a treatment visit cannot be scheduled within the specified window, the IP administration should be skipped. If 2 consecutive doses of the IP or more than 2 of the scheduled doses of IP are missed during course of the study the patient should be discontinued.

Further details on IP administration are provided in the IP Handling Instruction. IP administration must be carried out in line with the Instruction.

After investigational product administration

After IP administration the patient should be observed for a minimum of 2 hours for the appearance of any acute drug reactions.

Conditions requiring investigational product administration rescheduling

If any of the following should occur, the Investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The patient has an intercurrent illness, that in the opinion of the Investigator, may compromise the safety of the patient in the study (eg, viral illnesses)
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration

6.9 Management of investigational product-related reactions

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available. Study personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Simpson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

3. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction
4. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms, and/or persistent gastrointestinal symptoms
5. Reduced BP after exposure

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration and should be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample may be drawn as soon as safely possible to the event for additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

7. SAFETY REPORTING

7.1 Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

7.1.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.1.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the CSP.

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent throughout the treatment period and including the follow-up period (Visit 15, Week 36).

7.1.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at follow-up in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The requirement to follow-up AEs is not intended to delay database lock or production of the CSR. These activities should proceed as planned with ongoing AEs if necessary.

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca.

7.1.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 7.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

7.1.3.4 Causality collection

The Investigator will assess causal relationship between the IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

7.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.1.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator will use the clinical, rather than the laboratory term (eg, anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases in which a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs (please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions).

7.1.3.7 Symptoms of the disease under study

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Section 7.1.2
- The patient discontinues the study due to the sign or symptom
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

After randomization, asthma exacerbations should be recorded in the exacerbation eCRF (EXACA; see Section 5.1.1). If the exacerbation fulfils any of the above criteria, the sign or symptom should also be recorded as an AE.

7.1.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other center personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other center personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 h** from when he or she becomes aware of it.

Once the Investigators or other center personnel indicate an AE is serious in the Web-based Data Capture (WBDC) system, an automated email alert will be sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study center personnel is to report the SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study center personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

7.2 Overdose

- An overdose with associated AEs will be recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module
- An overdose without associated symptoms will be reported on the Overdose CRF module only

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other center personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 7.1.4. For other overdoses, reporting should be done within 30 days.

7.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

7.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other center personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 7.1.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy (PREGREP) module in the CRF will be used to report the pregnancy and the pregnancy outcome (PREGOUT) module will be used to report the outcome of the pregnancy.

7.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose.

Pregnancy of the patient's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

8. EVALUATION AND CALCULATION OF VARIABLES

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

For the primary endpoint of percentage reduction from baseline OCS dose, 70 patients per treatment arm are required to detect a difference between each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group).

8.3 Definitions of analysis sets

All efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

8.3.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

8.3.2 Full analysis set

All patients randomized and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

8.3.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on 1 or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen. All safety summaries will be based on this analysis set.

8.3.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol deviations (eg, disallowed medication) will be included in the PK analysis set. All PK summaries will be based on this analysis set.

8.3.5 Anti-drug antibodies analysis set

All patients in the safety analysis set who received at least 1 dose of benralizumab will be included in the ADA analysis set. Patients will be classified the same way as in the safety analysis set. All ADA summaries will be based on this analysis set. Both treatment induced and non-treatment induced (baseline) ADA responses will be summarized.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomized IP at Visit 6 and the conclusion of Visit 14, inclusive.

8.4.2 Percentage reduction from baseline in oral corticosteroid dose

The primary variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

For patients who lost asthma control between Visits 13 and 14, the final dose will be set to 1 dose level higher than that which directly preceded the loss of asthma control.

Similarly, for patients who withdrew from the study, the final dose will be set to 1 dose level higher than that which directly preceded withdrawal.

8.4.3 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation above results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

8.4.4 Proportion of patients with 100% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation in Section 8.4.2 results in a value of 100%, that patient will be classified as having a 100% reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with 100% reduction at final visit/number of patients in treatment group

8.4.5 Proportion of patients with ≤5 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

8.4.6 Proportion of patients with average final oral corticosteroid dose ≤5.0 mg daily

For each treatment group, the number of patients with average final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with average final OCS dose ≤5 mg daily at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

8.4.7 Forced expiratory volume in 1 second

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-BD measurements recorded at Visit 6 will be used as baseline FEV_1.

8.4.8 Rate of exacerbations

An asthma exacerbation is defined in Section 5.1.2. Refer to the SAP for exacerbation calculation rules.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of an increased OCS dose that is used to treat an exacerbation, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of an increased OCS dose that is used to treat an exacerbation or the date of discharge from a hospital, whichever occurs later. In the primary analysis, the number of exacerbations observed for a patient during the 28-week double-blind treatment period will be used as response variable.

NB. If the patient is not fulfilling criteria for down titration listed in Section 5.1.1.1 and needs to be up titrated, the patient should up titrated by 1 level and this up titration should not be considered the start of an exacerbation.

An additional bolus/burst of systemic corticosteroid, emergency room visit requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation, it must be preceded by at least 7 days in which neither criterion is fulfilled. Maximum follow-up time for a patient is approximately 28 weeks; defined as the time from randomization to the date of Visit 14. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For the production of summary statistics, the annual exacerbation rate per patient is calculated.

8.4.9 Proportion of patients with at least 1 exacerbation during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment will also be analyzed. The proportion of such patients will be calculated for each treatment group as:

Number of patients with at least on exacerbation/number of patients in treatment group

8.4.10 Time to first exacerbation

Time from randomization to the first asthma exacerbation will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation −Date of Randomization+1.

The time to first asthma exacerbation for patients who do t experience an asthma exacerbation during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.11 Time to first exacerbation requiring hospitalization

Time from randomization to the first asthma exacerbation requiring hospitalization will be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization for patients who do not experience an asthma exacerbation requiring hospitalization during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.12 Time to first exacerbation requiring hospitalization or emergency department visit

Time from randomization to the first asthma exacerbation requiring hospitalization or ED visit will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization or ED visit−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization or ED visit for patients who do not experience an asthma exacerbation requiring hospitalization or ED visit during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.13 Number of days in hospital due to asthma

The total number of days in hospital due to asthma during the 28 weeks of treatment will be calculated for each patient.

8.4.14 Mean number days with oral corticosteroids taken for exacerbations

The total number of days with OCS taken for exacerbations during the 28 weeks of treatment will be calculated for each patient.

8.4.15 Blood eosinophil levels

The blood eosinophil level change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated. The level recorded at Visit 6 will be used as baseline.

The eosinophil progenitor change from baseline to each of the post-randomization visits (post Visit 6) at which it is measured up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables (subset of patients). The level recorded at Visit 6 will be used as baseline.

8.4.16 Calculation or derivation of patient reported outcome variables

8.4.16.1 Asthma symptom score

The outcome variable for asthma symptom score will be the change in mean asthma symptom scores from baseline to each of the post-randomization periods. Asthma symptom daytime scores, night time scores, and total scores will be calculated separately.

8.4.16.2 Asthma Control Questionnaire

The outcome variable for ACQ-6 will be the change in mean score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (EOT – baseline) ≤-0.5 → Improvement
- -0.5 < ACQ-6 (EOT – baseline) <0.5 → No change
- ACQ-6 (EOT – baseline) ≥0.5 → Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ-6 responder variable takes value 1 if change from baseline to EOT in ACQ-6 ≤-0.5 and 0 otherwise. Furthermore, patients will be categorized according to their ACQ-6 EOT score as follows (Juniper et al 2006):

- ACQ-6 (EOT) ≤0.75 → Well controlled
- 0.75< ACQ-6 (EOT) < 1.5 → Partly controlled
- ACQ-6 (EOT) ≥ 1.5 → not well controlled

8.4.16.3 Asthma Quality of Life Questionnaire for patients 12 years or older

The AQLQ(S)+12 score will be summarized by domain (4 domains) and for overall. The outcome variable for the AQLQ(S)+12 will be the change in score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits:

- AQLQ(S)+12 (EOT – baseline) ≥0.5 → Improvement
- -0.5 < AQLQ(S)+12 (EOT – baseline) <0.5 → No change
- AQLQ(S)+12 (EOT – baseline) ≤-0.5 → Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to EOT in AQLQ(S)+12 ≥0.5 and 0 otherwise.

8.4.16.4 Electronic diary variables

Asthma PROs (ACQ-6, AQLQ(S)+12), and daily metrics (rescue medication, awakenings, and peak flow and asthma symptom scores) derived from the Asthma Daily Diary will be summarized as the mean for baseline period and each of the post-randomization periods.

Baseline is defined as the last non-missing value before randomization for the asthma PROs and as the mean of the last 14 days before randomization for the daily metrics. Each post-randomization period is defined as the period between 2 consecutive scheduled visits (until the Week 28 Visit 14). The change from baseline to each post-randomization period will be used as secondary efficacy variables.

8.4.17 Lung function as assessed through body plethysmography

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. Variables include TLC, RV, VC, IC, and FRC.

8.4.18 Calculation or derivation of safety variables

8.4.18.1 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (Visit 6) to each post-treatment time point where scheduled assessments are made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

8.4.18.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant Adverse Events (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

8.4.19 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at (or under the guidance of) AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarized using descriptive statistics at each visit by treatment group. Due to the sparse sampling schedule and if data allows, population modeling will be performed to further characterize the PK of benralizumab. The potential influence of demographic covariates such as body weight, race, gender, and age will be explored. The impact of ADA on PK will also be assessed. The PK results will be provided in a clinical PK report (as an addendum to the CSR). The population modeling results will be presented in a separate pharmacometrics report.

8.4.20 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). Evaluations will be made at baseline (prior to benralizumab administration), and at routine time points during the treatment and follow up phases of the study or discontinuation. ADA titers by treatment group and visit will be summarized. **All ADA positive samples from the study will be tested for neutralizing antibodies (nAb) using a validated bioanalytical method.**

8.4.21 Exploratory variables

8.4.21.1 Sputum differential cell counts and biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. These variables include sputum cell differential counts, quantification of sputum cytokines and biomarkers, and assessment of eosinophil progenitor cells in sputum.

8.4.21.2 Serum biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline.

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 28-week treatment period, including follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence. To emphasize the importance of collecting complete primary and secondary outcome data in all patients, the ICF form will ask that patients continue study assessments for the whole 28-week double-blind treatment period, including follow-up, even if they discontinue study treatment prematurely.

8.5.1 Testing strategy to account for multiplicity considerations

To account for multiplicity in testing the primary endpoint, the percentage reduction from baseline in OCS dose for the 2 dosing regimens, a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Hochberg 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the 2 p-values is less than 0.05, then reject both null hypotheses. If the larger of the 2 p-values is greater than 0.05, then proceed to Step 2.

Step 2: If the smaller of the 2 p-values is less than 0.025, then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (ie, unadjusted).

8.5.2 Primary analysis method(s)

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose, while maintaining asthma control. Each benralizumab dose regimen will be compared with placebo.

For each of the 2 benralizumab dose regimens, a Wilcoxon rank-sum test will be performed. The median difference in the percentage reduction of OCS dose between each benralizumab dose regimen and placebo, along with the 95% CI and p-value will be presented. In addition, the median percentage reduction in OCS dose and the corresponding 95% CI within each treatment group will be presented.

The above analyses will also be performed for patients with baseline blood eosinophils ≥300/μL while the multiplicity will not be adjusted for these analyses.

The percentage reduction in OCS dose will be summarized by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL separately.

8.5.3 Secondary analysis methods

8.5.3.1 Analysis methods for secondary efficacy variables

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- Proportion of patients with ≥1 asthma exacerbation
- Annual rate of asthma exacerbations
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- Time to the first asthma exacerbation
- Time to the first asthma exacerbation requiring hospitalization
- Time to the first asthma exacerbation requiring hospitalization or ED visit
- Number of days in hospital due to asthma
- Number of days with OCS taken for exacerbations
- Change from baseline in pre-bronchodilator FEV_1
- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom scores (total, daytime and nighttimes)

- Change from baseline in rescue medication use
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- TLC, RV, VC, IC, FRC

The secondary efficacy endpoints will be summarized by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL.

For the following variables, the proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with 100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Annual rate of asthma exacerbations will be analysed using a negative binomial model. The number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented. This analysis will only be performed if there is a sufficient number of patients who have multiple exacerbations.

Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization will be analysed similarly as for annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analysed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region, and number of exacerbations in the year before the study.

Time to first asthma exacerbation requiring hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit will be analysed similarly as for time to first asthma exacerbation.

Change from baseline in pre-bronchodilator FEV_1 will be compared between each of the 2 benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-BDFEV_1 and at least 1 post-randomization pre-BD FEV_1. The dependent variable will be the change from baseline in pre-BD FEV_1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline pre-BD FEV_1 will be used as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in FEV_1=Treatment group+baseline pre-BD FEV_1+country/region+visit +treatment*visit.

The following variables will be analysed separately using a similar model as the above model for change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score and night time score, total rescue medication use, change from baseline in the number of nights with awakening due to asthma requiring rescue medication, change from baseline in morning and evening PEF, and change from baseline in ACQ-6 and AQLQ(s)+12.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analysed using a logistic regression model with factors of treatment, country/region, and the baseline value as a covariate.

8.5.4 Analysis method for blood eosinophil levels

Blood eosinophil levels will be summarized using standard summary statistics and plots at each visit by treatment group.

8.5.5 Analysis methods for exploratory variables

Exploratory endpoints in this study will be obtained from sputum collection and body plethysmography and include (subset of patients):

- sputum cell differential counts
- quantification of sputum cytokines and biomarkers
- assessment of eosinophil progenitor cells in sputum

Other exploratory endpoints will be obtained from blood and include:

- assessment of eosinophil progenitor cells (subset of patients)
- serum biomarkers

Raw values and change from baseline for the above indicated sputum, blood endpoints, and lung volume measurements will be summarized by treatment group and study visit. Measurements may also be plotted over time.

8.5.6 Analysis methods for safety variables

Adverse events (AEs) will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each patient and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA.

Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate.

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis. Changes in vital signs and ECGs will be examined at each visit and at endpoint. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

8.5.7 Subgroup analysis (if applicable)

Full details of subgroup analyses will be pre-specified in the SAP.

8.5.8 Interim analysis and Data Monitoring Committee (if applicable)

No interim analyses are planned.

8.5.9 Sensitivity analysis

Full details of the sensitivity analysis will be pre-specified in SAP.

8.6 Independent adjudication committee for major adverse cardiac events and malignancies

An independent adjudication committee will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths and 2) Investigator-reported malignancies during the Phase 3 trials. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information the committee requires to enable a thorough adjudication.

8.7 Data safety monitoring board

The Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB will function independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee will operate in accordance with a DSMB Charter.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study center personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and WBDC, IWRS/IVRS, ePROs, and other systems to be utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study center, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Please refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Recording of data

A Web-based Data Capture (WBDC) system will be used for data collection and query handling. Trained study center personnel will be responsible for entering data on the observations, tests, and assessments specified in the CSP into the WBDC system and according to eCRF instructions. The eCRF instructions will also guide the study center in performing data entry.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be source data verified, reviewed/queried and updated as needed. The data will be validated as defined in the Data Management Plan. The Investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

9.2.3 Study agreements

The Principal Investigator at each/the study center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last patient undergoing the study’.

The study is expected to start in Q2 2014 and to end by Q3 2016.

The study may be terminated at individual study centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca

may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

Database lock and unblinding for the CSR will occur after the last subject has completed the EOT or IPD visit. If, at this time, there are any patients who do not elect to continue in the separate extension study (D3250C00021), and have yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments are still to be conducted and the data will be listed separately in an addendum to the CSR.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Center staff according to the Data Management Plan.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on eCRF as specified in the CSP and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) / GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The

Investigator will ensure the distribution of these documents to the applicable EC and to the study center staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs, and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the ECs/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each study center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File and kept for a period that is complaint with GCP/local regulatory requirements, whichever is longer
- Ensure a copy of the signed ICF is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and, where required, in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a study center's ICF, AstraZeneca and the study center's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study center.

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AstraZeneca
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Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
Date	10 April 2015
Protocol Dated	10 January 2014

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All

The protocol for the study is to be amended as follows:

Section of Protocol affected:

Protocol Synopsis: Study centre(s) and number of patients planned

Previous text:

This study will be conducted worldwide in approximately **72** study centers. Target is to randomize approximately **120** patients.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2014	Phase 3
Estimated date of last patient completed	Q**1** 2016	

Revised text:

This study will be conducted worldwide in approximately **100** study centers. Target is to randomize approximately **210** patients.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2014	Phase 3
Estimated date of last patient completed	Q**3** 2016	

Reason for the Amendment:

The previous estimate for sample size was made based on limited data from the literature. As new information is now available, a decision was made to increase the sample size to better power the study for statistical significance. The number of study centers has been increased to accommodate the increased target enrolment numbers. The estimated date for LPLV has also been pushed out to allow time to recruit these additional patients.

Person who initiated Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Protocol Synopsis, Objectives, (b) Secondary Objectives and STUDY OBJECTIVES; (b) Secondary Objectives

Previous text:

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	– Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control – Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control – Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	– Proportion of patients with ≥1 asthma exacerbation after randomization – Time to the first asthma exacerbation after randomization – Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	– Change from baseline in pre-bronchodilator forced expiratory flow in 1 second (FEV_1) – **Change from baseline in pre-bronchodilator Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)**
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	– Change from baseline in asthma symptom score (total, daytime, and night time) – Change from baseline in rescue medication use – Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) – Change from baseline in the number of nights with awakening due to asthma requiring rescue medication – Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	– Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)

Objective	Endpoint [a]
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	– PK parameters – Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	– Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	– Total lung capacity (TLC) – Residual volume (RV) – Vital capacity (VC) – Inspiratory capacity (IC) – Functional residual capacity (FRC)

Revised text:

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	– Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control – **Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control** – Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control – Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	– Proportion of patients with ≥1 asthma exacerbation after randomization – **Annual rate of asthma exacerbations after randomization** – Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization – **Time to first asthma exacerbation after randomization** – **Time to first exacerbation requiring hospitalization** – **Time to first exacerbation requiring hospitalization or emergency department**

Objective	Endpoint [a]
	[ED] visit – **Number of days in hospital due to asthma** – **Mean number of days with oral corticosteroids taken for exacerbations**
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	– Change from baseline in pre-bronchodilator forced expiratory flow in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	– Change from baseline in asthma symptom score (total, daytime, and night time) – Change from baseline in rescue medication use – Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) – Change from baseline in the number of nights with awakening due to asthma requiring rescue medication – Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	– Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	– PK parameters – Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	– Total lung capacity (TLC) – Residual volume (RV) – Vital capacity (VC) – Inspiratory capacity (IC) – Functional residual capacity (FRC)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	– **Blood eosinophils**

Reason for Amendment:

Pulmonary function objectives (IC, ERV, IRV, VCIN, VCEX, and VCMAX) will be analyzed and reported in the CSR; therefore, they have been moved from exploratory to secondary objectives.

Additional secondary objectives have been added to aid in the analysis and understanding of the efficacy of the 2 different dosing regimens of benralizumab.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Protocol Synopsis, Objectives, (d) Exploratory Objectives and STUDY OBJECTIVES (d) Exploratory Objectives

Previous text:

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	– **Blood eosinophils**
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	– Assessment of eosinophil progenitor cells
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	– Sputum cell differential count – Quantification of sputum cytokines and biomarkers – Assessment of eosinophil progenitor cells
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	– Serum biomarkers
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	– **TLC/RV/VC/IC/FRC**

Revised text:

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	– Assessment of eosinophil progenitor cells
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	– Sputum cell differential count – Quantification of sputum cytokines and biomarkers – Assessment of eosinophil progenitor cells **in sputum**

To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	– Serum biomarkers

Reason for Amendment:

Clarifying language added around assessment of eosinophil progenitor cells. Objectives for effect of benralizumab on blood eosinophil levels and lung function (body plethysmography) moved from exploratory objectives to secondary objectives. These parameters will be analyzed and reported in the CSR; therefore, they have been moved from exploratory to secondary objectives.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Protocol Synopsis, Study design

Previous text:

The study will recruit approximately **120** patients (randomized 1:1:1), stratified by country/region.

Revised text:

The study will recruit approximately **210** patients (randomized 1:1:1) stratified by **eosinophil level (≥150 to <300 vs ≥300 cells/µL) and** country/region. **Approximately 60 patients will be randomized into the lower eosinophil stratum (≥150 to <300/µL). Approximately 150 patients will randomize into the higher eosinophil stratum (≥300 cells/µL).**

Reason for Amendment:

Number for target enrolment increased to better power the study for statistical significance. Eosinophil count inclusion cutpoint lowered to 150 cells/µL to enhance enrolment because oral corticosteroids suppress blood eosinophils and 64% of screen failures were due to the eosinophil cutoff of ≥300 cells/µL. Stratification by eosinophil level added to assess the response to benralizumab in patients with ≥300 cells/µL since this is the targeted patient population in the pivotal studies. To ensure proper study powering, (enough subjects with eosinophils ≥300 cells/µL), stratification will be implemented as described above.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Protocol Synopsis, Study design and Duration of treatment; CSP 1.5: Overall study design

Previous text:

Maintenance (after Week 24 till Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate long-term safety extension study; **all patients who complete Week 28 (Visit 14) in the current study will be eligible to enrol in the safety extension study.**

Revised text:

Maintenance (after Week 24 until Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; **patients who remain on investigational product (IP) for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36)**.

Reason for Amendment:

To clarify that the patient must complete the predecessor study on investigational product and the patient must be evaluated for eligibility in the extension study prior to enrolment.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Protocol Synopsis, Duration of treatment

Previous text:

The total planned study duration is 46 weeks.

Revised text:

The total planned study duration is **up to** 46 weeks.

Reason for Amendment:

To clarify that the study duration is **up to** 46 weeks as some subjects may be optimized prior study entry and/or will not enter follow up

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected

Protocol Synopsis: Statistical Methods

Previous text

The primary efficacy variable is the percentage change in OCS dose from the patient's dose at baseline to the patient's final dose at Visit 14. The percentage change in OCS in each of the two benralizumab dose regimen groups will be compared to the percentage reduction in OCS in the placebo group using an analysis of covariance (ANCOVA) model. The response variable in the model is the percentage reduction in OCS dose from baseline to the final dose at Visit 14. The model will include covariates of treatment group, country/region, and baseline OCS dose.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization pre-dose/pre-bronchodilator FEV_1. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline pre-bronchodilator FEV1 will be used as covariates. Visit will be used as a categorical variable. The following variables will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score and total rescue medication use, change from baseline in post-bronchodilator FEV_1, change from baseline in morning and evening PEF and the change from baseline in ACQ-6 and AQLQ(s)+12.

For categorical or binary variables, the proportion in each of the two benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region.

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The number of nights with awakening due to asthma and requiring rescue medication will be analyzed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country/region and baseline value will be fit as covariates.

Multiplicity will be adjusted for the primary endpoint using Hochberg procedure (Hochberg 1988).

For sample size estimation, a Type I error rate of 5% and 90% power, were used. For the primary endpoint of percentage change in OCS dose, targeting a difference of 60% between

groups and assuming an estimate of 70%, the sample size required is 35 patients per treatment group.

Revised text

The primary efficacy variable is the percentage change in OCS dose from the patient's dose at baseline to the patient's final dose at Visit 14, **while maintaining asthma control**. The percentage change in OCS in each of the 2 benralizumab dose regimen groups will be compared with the percentage reduction in OCS in the placebo group using a **Wilcoxon rank sum test.** Multiplicity will **be adjusted using Hochberg procedure** (Hochberg 1988).

For the following variables, the proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: **the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with 100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.**

Annual exacerbation rates will be analyzed using a negative binomial model with a log-link function. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. Annual exacerbation rates that are associated with an emergency room visit or a hospitalization will be analyzed similarly to annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analyzed using a Cox proportional hazard model with the covariates of treatment, country/region and number of exacerbations in the year before the study. **Time to first asthma exacerbation requiring hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit will be analyzed similarly to time to first asthma exacerbation.**

Change from baseline in pre-bronchodilator (pre-BD) FEV_1 will be analyzed using a repeated measures analysis model which will include treatment group country/region and baseline pre-BD FEV_1 as covariates. Visit will be fitted as a categorical variable. The following variables will be analyzed similarly to change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score, total rescue medication use, change from baseline in number of nights awakening due to asthma requiring rescue medication use, change from baseline in morning and evening PEF, and the change from baseline in ACQ-6 and AQLQ(s)+12.

The study will recruit a total of 210 patients with blood eosinophils ≥150 to <300 and ≥300/µL. As the targeted patient population for the pivotal studies is ≥300

eosinophils/µL, this study will be stratified by ≥300 and ≥150 to <300 cells/µL. The eosinophil ≥150 to <300/µL stratum will randomize approximately 60 patients and the ≥300 cells/µL stratum will randomize approximately 150 patients. For sample size estimation, 70 patients per treatment arm are required to detect a difference in percent reduction of OCS dose each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014), which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

Results for exploratory variables will be summarized using descriptive statistics by treatment group.

All safety parameters will be analyzed descriptively. Safety analyses will be based on the **safety analysis set, defined as all patients who received at least 1 dose of IP.**

Reason for Amendment

The previous power calculation is based on a t-test assuming the data are normally distributed. However, according to the OCS sparing study data for mepolizumab (Bel et al 2014), the data are not normally distributed. The new power calculation is based on simulations using the Wilcoxon rank sum test. Therefore, the primary analysis for the primary endpoint will be conducted using the Wilcoxon rank sum test.

Person who initiated the Amendment

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

LIST OF APPENDICES

Additional text:

Appendix H OCS Dose Therapy Equivalence Table

Reason for Amendment:

Appendix H added

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.2 Rationale for conducting this study

Previous text:

The purpose of this trial is to confirm if benralizumab can reduce OCS dependence (after dose optimisation) in patients who are uncontrolled on high-dose ICS-LABA, and chronically dependent on OCS as part of their regular asthma controller regimen. In addition, this trial will further confirm the safety and clinical benefit of benralizumab administration.

Revised text:

The purpose of this trial is to confirm if benralizumab can reduce **the use of maintenance** OCS **in systemic corticosteroid dependent patients with severe refractory asthma with elevated eosinophils**.

In addition, this trial will further confirm the safety and clinical benefit of benralizumab **compared with placebo on markers of asthma impairment and risk including exacerbation rate, pulmonary function, asthma symptoms, and asthma-related quality of life.**

Reason for Amendment:

To clarify the purpose of the trial

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.3 Rationale for study design, doses, and control group

Previous text:

This is a global study designed to investigate the safety and efficacy of 2 dosing regimens of benralizumab (at a 30 mg fixed dose) administered subcutaneously (SC) in asthma patients who remain uncontrolled on chronic OCS and high-dose ICS-LABA therapy, with or without additional asthma controller(s). Patients on the first regimen will be dosed every 4 weeks throughout the treatment period, while patients on the second regimen will be dosed every 4 weeks for the first 3 doses and then every 8 weeks thereafter. Primary efficacy will be determined based on the percentage reduction in OCS dose over 24 weeks of benralizumab treatment versus placebo, following OCS dose optimization. **In order to avoid biasing the results, the study will be randomized and double-blinded, with stratification by country/region.**

The study will recruit patients with blood eosinophils ≥300/µL.

Revised text:

This is a global study designed to investigate the safety and efficacy of 2 dosing regimens of benralizumab (at a 30 mg fixed dose) administered subcutaneously (SC) in asthma patients who remain uncontrolled on chronic OCS and high-dose ICS-LABA therapy, with or without additional asthma controller(s). Patients on the first regimen will be dosed every 4 weeks (Q4W) throughout the treatment period, while patients on the second regimen will be dosed every 4 weeks for the first 3 doses and then every 8 weeks (Q8W) thereafter. Primary efficacy will be determined based on the percentage reduction in OCS dose over 24 weeks of benralizumab treatment versus placebo, following OCS dose optimization.

The study will recruit approximately 210 patients with blood eosinophils ≥150/µL. It is well established that corticosteroid administration can dramatically suppress blood eosinophil counts (Schleimer and Bochner 1994, Barnes 1998, Barnes and Adcock 2003), and some level of efficacy was seen in patients with peripheral blood eosinophil counts <300/µL from the 100 mg treatment arm Phase 2b study MI-CP220 (see Section 1.4); thus, the target population in this study will be patients with blood eosinophils ≥150/µL. In order to avoid biasing the results, the study will be randomized and double-blinded, with additional stratification by country/region.

All patients are required to be treated with oral corticosteroids for at least 6 months prior to Visit 1 and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization.

Reason for Amendment:

To explain the rationale behind lowering the eosinophil cutpoint to ≥150/µL and clarify the requirements for OCS therapy prior to randomization

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.4 Benefit/risk and ethical assessment

Previous text:

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA, benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/µL.

Revised text:

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA, benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of

asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/μL; **however, some level of efficacy(a 16% reduction in annual rate of asthma exacerbations) was seen in patients with peripheral blood eosinophil counts <300/μL from the 100 mg treatment arm of Study CP220 and should support a positive benefit/risk balance in this population. Furthermore, Bel et al saw a significant reduction in oral glucocorticoid dose with mepolizumab treatment in patients with blood eosinophil counts of 150/μL and above (Bel et al 2014).**

Reason for Amendment:

To provide the rationale for lowering the eosinophil cutoff to 150/μL

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.5 Overall study design

Previous text:

The study will recruit approximately 120 patients (randomized 1:1:1), and stratified by country/region.

Revised text:

The study will recruit approximately **210** patients (randomized 1:1:1) **with eosinophils ≥150 cells/μL, stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL)** and country/region.

Reason for Amendment:

The previous estimate for sample size was made based on limited data from the literature. As new information is now available, a decision was made to increase the sample size to better power the study for statistical significance. Eosinophil count inclusion cutpoint lowered to 150 cells/μL to enhance enrolment because oral corticosteroids suppress blood eosinophils and 64% of screen failures were due to the eosinophil cutoff of ≥300 cells/μL. Stratification by eosinophil level added to assess the response to benralizumab in patients with ≥300 cells/μL since this is the targeted patient population in the pivotal studies. To ensure proper study powering, (enough subjects with eosinophils ≥300 cells/μL), stratification will be implemented as described above.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.5 Overall study design

Previous text:

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control. Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit at Week 28.

Revised text:

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control. **If the patient meets all of the criteria listed for OCS titration in Section 5.1.1.1, his/her asthma will be considered stable and the patient will be eligible for further OCS dose reduction. All patients must be on either oral prednisone or prednisolone as their OCS. Patients who are on any other oral corticosteroid must switch over to an equivalent dose of either oral prednisone or prednisolone at Visit 1.** Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit at Week 28.

Reason for Amendment:

Clarifying language added around OCS therapy requirements prior to randomization.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

1.5 Overall study design; Figure 1 Study flow chart

Text added:

*Patients entering the extension study (D3250C00021) will receive their first dose of benralizumab at Visit 1 in that study, which must occur on the same day as Visit 14 (EOT) for this study (D3250C00020).

**Only those patients not entering the extension study will complete this Follow-up visit.

Reason for Amendment:

Footnotes added to study flow chart to clarify:

*V14 (EOT): Patients rolling over into Study 21 will receive their first dose of study drug for Study 21 at the EOT visit for Study 20.

**V15 (FU): Only those patients not rolling over into Study 21 will attend this visit.

Persons who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

6. Peripheral blood eosinophil count of ≥300 cells/μL assessed by local lab at visit 1.

Revised text:

6. Peripheral blood eosinophil count of ≥**150** cells/μL assessed by local lab at Visit 1**.**

Reason for Amendment:

Eosinophil cutoff for inclusion has been lowered to ≥**150** cells/μL.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

8. The ICS high-dose criterion can also be considered to be met by the highest locally approved maintenance dose for patients whose ICS-LABA dose, however maximal by local labelling, does not reach the GINA ICS high-dose level

Revised text:

8. **For ICS/LABA combination preparations,** the highest approved maintenance dose **in the local country will meet this ICS criterion**

Reason for Amendment:

To simplify the language around approved doses of ICS/LABA combinations meeting inclusion criterion 8

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

9. Chronic oral prednisone or prednisolone for at least 6 continuous months directly preceding Visit 1, and on a stable dose for at least one month prior to Visit 1.

Revised text:

9. Chronic oral **corticosteroid** therapy for at least 6 continuous months directly preceding Visit 1. **Subjects must be on doses equivalent to 7.5 – 40 mg/day of prednisolone/prednisone at Visit 1 and be** on a stable dose for at least **2 weeks** prior to **randomization. In order to aid the dose assessment, a guide for OCS dose equivalence is presented in Appendix H. Patients must agree to switch to study-required prednisone/prednisolone as their oral corticosteroid for the duration of the study.**

Reason for Amendment:

To clarify the OCS dose requirements for inclusion in the study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

11. Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline), that have been stable for at least 30 days prior to Visit 1 randomisation, are allowed. Five- lipoxygenase inhibitors (eg, Zileuton) are prohibited

Revised text:

11. Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline) are allowed. Five- lipoxygenase inhibitors (eg, zileuton) **and roflumilast** are prohibited

Reason for Amendment:

To simplify the language around additional maintenance asthma controller medications

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria

Previous text:

13. Either documented post bronchodilator (post-BD) reversibility of ≥ 12% and ≥ 200 mL in FEV_1 or PC_{20} FEV1 methacholine concentration ≤ 8mg/mL within 60 months prior to planned date of randomization

Revised text:

13. Evidence of asthma as documented by either:

- **Airway reversibility** (FEV_1 ≥12% and 200 mL) **demonstrated at Visit 1, Visit 2, or Visit 3 using the Maximum Post-bronchodilator Procedure OR**
- **Documented reversibility in the previous 24 months prior to Visit 1 OR**
- **Airway hyperresponsiveness** (PC_{20} FEV_1 methacholine concentration ≤8mg/mL) **documented in the previous 12 months prior to planned date of randomization OR**
- **Airflow variability in clinic FEV1 ≥20% between 2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV_1 recorded during an exacerbation should not be considered for this criterion).**

Note: **All patients must have reversibility testing performed before randomization to establish a baseline characteristic.**

If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomisation, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

Reason for Amendment:

To further define and clarify the requirements around evidence of asthma for inclusion in the study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria at randomization

Previous text:

17. Additional asthma controller medication must not have been initiated during run-in period/optimization period

Revised text:

17. Additional asthma controller medication must not have been initiated during **run-in/optimization period (not applicable for management of exacerbations during screening/run-in optimization phase)**

Reason for Amendment:

To clarify restrictions on initiation of additional asthma controller medications during the run-in/optimization phase of the study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.1 Inclusion criteria at randomization

Previous text:

21. No documented asthma exacerbations during the screening/dose optimization period

Deleted text:

Removing criterion #21

Reason for Amendment:

To help with patient retention and to adjust inclusion criterion to target population as it is expected that in such a severe population patients may exacerbate during OCS optimization

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

13. History of cancer:

- Patients who have had basal cell carcinoma, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained

Revised text:

13. History of cancer:

Patients who have had basal cell carcinoma, **localized squamous cell carcinoma of the skin**, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained

Reason for Amendment:

To align the wording of this exclusion criterion with that of the pivotal studies, CALIMA and SIROCCO

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids, or an increase in maintenance dose of OCS **30 days** prior to the date of informed consent.

Revised text:

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids, or an increase in maintenance dose of OCS **2 weeks** prior to the date of informed consent.

Reason for Amendment:

To clarify wording for exclusion criterion and to define minimal timeframe between use of systemic corticosteroids or OCS maintenance dose increase during exacerbation and study inclusion/informed consent signature

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

19. Receipt of oral dexamethasone as the maintenance oral steroid controller for asthma symptoms

Revised text:

19. Receipt of oral corticosteroids **other than prednisone or prednisolone** as the **maintenance** oral steroid controller for asthma symptoms **from Visit 1 and throughout the study**

Reason for Amendment:

Patients on oral corticosteroids other than prednisone or prednisolone will be allowed into the trial but have to switch to prednisone or prednisolone at Visit 1.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

22. Receipt of live attenuated vaccines 30 days prior to **the date of randomization**

Revised text:

22. Receipt of live attenuated vaccines 30 days prior to **Visit 1**

Reason for Amendment:

To bring in line with Appendix G

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

25. Change to allergen immunotherapy or new allergen immunotherapy within 30 days prior to the date of informed consent and anticipated changes in immunotherapy throughout the study

Revised text:

25. **Initiation of new** allergen immunotherapy **is not allowed** within 30 days prior to **Visit 1. Immunotherapy initiated prior to this period, or as a routine part of the patient's seasonal treatment, is allowed. If the immunotherapy is delivered as an injection, there should be a gap of 7 days between the immunotherapy and IP administration**

Reason for Amendment:

To clarify wording related to immunotherapy initiation prior to informed consent signature and immunotherapy continuation during study participation to adjust exclusion criterion to target population, as it is expected that in such a severe population, patients may receive seasonal immunotherapy treatment

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Previous text:

26. Current use of any oral or ophthalmic β-adrenergic antagonist (eg, propranolol)

Revised text:

26. Current use of any oral or ophthalmic **non-selective** β-adrenergic antagonist (eg, propranolol)

Reason for Amendment:

To clarify wording related to restrictions on use of β-adrenergic antagonists

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.2 Exclusion criteria

Additional text:

33. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) confirmed during screening period

Reason for Amendment:

Additional exclusion criteria added to further clarify that ALT or AST ≥2.5 times the upper limit of normal constitutes a significant abnormal finding that could potentially influence the findings of the study or its interpretation

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.3 Patient enrolment and randomization

Previous text:

Patients will be allocated to 1 of 3 treatment arms in a 1:1:1 ratio. The randomization will be stratified by country/region and the randomization numbers will be grouped in blocks.

Revised text:

Patients will be allocated to 1 of 3 treatment arms in a 1:1:1 ratio. The randomization will be stratified by **eosinophil level (≥150 to <300 vs ≥300 cells/μL) and** country/region and the randomization numbers will be grouped in blocks.

Reason for Amendment:

To add the additional stratification by eosinophil level as the eosinophil cutpoint had been reduced to ≥150 cells/μL

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.3 Patient enrolment and randomization

Previous text:

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from IP administration will not be replaced.

Revised text:

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from IP administration will not be replaced. **When a stratum is full, patients who fall within that stratum will not be randomized and will be screen failed from the study (see Section 3.7.2).**

Reason for Amendment:

To add the procedure for when a stratum is full since patients will now be stratified by eosinophil count

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.1.1 Background medication; Oral corticosteroids

Previous text:

For eligibility purposes all patients are required to be treated with prednisone or prednisolone for at least 6 months prior to Visit 1 and be on the stable maintenance dose for at least **1 month** prior to **visit 1**.

Revised text:

For eligibility purposes all patients are required to be treated with **oral corticosteroids** for at least 6 months prior to Visit 1 and be on the stable maintenance dose of **prednisone or**

prednisolone for at least **2 weeks** prior to randomization. **In order to aid the dose assessment, a guide for OCS dose equivalents is presented in Appendix H.**

Reason for Amendment:

To clarify the background OCS requirements

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.1 Asthma medication restrictions; (d) Maintenance of asthma controller medications

Previous text:

The patient's usual pre-study ICS-LABA formulation, dose and regimen, and any other additional allowed asthma controllers that they may have been taking prior to enrolment, should be continued unchanged throughout the run-in and treatment period. Please refer to Section 3.1, inclusion criterion 11 for examples of allowed additional controller therapies for this study.

Revised text:

The patient's usual pre-study ICS/LABA formulation, dose and regimen, and any other additional allowed asthma controllers that they may have been taking prior to enrolment **aside from oral corticosteroids**, should be continued unchanged throughout the run-in and treatment period. Please refer to Section 3.1, inclusion criterion 11 for examples of allowed additional controller therapies for this study.

Reason for Amendment:

To clarify all asthma controller medications, except oral corticosteroids are to be maintained unchanged throughout the run-in and treatment periods

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.1 Asthma medication restrictions; (e) Asthma medication restriction on the days of the scheduled spirometry visit

Previous text:

Visit 2-5: Patients will be asked to withhold their usual bronchodilator medications on the morning of scheduled spirometry measurements. ICS-LABA medications should be withheld for 12 hours. In addition, SABA should not be used within 6 hours of these spirometry assessments. The patient's usual asthma medications may be administered following completion of the screening lung function procedures.

Treatment Visits 6-14: Patients will be asked to withhold their usual ICS-LABA medications on the mornings of scheduled spirometry visits for at least 12 hours prior to the spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in Section 5.1.3.

If the patient has taken their usual ICS-LABA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day, within the allowed window. If rescheduling is absolutely not feasible for the patient, spirometry may be performed with a notation indicating that pre-BD spirometry was performed after usual ICS-LABA was administered.

If the patient has taken rescue SABA within 6 hours of the planned spirometry assessment, they should ideally 1) remain at the centre until such time that the 6-hour withholding time has been reached if it does not exceed the 1.5-hour spirometry window or 2) return on another day, within the visit window. If neither of options is feasible for the patient, spirometry may be performed with a notation indicating that the pre-BD spirometry was conducted within 6 hours of SABA use.

Revised text:

Visits 2-14: Patients will be asked to withhold their usual ICS/LABA medications on the mornings of scheduled spirometry visits. Twice daily ICS and LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments.

For Visits 2-5, the patient's usual asthma medications may be administered following completion of the screening lung function procedures. For Visits 6-14, the patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma

controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in Section5.1.3.

If the patient has taken their usual ICS/LABA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day, within the allowed window.

If the patient has taken rescue SABA within 6 hours of the planned spirometry assessment, they should ideally either

- **remain at the center until such time that the 6-hour withholding time has been reached if it does not exceed the 1.5-hour spirometry window or**
- **return on another day, within the visit window.**

Reason for Amendment:

To simplify the language and clarify the timing around withholding bronchodilator medications prior to spirometry testing

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.1 Asthma medication restrictions; (f) Asthma medication restrictions prior to home lung function testing

Previous text:

(f) Asthma medication restrictions prior to home lung function testing

Patients should avoid taking their morning asthma controllers prior to the morning home lung function testing and should conduct the evening home lung function testing before taking evening asthma controllers. When possible, home lung function testing should be performed at least 6 hours after the last dose of SABA rescue medication.

Revised text:

(f) Asthma medication restrictions prior to home **peak expiratory flow** testing

Patients should avoid taking their morning asthma controllers prior to the morning home **peak expiratory flow (PEF)** testing and should conduct the evening home **PEF** testing before taking evening asthma controllers. When possible, home **PEF** testing should be performed at least 6 hours after the last dose of SABA rescue medication.

Reason for Amendment:

To clarify that home lung function testing is peak expiratory flow

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.2 Other medication restrictions

Previous text

(a) Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines is not allowed. Please see Section 3.2 exclusion criteria 14 and 22 for examples and further details.

Revised text:

(a) Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines is not allowed. **Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca study physician.** Please see Section 3.2 exclusion criteria 14 and 22 for examples and further details.

Reason for Amendment:

To clarify the use of topical immunosuppressive medication

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.2 Other medication restrictions

Added text

(d) When enrolling a patient who is on theophylline, digoxin or other drugs with a narrow therapeutic range, the Investigator should ensure the levels of each of these medications must not exceed the upper limit of therapeutic range. The Investigator will also be responsible for ensuring that these levels are regularly checked, assessed and documented as per local practice (see Table 1).

Reason for Amendment:

Establishing levels of drugs with a narrow therapeutic range will ensure that patients are monitored and maintained on an optimum regimen.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.5.2.2 Other medication restrictions

Previous text

(e) Patients should not take any other excluded medications:

- Five-lipoxygenase inhibitors (eg, Zileuton)
- Oral or ophthalmic β-adrenergic antagonist (eg, propranolol)

Revised text:

(e) Patients should not take any other excluded medications:

- Five-lipoxygenase inhibitors (eg, zileuton)
- **roflumilast**
- Oral or ophthalmic **non-selective** β-adrenergic antagonist (eg, propranolol)

Reason for Amendment:

Roflumilast added to list to bring in line with exclusion criterion 11 and to clarify wording related to restrictions on use of β-adrenergic antagonists

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.6 Discontinuation from investigational product

Previous text:

1. Development of any study specific criteria for discontinuation:

(a) Anaphylactic reaction to the IP requiring administration of epinephrine

(b) Development of helminth parasitic infestations requiring hospitalization

(c) If 2 consecutive doses of IP missed or more than 2 scheduled doses of IP are missed during course of the study

(d) **Intensive care unit admission for** asthma-related event

Revised text:

8. Development of any study specific criteria for discontinuation:

(a) Anaphylactic reaction to the IP requiring administration of epinephrine

(b) Development of helminth parasitic infestations requiring hospitalization

(c) If 2 consecutive doses of IP are missed or more than 2 scheduled doses of IP are missed during course of the study,

(d) **An asthma-related event requiring mechanical ventilation**.

Reason for Amendment:

To clarify parameters for discontinuation due to an asthma-related event

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.6 Discontinuation from investigational product

Previous text:

When feasible, compliant patients who are discontinued from the IP should be encouraged to continue to undergo all study related visits/procedures for the full 28-week double-blind treatment period, including follow-up, in order to support the final efficacy and safety analyses for benralizumab. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

Patients who prematurely discontinued IP and are not willing to continue participation in the study should return to the study centre and complete procedures described for the EOT (4±1 weeks after last dose of IP) and Follow up visit 12±1 weeks after last dose of IP).

Revised text:

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7days) after last IP administration. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

Reason for Amendment:

Sections have been amended to describe the process for collection of data for patients who prematurely discontinued IP

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.7.2 **Withdrawal due to recruitment completion in a randomization stratum** (section added)

Added text:

When a specific stratum is full, patients in completed stratum will not be randomized and will be withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF as a development of study specific criteria for discontinuation. As with screen failures, no further study related follow-up of these patients is required.

Strata closure process:

1. **The eosinophil ≥150 to <300/µL stratum will be closed to patients when the total number of adult patients in the stratum reaches approximately 60**

2. **The eosinophil ≥300/µL stratum will be closed to patients when the total number of patients in the stratum reaches approximately 150**

The whole study will be closed for recruitment when the total number of patients reaches approximately 210.

Reason for Amendment:

To clarify that the patient will be not be randomized into the study if his/her eosinophil stratum if full.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.7.**3** Withdrawal of the informed consent

Previous text:

If patient agrees, he/she will be asked to return to the study center and complete procedures described for the EOT (4±1 weeks after last dose of IP) and Follow-up visit (12±1 weeks after last dose of IP).

Revised text:

If patient agrees, he/she will be asked to return to the study center and complete procedures described for the **IPD within 4 weeks (+7 days) after last dose of IP and Follow-up visit 12 weeks ±3 days after last dose of IP for final study-related assessments**.

Reason for Amendment:

To clarify that the patient will be asked to follow the procedures for the premature discontinuation of IP visit if he/she withdraws consent.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

3.8 Withdrawal of informed consent for donated biological samples

Previous text:

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Revised text:

As **use** of the biological samples is an integral part of the study, **withdrawal of informed consent for the use of donated samples by** the patient **will result in the patient being** withdrawn from further study participation.

Reason for Amendment:

To clarify that the patient will be withdrawn from further study participation if he/she withdraws consent for use of donated biological samples.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4. Study Plan and Procedures; Table 1

Revised text:

Sputum collection removed from table.

Blood concentration for theophylline and digoxin added at Visit 1.

ACQ-6 completion on site added to table for Visit 1.

AQLQ(S)+12 completion on site added to table for Visit 1.

Screening pre-BD spirometry added at Visit 1

Screening post-BD spirometry added at Visits 1 and 3

Footnote b added: If and when appropriate prior to randomization; for patients who are on theophylline or digoxin, (see Section 3.5.2.2 [d])

Footnote d deleted and subsequent footnotes promoted.

Footnote e (now d) added: If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomisation, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

Footnote f (now e) revised: The screening post-BD FEV_1 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in Section 3.1. The post-BD FEV_1**; however, still needs to be completed as a baseline characteristic and** should be performed using the guidance in Section 5.1.3.

Reason for Amendment:

Sputum collection removed as this will be done in only a subset of patients.

Blood concentration for theophylline and digoxin to be assessed at Visit 1 (prior to randomization is recommended) for patients who are on these drugs.

ACQ-6 and AQLQ(S)+12 completion on site added to clarify that these assessments will be done on site at Visit 1 but only adherence-checked at subsequent visits.

Screening pre- and post-BD spirometry updated to reflect that these assessments will be done, as necessary, at Visits 1, 2, and 3 to qualify the patient for randomization.

Footnote d added and footnote e revised to add clarity to the spirometry requirements for randomization and baseline assessments.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4. Study Plan and Procedures; Table 2

Revised text:

Visit windows for V14 and IPD visit revised to +7 (days)

Weight removed from table.

Blood for flow cytometry removed from table.

IPD (IP discontinuation) visit and assessments added.

Footnote d revised: The assessment is applicable for designated sites only. **Post-BD spirometry as part of sputum induction procedure must be performed on site-owned devices.**

Footnote g removed: Slow spirometry included in the pre-BD assessment.

Footnote h revised: If unscheduled visit caused by exacerbation or infection (if applicable). Up titration only

Reason for Amendment:

To clarify that V14 and the IPD visit should not be earlier than the scheduled time point.

Weight removed as no significant changes expected between Visit 1 and Visit 6.

Blood for flow cytometry removed as this will be done in only a subset of patients.

IPD visit and assessments added to describe process for data collection for patients prematurely discontinued IP

Footnoted revised to clarify requirements for post-BD spirometry part of sputum induction procedure which will be performed in a subset of sites.

Footnote d removed as slow spirometry removed from the list of study assessments.

Footnote h revised to add clarity to OCS titration during unscheduled visit

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.1 Enrolment (Visit 1)

Previous text:

Examples of acceptable documentation of the asthma disease state and prior asthma exacerbations include clinic visit (primary or specialist HCP), emergency room or hospital records listing asthma as a current problem, plus documentation of at least 1 asthma exacerbations during the 12 months prior to ICF:

Revised text:

Examples of acceptable documentation of **physician-diagnosed** asthma and prior asthma exacerbations **can** include clinic visit (primary or specialist **healthcare provider** [HCP]), emergency room or hospital records listing asthma as a current problem, plus documentation of at least 1 asthma exacerbation during the 12 months prior to **signing the** ICF.

Reason for Amendment:

To clarify that documentation of asthma must be of **physician-diagnosed** asthma

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.1 Enrolment (Visit 1)

Previous text:

Current, regular use of a high-dose ICS and LABA for at least 6 months prior to enrolment and OCS use for at least 6 continuous months prior to enrolment must be documented in the source. ICS and LABA may have been administered as either as fixed dose or 2 separate

inhalers, and consistent with dose limits set by inclusion criterion 8. Stable dose of OCS must have been maintained for at least **1 month** prior to **visit 1**. This documentation may be in the form of a recent, active medication list as per an HCP note, or filled prescriptions based on a pharmacy record.

Revised text:

Current, regular use of a high-dose ICS and LABA for at least 6 months prior to enrolment and OCS use for at least 6 continuous months prior to enrolment must be documented in the source. Inhaled corticosteroid and LABA may have been administered as either as fixed dose or 2 separate inhalers, and consistent with dose limits set by inclusion criterion 8. This documentation may be in the form of a recent, active medication list as per an HCP note, or filled prescriptions based on a pharmacy record.

Reason for Amendment:

To remove the requirement for the patient to be on a stable dose of OCS for at least 1 month prior to Visit 1. This has been updated to a stable dose for at least 2 weeks prior to randomization (inclusion criterion 10).

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.1 Enrolment (Visit 1)

Previous text:

After confirmation of initial entry criteria the patient will be supplied with an electronic hand-held spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.3.2 for further details).

Revised text:

After confirmation of initial entry criteria the patient will be supplied with an electronic hand-held spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.3.2 for further details). **ACQ-6 and AQLQ(S)+12 should be completed during this visit.**

Reason for Amendment:

To clarify that the first recording of ACQ-6 and AQLQ(S)+12 should be completed on site during Visit 1.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.1 Enrolment (Visit 1)

Previous text:

Patients will continue on their current ICS-LABA and other controller(s) (if applicable) treatment with no changes.

Revised text:

Patients will continue on their current ICS/LABA and other controller(s) (if applicable) treatment with no changes. **All patients must be on either prednisone or prednisolone as their OCS at Visit 1. If patients are on any other oral corticosteroids, they must agree to switch to an equivalent dose of the study-required prednisone/ prednisolone as their OCS for the duration of the study. Please refer to Appendix H for the OCS dose-equivalence guide.**

Reason for Amendment:

To clarify that all patients must be on or switched to either prednisone or prednisolone as their OCS at this visit.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.2 Run-in/oral corticosteroid optimization phase (Visit 2 to Visit 5)

Previous text:

The run-in/OCS optimization phase will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0). The patient should remain on their current ICS-LABA treatment with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

During the OCS optimization phase, a patient's OCS dose will be titrated (see Section 5.1.1.1) to ensure the patient is taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration will be initiated at Visit 2. Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture

period is not yet complete. The decision to initiate OCS dose reduction at Visit 2 is under the discretion of the investigator and can include consideration of Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months. Patients who do not have historic evidence of dose optimization and who are judged not to be candidates for OCS dose reduction, based upon asthma symptoms or other clinical reasons in the opinion of the investigator, should be screen-failed.

From Visit 3 onwards, the dose of OCS may be reduced only if criteria listed in Section 5.1.1.1 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). The optimized dose of OCS is defined as a lowest dose of OCS at which patient meets criteria listed in section 5.1.1.1. In cases when the patient is optimized on their OCS dose prior to Visit 5 (Week-2), he/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized. The optimized dose reached during the OCS optimization phase becomes the patient's baseline OCS dose for analysis purposes.

If a patient does not meet down titration criteria, the OCS dose should be returned to the previous effective dose (i.e., the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until randomization (Visit 6).

If the patient experiences an asthma exacerbation requiring evaluation in an Urgent Care Centre, in Emergency Department (ED), Hospitalization, or temporary increase (bolus/burst) of systemic steroids, they will be screen failed.

If a patient reaches asthma control at an OCS dose of ≤5mg during this phase, the patient will be a screen failure and will not be randomized. If the patient does not reach optimized dose of the OCS by the end of the run-in/optimization phase the patient should be screen failed and cannot be randomized. An asthma exacerbation during dose optimization will result in screen-failure with possibility of re-screening.

The screening post-BD FEV_1 performed at Visit 2 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in Section 5.1.1.1. The post-BD FEV_1 should be performed using the guidance in section 5.1.3.1

Patient's eligibility should be evaluated at each visit during the run-in/OCS optimization phase with the relevant documentation entered in the source and eCRF.

Patients whose compliance with the electronic diary is <70% will be given the option, one time during screening, to reschedule a study visit (with the exception of Visit 6) within 72 hours. Compliance <70% on more than one visit during screening will result in screen failure.

Revised text:

Pulmonary function tests and assessment of reversibility (maximum post-BD value of lung function) may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 and this is needed to qualify the patient for randomisation (see Section 5.1.3.1).

The run-in/OCS optimization phase will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0). The patient should remain on their current ICS/LABA treatment with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

Patients with documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criterion 10) will not be required to proceed through the OCS optimisation phase during the run-in period. For these patients, Visit 2 must be combined with Visit 5. The patient must be maintained on the same OCS dose until randomisation at Visit 6. In such cases, all assessments listed in Table 1 for Visit 2 should be conducted at this visit. All eligibility criteria must be met prior to randomization at Visit 6.

Patients who do not have documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criteria 10), will enter the OCS optimisation phase. Their OCS dose will be titrated (see Section 5.1.1.1) to ensure **they are** taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration **must** be initiated at Visit 2. **The Investigator should follow the titration schedule list in Table 3.** Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture period is not yet complete. The decision to initiate OCS dose reduction at Visit 2 is **at** the discretion of the Investigator and can include consideration of Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months. **If inclusion criterion 13 has not been met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility (as per inclusion criterion 13). The patient must be screen failed if they fail to demonstrate reversibility. All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase.**

If at Visit 2, the patient is judged not to be a candidate for OCS dose reduction based upon asthma symptoms or other clinical reasons in the opinion of the Investigator, he/she should be screen-failed.

At Visit 3 **and Visit 4**, the dose of OCS may be reduced only if **all** criteria listed in Section 5.1.1.1 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). **If** a patient **does not meet all** criteria listed in Section 5.1.1.1, the OCS dose should be returned to **at least** the previous effective dose (**ie, the higher dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5. Once the OCS dose is uptitrated, no further OCS dose reductions should be performed. The patient should be maintained on that OCS dose until randomisation (Visit 6).**

At Visit 5, if the patient still meets all of the criteria for OCS dose down-titration, this patient must be screen-failed (refer to exclusion criterion 18**). If the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie,** the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until randomisation (Visit 6).

The optimized dose of OCS is defined as a lowest dose of OCS at which patient meets criteria listed in Section 5.1.1.1. In cases when the patient is optimized on their OCS dose prior to Visit 5 (Week-2), that visit should be combined with Visit 5 (eg, Visit 3 would be combined with Visit 5). He/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized at Visit 6. Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. The optimized dose reached during the OCS optimisation phase becomes the patient's baseline OCS dose for analysis purposes.

It is possible that the patient's asthma symptoms may worsen (excluding exacerbation and/or infection requiring antiviral or antibiotic therapy), in between visits, during the run in/optimisation period, as evidenced through patient history and corroborated through the data collect through eDiary. In this case, the OCS dose can be increased to a previous effective dose without a visit to the clinic. The patient can be assessed in clinic at the earliest opportunity or at the next scheduled visit (at the Investigator's discretion). If the patient is assessed during an unscheduled visit, he/she should still return for the next scheduled visit. This scheduled visit can be combined with Visit 5. The patient should be maintained on this new OCS dose for at least 2 weeks prior to randomisation (Visit 6).

If the patient experiences an asthma exacerbation requiring evaluation in an Urgent Care Center, in an Emergency Department (ED), Hospitalization, or temporary increase (bolus/burst) of systemic steroids, they **do not need to be screen failed. The exacerbation should be treated according local standard of care. After completing the treatment for the exacerbation, the patient should return back to his/her regular maintenance dose of OCS. He/she must remain on this dose for 2 weeks and then return for Visit 5. The maintenance OCS dose must be at least 1 dose-level higher than the dose at which the exacerbation occurred. The patient should be maintained on this OCS dose for 2 weeks prior to randomisation (Visit 6). The patient should continue to complete the eDiary daily during the asthma exacerbation. This is important as compliance will be assessed as per inclusion criteria 18, 19, and 20.**

If a patient reaches asthma control at an OCS dose of ≤5mg during **the optimization** phase, the patient will be a screen failure and will not be randomized **(refer to exclusion criterion 17; at Visit 6, the OCS dose must be >5 mg).** If the patient does not reach an optimized dose of the OCS by the end of the run-in/optimization phase, the patient should be screen failed and cannot be randomized.

The post-BD FEV_1 should be performed using the guidance in Section 5.1.3.1, if necessary. If inclusion criterion 13 was not met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility. The patient must be screen failed if they fail to demonstrate reversibility. Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics.

Patient eligibility should be evaluated at each visit during the run-in/OCS optimization phase with the relevant documentation entered in the source and eCRF.

Patients whose compliance with the electronic diary is <70% will be given the option once during screening to reschedule a study visit (with the exception of Visit 6) within 72 hours.

Table 3 Oral corticosteroid titration schedule during the optimization phase (Visit 2 to Visit 5)

Enrolment Visit	Run in/Optimization Phase (OCS dose in mg)			
V1/W -10	V2/W -8	V3[a]/W -6	V4[a]/W -4	V5/W -2
40	35	30	25	A
37.5	32.5	27.5	22.5	A
35	30	25	20	A
32.5	27.5	22.5	17.5	A
30	25	20	15	A
27.5	22.5	17.5	12.5	A
25	20	15	10	A
22.5	17.5	12.5	7.5	A
20	15	10	7.5	A
17.5	12.5	7.5	5	A & B
15	10	7.5	5	A & B
12.5	7.5	5	B	
10	7.5	5	B	
7.5	5	B		

[a] **Check if the patient meets all the criteria listed in Section 5.1.1.1. If yes, then down titrate as per Table 3. If no, the OCS dose should be returned to at least the previous effective dose (ie, the higher**

dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5 (eg, a patient met the criteria and was down titrated to 20 mg at Visit 3; at Visit 4, the patient does not meet the criteria for down titration; therefore, the patient must be uptitrated to at least 25mg).

A. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 18).

B. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 17).

Reason for Amendment:

To clarify the parameters and procedures for the optimization phase

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.1.3 Re-Screening

Previous text:

Patients who experience an asthma exacerbation within 30 days prior to ICF date or during the run-in/optimization phase should be screen failed (exclusion criterion 15). They may be re-screened no sooner than 30 days after their last dose of systemic steroids, or for those patients on chronic oral steroid controller therapy, 30 days after their dose has returned to their regular maintenance levels.

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization phase may also be re-screened (exclusion criterion 6). They may be re-screened 30 days after recovery, e.g., completion of the therapy.

Re-screening for the above mentioned reasons is allowed only once for the patient.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

Revised text:

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization phase may also be re-screened (exclusion criterion 6). They may be re-screened 30 days after recovery, eg, completion of the therapy.

Re-screening for the above mentioned reasons is allowed only once for the patient.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

Rescreening of patients for any other reason will be allowed only upon approval of the medical monitor or AstraZeneca Study Physician.

Reason for Amendment:

To remove the requirement to screen fail a patient for an exacerbation within the 30 days prior to signing the ICF or during run-in/optimization and to require approval of the AstraZeneca Study Physician for rescreening for reasons other than those stated.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.2 Randomized treatment period

Previous text:

Patients will have scheduled visits at 4-week interval to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see Section 5.1.2), patients should be evaluated at the study centre, when feasible, at UNS visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using ePRO device throughout the 28-week treatment period (see Section 5.3.2 for details).

At Week 28 patients will come to the centre for the EOT visit.

Patients who prematurely discontinued IP (see Section 3.6) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for Visits 14 (EOT), 15 (FU) within 4 weeks (±7 days) and 12 weeks (±7 days) after the last dose of IP, respectively.

Revised text:

Starting at Visit 8, patients will have scheduled visits at 4-week intervals to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using the ePRO device throughout the 28-week treatment period (see Section 5.3.2 for details).

At Week 28, patients will come to the center for the EOT **(or IPD, if applicable)** visit.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for **the Premature IP Discontinuation visit (IPD)** within 4 weeks **(+7days). At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments, or alternatively agree to be contacted by phone at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at** 12 weeks (±3 days) after the last dose of IP **for final study-related assessments.**

Reason for Amendment:

To remove the requirement to for the patient to be visit the study center for an asthma worsening/exacerbation and to clarify procedures for premature IP discontinuation and to reduce the window for the follow-up visit to ±3 days.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.2.1 Induction phase

Previous text:

The induction phase will start at Week 0 (Visit 6) and will continue up till Week 4 (Visit 8). During this time, patients will remain on all of their regular asthma controller medications. No dose adjustments to OCS will be made during this period; patients will continue the optimized OCS dose that was achieved during OCS optimization phase.

Revised text:

The induction phase will start at Week 0 (Visit 6) and will continue until Week 4 (Visit 8). During this time, patients will remain on all of their regular asthma controller medications. No dose adjustments to OCS will be made during this period; patients will continue the

optimized OCS dose that was achieved during OCS **optimization phase. The pre-BD spirometry of acceptable quality must be performed at Visit 6. The pre-BD spirometry will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent post randomization visits until Visit 13.**

Reason for Amendment:

To clarify when pre-BD spirometry is to be done during the optimization and titration phases

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.2.2 Reduction phase

Previous text:

The reduction phase will start at Week 4 (Visit 8) and will be completed at Week 24 (Visit 13). The first reduction of OCS dose can occur at the Week 4 (Visit 8). Subsequent OCS dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4. The presence of exacerbation, changes in symptoms, and rescue medication use will be assessed.

Revised text:

The reduction phase will start at Week 4 (Visit 8) and will be completed at Week 24 (Visit 13). The first reduction of OCS dose **should** occur at the Week 4 **visit** (Visit 8). **Visit 8 is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose. At all other visits in the reduction phase, the OCS dose reduction must take place only when all the titration criteria are met as per Section 5.1.1.1. If at Visits 9, 10, 11, 12, and 13, if the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met). Oral corticosteroid** dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4. **Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. This dose should be maintained until the EOT (Visit 14). The occurrence of exacerbations**, changes in symptoms, and rescue medication use will be assessed.

Table 4 Oral corticosteroid dose titration schedule during the reduction phase (Visit 8 to Visit 13) [a, b]

Optimized dose at V6	V8/W4	V9/W8	V10/W12	V11/W16	V12/W20	V13/W24
40	35	30	25	20	15	10

Table 4 Oral corticosteroid dose titration schedule during the reduction phase (Visit 8 to Visit 13) [a, b]

Optimized dose at V6	V8/W4	V9/W8	V10/W12	V11/W16	V12/W20	V13/W24
37.5	32.5	27.5	22.5	17.5	12.5	7.5
35	30	25	20	15	10	7.5
32.5	27.5	22.5	17.5	12.5	7.5	5
30	25	20	15	10	7.5	5
27.5	22.5	17.5	12.5	7.5	5	5
25	20	15	10	7.5	5	5
22.5	17.5	12.5	7.5	5	5	5
20	15	10	7.5	5	5	5
17.5	12.5	7.5	5	5	5	2.5
15	10	7.5	5	5	2.5	1.25
12.5	7.5	5	2.5	1.25	0	0
10	7.5	5	2.5	1.25	0	0
7.5	**5**	**2.5**	**1.25**	**0**	**0**	**0**

[a] **All doses expressed in mg/day**
[b] **A daily dose of 1.25 mg may be administered as 2.5 mg every other day**

Patients who experience an asthma exacerbation requiring evaluation in an Urgent Care Center, in ED, Hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) should be returned to the previous effective OCS dose (ie, the higher dose level prior to the titration criterion not being met) after they have returned to their baseline level of asthma control. This dose should be maintained until the EOT (Visit 14).

NOTE: OCS dose reduction may take place only when criteria for OCS dose reduction are met (not applicable for Visit 8, see Section 5.1.1.1).

Reason for Amendment:

To clarify the parameters and procedures for the reduction phase

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.2.3 Maintenance phase

Previous text:

Patients will be maintained for the 4-week period after Week 24 to Week 28 on the stable dose of OCS achieved during the reduction phase, or if requirement for OCS was eliminated then maintained without OCS. Patients will be maintained without further OCS dose adjustments until their last visit within the study to assess symptoms, ACQ-6 and exacerbations.

Revised text:

Patients will be maintained for the 4-week period after Week 24 to Week 28 on the stable dose of OCS achieved during the reduction phase, or if requirement for OCS was eliminated, then maintained without OCS. Patients will be maintained without further OCS dose adjustments until their last visit within the study to assess symptoms, ACQ-6**, and exacerbations. Patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).**

Reason for Amendment:

To clarify that exacerbations will also be assessed at the last visit and that patients who are eligible may enrol in the follow-on extension study at the EOT visit

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

4.3 Follow-up period

Previous text:

Patients that complete 28-week double blind randomized treatment period may be enrolled into a separate long-term safety extension study.

Patients who complete Week 28 (Visit 14) and do not enter the safety extension study will be requested to return to the study centre at Week 36 for the follow-up assessments. During these visits patients will be assessed for any ongoing safety issues and any potential prospective AEs; serum biomarker, PK and immunogenicity samples will be collected (see Table 2).

Revised text:

Patients **who have remained on IP for the** double-blind treatment period **as defined in the protocol (see Section 1.5)** may be **eligible to enrol in the follow-on** extension study.

Patients who complete Week 28 (Visit 14) and do not enter the **follow-on** extension study will be requested to return to the study center at Week 36 for the follow-up assessments. During

these visits, patients will be assessed for any ongoing safety issues, and any potential prospective AEs; serum biomarker, PK, and immunogenicity samples will be collected (see Table 2).

Reason for Amendment:

To clarify which patients will be eligible for the follow-on extension study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.1 Assessment of oral corticosteroid dose

Previous text:

If dose reduction criteria are met (see below), the dose reduction of the OCS will commence at Visit 8 and will continue at 4-week intervals until Visit 13 in accordance with OCS dose titration schedule provided in Table 4 (reduction phase). During reduction phase, a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each patient.

Revised text:

The reduction of the OCS dose will commence at Visit 8 and will continue at 4-week intervals until Visit 13 in accordance with OCS dose titration schedule provided in Table 4 (reduction phase). During reduction phase, a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each patient.

Reason for Amendment:

To clarify the timing of the OCS dose reduction phase

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.1.1 Oral corticosteroid dose titration

Previous text:

For the optimization phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between

Visit 1 and Visit 2. Dose titration begins at Visit 2. Baseline FEV1 for the optimization phase will be collected at Visit 2.

For the dose reduction phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between visit 5 and visit 6. Dose titration begins at Visit 8. Baseline FEV1 for dose reduction phase will be collected at Visit 6.

Patients who meet all of the following criteria are eligible for OCS dose titration:

- Pre-BD FEV_1 ≥80% of baseline
- Morning PEF ≥80% of mean morning measures over the 14 days period prior to the scheduled study visit as compared to baseline
- Mean night time awakenings ≤50% increase over the 14 days period prior to the scheduled study visit, as compared to baseline
- SABA rescue medication use of not more than 4 inhalations/day above the mean value over 14 days period prior to the scheduled study visit, as compared to baseline, or above 12 inhalations/day
- No requirement to increase the dose of OCS for asthma symptoms since the last visit

When a patient doesn't meet the above criteria, further reduction of the OCS dose will be stopped for the duration of the study and the patient will be returned to the dose one level higher.

During the post-randomization phase, not all patients will be allowed to reduce their OCS dose to 0. A minimum maintenance dose will be required for patients whose dose at Visit 6 is 15 – 40 mg/day (Table 4); these patients may not be reduced to doses lower than that which is specified.

If, in the opinion of the investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect patient safety), titration may be stopped. The patient should be returned to a dose one level higher (unless a temporary bolus/burst of steroid is warranted) and no further reductions may take place.

For statistical analysis purposes in the event that titration is terminated prior to Visit 13, a patient's final OCS dose will be recorded as one dose level higher than that, which directly preceded termination.

Revised text:

Oral corticosteroid dose titration occurs during the Optimization Phase (Table 3) and again during the Reduction Phase (Table 4).

For the optimization phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 1 and Visit 2. Dose titration begins at Visit 2 **at the discretion of the Investigator (refer to Section 4.1.2)**. Baseline FEV_1 for the optimization phase will be collected at Visit 2.

For the dose reduction phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 5 and Visit 6. Dose titration begins at Visit 8 **and is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose.** Baseline FEV_1 for dose reduction phase will be collected at Visit 6.

Patients who meet all of the following criteria are eligible for OCS dose **reduction during the optimization phase (Table 3) and during the reduction phase (Table 4):**

- Pre-BD FEV_1 ≥80% of baseline
- Morning PEF ≥80% of mean morning measures over the 14 days period prior to the scheduled study visit as compared with baseline
- Mean night time awakenings ≤50% increase over the 14 days period prior to the scheduled study visit, as compared with baseline
- SABA rescue medication use of not more than 4 inhalations/day above the mean value over 14 days period prior to the scheduled study visit, as compared with baseline, or above 12 inhalations/day
- No requirement to increase the dose of OCS for asthma symptoms since the last visit

During the optimization phase, if the patient **fails to** meet **all of** the above criteria **at Visit 3**, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose **that is at least 1 dose** level higher t**han the OCS dose at which further titration criteria was not met. If randomized at Visit 6, the patient will then be maintained at this OCS dose until the reduction phase (Visit 8).**

At Visit 8, the down titration will be initiated. If, at any subsequent visits during the reduction phase, the patient fails to continue to meet the criteria for down titration, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose that is at least 1 dose level higher than the OCS dose at which the down titration criteria were not met. Once the OCS has been uptitrated, no further OCS dose reduction should be performed.

During the post-randomization phase, not all patients will be allowed to reduce their OCS dose to 0. A minimum maintenance dose will be required for patients whose dose at Visit 6 is 15 – 40 mg/day (Table 4); these patients may not be reduced to doses lower than that which is specified.

If, in the opinion of the Investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect patient safety), titration may be stopped **after**

discussion with the AstraZeneca Study Physician. The patient should be returned to a dose **at least 1** level higher (unless a temporary bolus/burst of steroid is warranted) and no further reductions may take place. **In these instances, the reason(s) for stopping the OCS dose reductions must be documented in the source notes.**

For statistical analysis purposes, in the event that titration is terminated prior to Visit 13, a patient's final OCS dose will be recorded as 1 dose level higher than that which directly preceded termination.

The titration schedule of OCS dose **reduction during the reduction phase** is presented in Table 4.

Reason for Amendment:

To clarify the parameters for and requirements during OCS dose optimization and reduction

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.2 Assessment of asthma exacerbations

Previous text:

- A temporary bolus/burst of systemic corticosteroids (at a dose above one level higher than the current titration step) for at least 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
    - Discontinuation due to exacerbation after V6 is not mandatory. Patients who experience an exacerbation during screening (between Visits 1 and 6) should be screen failed. Those who experience an exacerbation after randomization may remain on investigative product at the PI's discretion. However, they will not be eligible for additional OCS dose titration steps. After the bolus/burst is complete, they should be returned to one dose level higher than the dose that preceded their exacerbation
    - Up titration of OCS dose during optimization to one level higher is not considered an exacerbation
- An emergency room visit due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization due to asthma

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven).

For the optimization phase, the baseline will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected on each day between visit 5 and visit 6.

The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of one new or additional nebulized β2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7 day period compared with the average during baseline, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An asthma exacerbation that occurs ≤7 days of the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so.

Reasonable attempts should be made by the Investigator to bring the patient into the study centre for evaluation of a diary alert or patient initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study centre evaluations for asthma worsening may occur as an UNS visit or as part of an ordinary centre visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (eg, by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

Revised text:

- A temporary bolus/burst of systemic corticosteroids (at a dose **at least 1** level higher than the current titration step for at least 3 days to treat symptoms of asthma worsening,
- **an emergency room visit due to asthma that required systemic corticosteroids, or**
- **an inpatient hospitalization due to asthma.**

Discontinuation due to exacerbation after **Visit 6 (the OCS dose reduction period)** is not mandatory. Those who experience an exacerbation after randomization may remain on IP at the Principal Investigator's discretion. **Following resolution of the exacerbation, the patient should be placed on the OCS dose 1 step** higher than that **which they were on when the** exacerbation occurred (see Table 4).

Up titration of OCS dose during optimization to 1 level higher is not considered an exacerbation

Worsening of asthma is defined as new or increased symptoms and/or signs (eg, examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (ie, diary-driven).

The baseline during the optimization phase will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected on each day between visit 5 and visit 6.

The ePRO device will be programmed to alert both the patient and study center when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of 1 new or additional nebulized β_2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7-day period compared with the average during baseline, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the baseline average or the highest possible score [daily score of 6]), on at least 2 consecutive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An asthma exacerbation that occurs **within** ≤7 days of the last dose of systemic steroids prescribed for a prior exacerbation will be counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centers (eg, by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

Reason for Amendment:

To further define an asthma exacerbation and the procedure for OCS titration following an asthma exacerbation.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.3 Spirometry

Text added:

During the run in/optimization phase, all patients must perform pre-BD and post-BD spirometry. Assessment of reversibility may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 (refer to Section 5.1.3.1)

Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to the planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics. Nevertheless, their historical data will be used to meet eligibility prior to randomization as per inclusion criterion 13.

All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase.

For the reduction phase, pre-BD FEV_1 must be performed at Visit 6 and will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits.

Reason for Amendment:

To clarify the requirements for reversibility testing

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.3 Spirometry; General requirements

Previous text:

Important! Patients should be instructed not to use their usual ICS-LABA medication within 12 hours of scheduled centre visit spirometry **as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the centre.** For the same reason patients should not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled centre visit spirometry. **This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening FEV_1 and reversibility eligibility criteria.**

Revised text:

Important! Patients should be instructed to restrict the use of their usual ICS/LABA medication prior to scheduled center visit spirometry as this will affect the pre-BD FEV_1 value **that** may be taken subsequently at the center. **Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment. For the same reason, patients should not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled center visit spirometry.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening FEV_1 and reversibility eligibility criteria.

Reason for Amendment:

To clarify the schedule for withholding medications prior to spirometry testing

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.3 Spirometry; Time of day for scheduled center visit spirometry

Previous text:

Spirometry testing should be initiated in the morning between 6:00 AM and 11:00 AM according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ±1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00

AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Revised text:

Spirometry testing should be **done** according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ±1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Reason for Amendment:

To remove the requirement for spirometry testing to be done between 6:00 AM and 11:00 AM, permitting more flexibility for the patient in having this assessment done

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.3 Spirometry; Spirometry technique

Previous text:

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the centre. Slow spirometry will be conducted prior to the forced manoeuvres. Both slow and forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each slow spirometry and forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

Instruct the patient to inhale and exhale slowly (at least 10 breaths).

From normal breathing, the patient should slowly exhale to a maximum (ERV manoeuvre).

For reaching the end-expiratory level the following two criteria must be complied with according to ATS/ERS.

- Duration of expiration
    - Patients must exhale for at least 6 seconds.

- End of Test Criteria
    - Towards the end of the expiration it is important to motivate the patient to try hard. Within the last second of expiration the exhaled volume must not exceed 25 mL.

Next, the patient should slowly inhale to a maximum (VCIN) and then slowly exhale to tidal breathing. According to ATS/ERS criteria at least three trials should be performed.

If the difference between the best and second VCIN and/or VCmax is greater than 0.150 L further trials should be performed.

For IC only: If the coefficient of variation is greater than 6% further trials should be performed.

Revised text:

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the center. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the maneuver. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

For reaching the end-expiratory level, the following 2 criteria must be complied with according to ATS/ERS:

- Duration of expiration
    - Patients must exhale for at least 6 seconds.
- End of Test Criteria
    - Towards the end of the expiration, it is important to motivate the patient to try hard. Within the last second of expiration the exhaled volume must not exceed 25 mL.

Reason for Amendment:

To remove the requirement for slow spirometry testing

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.3 Spirometry; Order of administration of usual asthma controller medication and investigational product relative to scheduled pre-and post-bronchodilator spirometry

Previous text:

The patient's usual asthma morning asthma controller therapy must not be given until after the initial pre-medication, pre-bronchodilator spirograms are complete for the reasons discussed above; usual asthma controller may be given after final post-bronchodilator spirograms. IP dosing should also be withheld until pre-bronchodilator spirometry is complete.

The screening post-BD FEV1 performed at Visit 2 is not part of the eligibility criteria for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in section 3.1.

Revised text:

The patient's asthma morning asthma controller therapy must not be given until after the initial pre-**BD spirometry** is complete; asthma controller **medications** may be given after final post-**BD spirometry assessments. Investigational product** dosing should also be withheld until pre-BD spirometry is complete.

Reason for Amendment:

To simplify the language around post-BD administration of asthma controller medications and IP

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

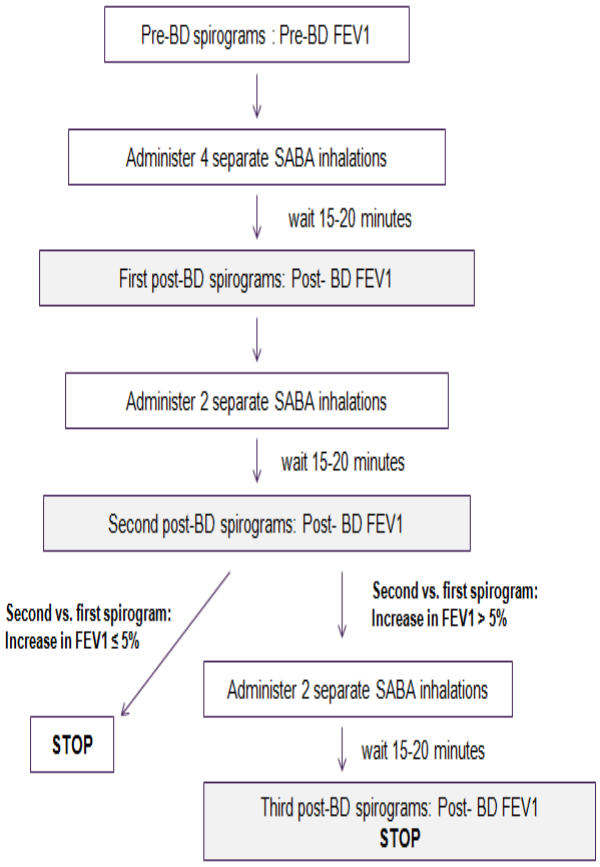
Section of protocol affected:

5.1.3.1 Reversibility test and post-bronchodilator FEV_1 assessment

Added text:

The procedure described in this section refers to the reversibility testing at Visit 1 or Visit 2 or Visit 3 (to evaluate inclusion criterion 13, if applicable). Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose) up to a maximum of 8 inhalations). It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 2.

Figure 2 Reversibility testing algorithm



1 Verify with the patient that the medication restrictions to allow the reversibility assessment have been met (Section 3.5.2)

2 After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in 1 breath to total lung capacity (TLC) from a spacer device. The breath is then held for 5–10 seconds before the patient exhales. Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 15-20 minutes later.

3 If the patient has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). A second post-BD spirometry should be performed 15-20 minutes later.

4 If the patient still has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalation, 30 seconds apart (for a total of 8 inhalations). A third post-BD spirometry should be performed 15-20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffs, and/or a total of less than 8 puffs, can be used if there is a concern about any effect on the patient's heart rate, tremor, or safety. **For reversibility testing at Visit 1, Visit 2, or Visit 3, it is acceptable to stop the procedure when eligibility criterion is met.**

The highest pre- and post-BD FEV_1 should be used to determine reversibility.

Reversibility is calculated as follows:

$$\% \text{ Reversibility} = \frac{(\text{post-BD } FEV_1 - \text{pre BD } FEV_1) \times 100}{\text{pre-BD } FEV_1}$$

Reason for Amendment:

Maximum Post-bronchodilator Procedure added for reversibility testing to bring this assessment in line with reversibility testing in the pivotal studies.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.1.4 Home lung function testing

Previous text:

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 1 (Week **-9**) until the morning of Visit 14 (Week 28) using the provided ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Revised text:

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 1 (Week **-10**) until the morning of Visit 14 (Week 28) using the provided ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Reason for Amendment:

Typo. Visit 1 is at Week -10 not Week -9.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.2.4 Safety laboratory tests

Text deleted:

The blood eosinophil count from the sample drawn at Visit 1 will be used to inform primary and secondary efficacy of benralizumab.

Reason for Amendment:

To remove erroneous information

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.2.4 Safety laboratory tests, Table 5 List of safety laboratory tests

Text added:

Serum concentration added to table.

Footnote b added: If and when appropriate prior to randomization; For patients who are on theophylline and digoxin (see Section 3.5.2.2 [d])

Reason for Amendment:

Assessments of serum concentration of theophylline and digoxin at Visit 1 for patients on these drugs

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.2.4 Safety laboratory tests, Table 6 Schedule of serum chemistry tests

Text added:

Serum calcium, serum chloride, carbon dioxide, glucose, serum phosphorus, serum potassium, serum sodium, total cholesterol, and uric acid added to V14.

IPD visit added with assessments matching EOT visit.

Reason for Amendment:

To align the EOT and IPD assessments with the V1 assessments for serum chemistry to allow the assessment of change from baseline

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.1 Weight and height

Previous text:

Note: Height will be taken on screening Visit 1 only.

Revised text:

Note: **Weight and h**eight will be taken on screening Visit 1 only.

Reason for Amendment:

To clarify that both weight and height will be taken at Visit 1 only.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.3.1 Local laboratory eosinophil test

Previous text:

Only patients with an absolute blood eosinophil count of **≥300** cells/μL at Visit 1, as assessed at the local laboratory, will be eligible for randomization (see inclusion criterion 6).

Revised text:

Only patients with an absolute blood eosinophil count of **≥150** cells/μL at Visit 1, as assessed at the local laboratory, will be eligible for randomization (see inclusion criterion 6).

Reason for Amendment:

To reflect that the eosinophil cutpoint has been lowered to 150 cells/μL. Justification for this change is given above.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.5 Sputum collection

Previous text:

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients; in addition, in a sub-set of approximately 20 patients flow cytometry will be performed to assess eosinophil progenitor cells in sputum.

Revised text:

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients.

Reason for Amendment:

Flow cytometry statement removed as it is discussed with assessment of eosinophil progenitor cells.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.5 Sputum collection

Previous text:

The samples will be analyzed by a central laboratory on behalf of AstraZeneca.

Revised text:

The samples will be analyzed by a central laboratory on behalf of AstraZeneca. **AstraZeneca or a designee will retain sputum biomarker samples for investigation of the pharmacology of benralizumab for a maximum of 15 years following the Last Patient's Last Visit. The results from the investigation of such samples, including sputum biomarkers will not be reported in the CSR, but in separate reports and in scientific publications as appropriate.**

Reason for Amendment:

To clarify the retention period of the sputum samples and to clarify where the results of the analyses will be reported

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.5 Body plethysmography (now 5.3.6)

Previous text:

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the investigator or qualified designee according to ATS/ERS guidelines (Wanger et al, 2005) according to the study schedule. Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is < 0.05) should be obtained and the mean value reported. Measurements using the body plethysmography will be conducted at visit 6, 10 and 14. Prior to the assessment, certain restrictions need to be adhered to. Patients should be instructed not to use their usual ICS-LABA medication within 12 hours of scheduled assessment. Patients should also not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled assessment. This assessment is to be performed on all subjects enrolled for sputum collection. Each site will be allowed to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centres.

Revised text:

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the Investigator or qualified designee according to ATS/ERS guidelines (Wanger et al 2005)) according to the study schedule (see Table 2). Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is <0.05) should be obtained and the mean value reported. Measurements using the body plethysmography will be conducted at visit 6, 10 and 14. Prior to the assessment, certain restrictions need to be adhered to. **Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours to scheduled assessment.** Patients should also not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled assessment. This assessment is to be performed on all subjects enrolled for sputum collection. Each site will be allowed to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centers.

Reason for Amendment:

Text added to clarify schedule for withholding medications prior to this assessment

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

5.3.8.1 Blood biomarkers

Previous text:

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including IL-5, Eosinophil-derived neurotoxin [EDN], and eotaxin), and eosinophil- and inflammation-related biomarkers of asthma.

Revised text:

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including IL-5, Eosinophil-derived neurotoxin [EDN], and eotaxin). Eosinophil**-, basophil**- and inflammation-related biomarkers of asthma **may also be assessed**.

Reason for Amendment:

To add basophil-related biomarkers of asthma to the list of biomarkers that may be assessed.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

6.5 Methods for assigning treatment groups

Previous text:

Randomization codes will be assigned strictly sequentially in each stratum (country/region) as patients become eligible for randomization.

Revised text:

Randomization codes will be assigned strictly sequentially in each stratum **(combination of eosinophil level and** country/region) as patients become eligible for randomization.

Reason for Amendment:

Eosinophil level added as a randomization stratum as the ≥150 to 300 cells/μL stratum has been added to the study.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

6.8 IP administration and treatment compliance

Added text:

If an Investigator decides to skip the IP administration due to exacerbations, the above rule does not apply.

Reason for Amendment:

To clarify that a decision by the Investigator to skip an IP administration due to an exacerbation does not mean the patient should be discontinued. This is an exception to the rule of missing 2 consecutive doses or missing more than 2 of the scheduled doses leading to the patient being discontinued from IP. The patients are having their background OCS dose reduced, so it is expected that they might exacerbate during the course of the study.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

6.9 Management of investigational product-related reactions

Previous text:

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

Revised text:

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample **may** be drawn **as soon as safely possible to the event** for additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

Reason for Amendment:

To clarify the timing around the collection of a blood sample for ADA testing following an anaphylactic event

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

7.1.3.7 **Symptoms of the disease under study** (section added)

Added text:

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness and phlegm, will be recorded as AEs only when:

- **The sign or symptom is serious according to definitions, see Section 7.1.2**
- **The patient discontinues the study due to the sign or symptom**
- **The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.**

After randomization, asthma exacerbations should be recorded in the exacerbation eCRF (EXACA; see Section 5.1.1). If the exacerbation fulfils any of the above criteria, the sign or symptom should also be recorded as an AE.

Reason for Amendment:

A new section to clarify how the Investigator should report symptoms of disease under study has been added to the CSP. The Sponsor considers it justifiable not to record symptoms of the disease under study or other endpoints as AEs, since details of the disease under study, including asthma exacerbations, are recorded as efficacy measurements and collected during the study in the case report form, as specified in the CSP. Unless more severe in intensity, or more frequent than expected for the patient's condition, expected progression of the disease (or signs and symptoms of the disease) should not be reported as an AE.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.2 Sample size estimate

Previous text:

For sample size estimation purposes, the targeted difference in the percentage reduction of the OCS dose between the active drug regimens and placebo is 60%. That is, the final OCS reduction from baseline in benralizumab groups is targeted to be 60% greater than the final OCS reduction from baseline in the placebo group. Based on previous studies of OCS reduction, an estimate of 70% was used for the standard deviation. Assuming a Type I error rate of 5% and 90% power, the sample size required is 35 patients per treatment group.

Revised text:

For the primary endpoint of percentage reduction from baseline OCS dose, 70 patients per treatment arm are required to detect a difference between each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

Reason for Amendment:

The previous power calculation is based on a t-test assuming the data are normally distributed. However, according to the OCS sparing study data for mepolizumab (Bel et al 2014), the data are not normally distributed. The new power calculation is based on simulations using the Wilcoxon rank sum test. Therefore, the primary analysis for the primary endpoint will be conducted using the Wilcoxon rank sum test.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.2 Percentage reduction from baseline in oral corticosteroid dose

Previous text:

The primary variable is the percentage reduction from baseline in the final OCS dose. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

Revised text:

The primary variable is the percentage reduction from baseline in the final OCS dose **while maintaining asthma control**. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

For patients who lost asthma control between Visits 13 and 14, the final dose will be set to 1 dose level higher than that which directly preceded the loss of asthma control.

Similarly, for patients who withdrew from the study, the final dose will be set to 1 dose level higher than that which directly preceded withdrawal.

Reason for Amendment:

To explain how the primary variable will be handled for those patients who lose asthma control between Visits 13 and 14 and for those patients who withdraw from the study.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.4 Proportion of patients with **100%** reduction from baseline in oral corticosteroid dose

Previous text:

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

Revised text:

For **an individual patient, if** the **calculation in Section 8.4.2 results in a value** of **100%, that patient will be classified as having a 100%** reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with 100% reduction at final visit/number of patients in treatment group

Reason for Amendment:

To provide derivation of proportion of patients with 100% reduction from baseline in oral corticosteroid dose

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.5 Proportion of patients with **≤5 mg reduction from baseline in oral corticosteroid dose**

Text moved (formerly Section 8.4.4):

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

Reason for Amendment:

To clarify the definition of this endpoint for the patients who either lost asthma control between Visits 13 and 14 or withdrew from the study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.6 **Proportion of patients with** average final **oral corticosteroid** dose ≤5.0 mg daily

Text moved (formerly Section 8.4.5):

For each treatment group, the number of patients with average final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with average final OCS dose ≤5 mg daily at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

Reason for Amendment:

To clarify the definition of this endpoint for the patients who either lost asthma control between Visits 13 and 14 or withdrew from the study

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.7 Inspiratory capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)

Text deleted (entire section):

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-bronchodilator measurements recorded at Visit 6 will be used as baseline IC, ERV, IRV, VCIN, VCEX, and VCMAX.

Reason for Amendment:

Slow spirometry removed from the list of assessments

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.8 Rate of exacerbations

Text added:

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of an increased OCS dose that is used to treat an exacerbation, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of an increased OCS dose that is used to treat an exacerbation, or the date of discharge from a hospital, whichever occurs later. In the primary analysis, the number of exacerbations observed for a patient during the 28-week double-blind treatment period will be used as response variable.

NB. If the patient is not fulfilling criteria for down titration listed in Section 5.1.1.1 and needs to be up titrated, the patient should up titrated by 1 level and this up titration should not be considered the start of an exacerbation.

Reason for Amendment:

To clarify the start and stop points of an exacerbation

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.8 Rate of exacerbations

Previous text:

In the statistical analysis, the number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. For the production of summary statistics, the annual exacerbation rate per patient is calculated.

Revised text:

For the production of summary statistics, the annual exacerbation rate per patient is calculated.

Reason for Amendment:

To remove the details of analyses from this section since this is covered in the Methods for Statistical Analyses Section

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.11 Time to first exacerbation requiring hospitalization

Text added:

Time from randomization to the first asthma exacerbation requiring hospitalization will be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization for patients who do not experience an asthma exacerbation requiring hospitalization during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

Reason for Amendment:

To clarify the definition of time to first exacerbation requiring hospitalization

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.12 Time to first exacerbation requiring hospitalization or emergency department visit

Text added:

Time from randomization to the first asthma exacerbation requiring hospitalization or ED visit will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization or ED visit−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization or ED visit for patients who do not experience an asthma exacerbation requiring hospitalization or ED visit during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

Reason for Amendment:

To clarify the definition of time to first exacerbation requiring hospitalization or emergency department visit

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.13 Number of days in hospital due to asthma

Text added:

The total number of days in hospital due to asthma during the 28 weeks of treatment will be calculated for each patient.

Reason for Amendment:

To provide details for the calculation of number of days in hospital due to asthma

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.14 Number of days with oral corticosteroids taken for exacerbations

Text added:

The total number of days with OCS taken for exacerbations during the 28 weeks of treatment will be calculated for each patient.

Reason for Amendment:

To provide details for the calculation of number of days with oral corticosteroids taken for exacerbations

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.15 Blood eosinophil levels

Text added:

The blood eosinophil level change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated. The level recorded at Visit 6 will be used as baseline.

The eosinophil progenitor change from baseline to each of the post-randomization visits (post Visit 6) at which it is measured up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables (subset of patients). The level recorded at Visit 6 will be used as baseline.

Reason for Amendment:

Moved from an exploratory variable to a secondary variable

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.4.17 Lung function as assessed through body plethysmography

Text moved (formerly Section 8.4.15.4):

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. Variables include TLC, RV, VC, IC, and FRC.

Reason for Amendment:

Moved from an exploratory variable to a secondary variable

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.2 Primary analysis method(s)

Previous text:

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose. Each benralizumab dose regimen will be compared with placebo.

For each of the two benralizumab dose regimens, the null hypothesis is that the percentage reduction in OCS on benralizumab is equal to the percentage reduction in OCS on placebo. The alternative hypothesis is that the percentage reduction in OCS on benralizumab is not equal to the percentage reduction in OCS on placebo, ie:

H0: % reduction OCS (benralizumab vs Placebo)=0

Ha: % reduction OCS (benralizumab vs Placebo)≠0

The percentage reduction in OCS in each of the two benralizumab dose regimen groups will be compared to the percentage reduction in OCS in the placebo group using an analysis of covariance (ANCOVA) model.

The response variable in the model is the percentage reduction in OCS dose from baseline to the final dose that the patient is receiving at Visit 14. The model will include covariates of treatment group, country/region, and baseline OCS dose.

The estimated treatment effect (ie, difference in mean percentage reduction of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the difference will be presented. In addition, the percentage reduction in OCS and the corresponding 95% CI within each treatment group will be presented.

In addition, the percentage reduction in OCS will also be summarized in patients with baseline blood eosinophil counts 300-450/μL, and >450/μL separately for descriptive purposes only.

Revised text:

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose**, while maintaining asthma control.** Each benralizumab dose regimen will be compared with placebo.

For each of the 2 benralizumab dose regimens, **a Wilcoxon rank-sum test will be performed. The median difference in** the percentage reduction **of** OCS **dose between** each benralizumab dose regimen and **placebo, along with the** 95% CI and p-value will be presented. In addition, the **median** percentage reduction in OCS **dose** and the corresponding 95% CI within each treatment group will be presented.

The above analyses will also be **performed for patients with baseline blood eosinophils ≥300/µL while the multiplicity will not be adjusted for these analyses.**

The percentage reduction in OCS dose will be summarized **by treatment group** in patients with baseline blood eosinophil counts **≥150-299/µL,** 300-450/µL, and >450/µL separately.

Reason for Amendment:

The previous power calculation is based on a t-test assuming the data are normally distributed. However, according to the OCS sparing study data for mepolizumab (Bel et al 2014), the data are not normally distributed. The new power calculation is based on simulations using the Wilcoxon rank sum test. Therefore, the primary analysis for the primary endpoint will be conducted using the Wilcoxon rank sum test.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.3.1 Analysis methods for secondary efficacy variables

Previous text:

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- PK and immunogenicity variables
- Proportion of patients with ≥1 asthma exacerbation
- Time to the first asthma exacerbation
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- Change from baseline in pre-bronchodilator FEV1

- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom daytime/night time scores
- Change from baseline in rescue medication use
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- PK parameters
- ADA

The secondary efficacy endpoints will be analyzed in patients with baseline blood eosinophil counts 300-450/μL and >450/μL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization pre-dose/pre-bronchodilator FEV_1. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline pre-bronchodilator FEV_1 will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in FEV_1=Treatment group+baseline FEV_1+country/region+visit +treatment*visit

The following variables will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score and total rescue medication use, change from baseline in post-bronchodilator FEV_1 and change from baseline in morning and evening PEF.

For the following variables, the proportion in each of the two benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: the proportion of patients with ≥1 asthma

exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The number of nights with awakening due to asthma and requiring rescue medication will be analyzed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country/region and baseline value will be fit as covariates.

The change from baseline in ACQ-6 and AQLQ(s)+12 will be analyzed using a similar repeated measures model as described for the change from baseline in pre-dose/pre-bronchodilator FEV1.

Revised text:

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- **The proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control**
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- Proportion of patients with ≥1 asthma exacerbation
- **Annual rate of** asthma **exacerbations**
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- **Time to the first asthma exacerbation**
- **Time to the first asthma exacerbation requiring hospitalization**
- **Time to the first asthma exacerbation requiring hospitalization or ED visit**
- **Number of days in hospital due to asthma**
- **Number of days with OCS taken for exacerbations**
- Change from baseline in pre-bronchodilator FEV_1

- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom **scores (total,** daytime **and nighttimes)**
- Change from baseline in rescue medication use
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- **TLC, RV, VC, IC, FRC**

The secondary efficacy endpoints will be **summarized by treatment group** in patients with baseline blood eosinophil counts **≥150-299/µL,** 300-450/µL, and >450/µL.

For the following variables, the proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with **100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with** ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Annual rate of asthma exacerbations will be analysed using a negative binomial model. The number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented. This analysis will only be performed if there is a sufficient number of patients who have multiple exacerbations.

Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization will be analysed similarly as for annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analysed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox

proportional hazard model will be fitted to data with the covariates of treatment, country/region, and number of exacerbations in the year before the study.

Time to **first** asthma **exacerbation** requiring **hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit** will be analysed **similarly** as **for time to first asthma exacerbation.**

Change from baseline in pre-bronchodilator FEV_1 will be compared between each of the 2 benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-BDFEV$_1$ and at least 1 post-randomization pre-BD FEV_1. The dependent variable will be the change from baseline in pre-BD FEV_1 at post baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and country/region and baseline **pre-BD FEV_1** will be **used** as covariates. **Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then a compound symmetric variance-covariance matrix will be used instead. The model is:**

Change in FEV_1=Treatment group+baseline pre-BD FEV_1+country/region+visit +treatment*visit.

The following variables will be analysed separately using a similar model as the above model for change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score and night time score, total rescue medication use, change from baseline in the number of nights with awakening due to asthma requiring rescue medication, change from baseline in morning and evening PEF, and change from baseline in ACQ-6 and AQLQ(s)+12.

Reason for Amendment:

To clarify the analyses methods to be used for all secondary endpoints

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.4 Analysis method for blood eosinophil levels (Section added)

Added text:

Blood eosinophil levels will be summarized using standard summary statistics and plots at each visit by treatment group.

Reason for Amendment:

To provide details on the summary of blood eosinophil levels

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.5 Analysis methods for exploratory variables

Previous text:

Exploratory endpoints in this study will be obtained from sputum collection and body plethysmography and include (subset of patients):

- sputum cell differential counts
- quantification of sputum cytokines and biomarkers
- assessment of eosinophil progenitor cells
- TLC, RV, VC, IC, FRC

Other exploratory endpoints will be obtained from blood and include:

- blood eosinophils
- assessment of eosinophil progenitor cells (subset of patients)
- serum biomarkers

Revised text:

Exploratory endpoints in this study will be obtained from sputum collection and body plethysmography and include (subset of patients):

- sputum cell differential counts
- quantification of sputum cytokines and biomarkers
- assessment of eosinophil progenitor cells **in sputum**

Other exploratory endpoints will be obtained from blood and include:

- assessment of eosinophil progenitor cells (subset of patients)
- serum biomarkers

Reason for Amendment:

Wording amended for clarity

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.7 Subgroup analysis (if applicable)

Previous text:

No subgroup analyses are planned.

Revised text:

Full details of subgroup analyses **will be pre-specified in the SAP**.

Reason for Amendment:

Wording amended to introduce information about subgroup analysis and to indicate that SAP will contain full details related to subgroup analysis.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.5.6 Sensitivity Analysis

Previous text:

No sensitivity analyses are planned but may be conducted as suggested by the data.

Revised text:

Full details of the sensitivity analysis **will be pre-specified in SAP**.

Reason for Amendment:

Wording amended to introduce information about sensitivity analysis and to indicate that SAP will contain full details related to that analysis.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.6 Independent adjudication committee for major adverse cardiac events and malignancies (Section added)

Additional text:

An independent adjudication committee will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm the diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths and 2) Investigator-reported malignancies during the Phase 3 trials. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information the committee requires to enable a thorough adjudication.

Reason for Amendment:

AstraZeneca has decided to proactively implement independent adjudication of cardiovascular (CV) events and malignancies across all Phase 3 studies conducted with humanized antibodies in patients with severe asthma. The rationale for this decision is that patients with severe asthma have an increased risk of co-morbidities, which complicates the evaluation of the CV and malignancy events. Standard adverse event reporting provides a thorough basis for the safety evaluation in general; however, for certain events of particular clinical importance such as cardiovascular events and malignancies, an unbiased adjudication committee with specialist members, can facilitate the collection of appropriate data and perform accurate evaluation of each case.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

8.7 Data safety monitoring board (Section added)

Additional text:

The Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB will function independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee will operate in accordance with a DSMB Charter.

Reason for Amendment:

To align with CALIMA and SIROCCO, so that all BORA predecessor studies, as well as BORA, include a DSMB to evaluate safety and other clinical trial data

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

9.3 Study timetable and end of study

Previous text:

The study is expected to start in Q2 2014 and to end by Q**1** 2016.

Revised text:

The study is expected to start in Q2 2014 and to end by Q**3** 2016.

Reason for Amendment:

Duration of study extended due to increase in recruitment target.

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Appendix E Background Therapy Equivalence Table

Previous text:

Estimated daily dosage for inhaled corticosteroids *

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
Beclomethasone dipropionate	>500 - 1000	**>1000 -** 2000
Beclomethasone HFA	>240 - 480	**>480**
Beclomethasone dipropionate (Fostair)	>200 - 400	**>400** - 800
Beclomethasone HFA Ciclesonide	>160 - 320	**>320** - 1280
Beclomethasone diproponate (Fostair) Triamcinolone acetonide	>1000 - 2000	**>2000**
Flunisolide	>1000 - 2000	**>2000**
Fluticasone propionate	>250 - 500	**>500** - 1000
Fluticasone propionate HFA	>364 - 440	**>440**

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
Budesonide	>400 to 800	**>800** - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to 640	**>640** - 1280
Mometasone furoate	≥400	**≥800**

Revised text:

Estimated daily dosage for inhaled corticosteroids *

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
Beclomethasone dipropionate	>500 - 1000	**>1000** - 2000
Beclomethasone HFA	>240 - 480	**>480**
Beclomethasone dipropionate (Fostair)	>200 - 400	**>400** - 800
Ciclesonide	>160 - 320	**>320** - 1280
Triamcinolone acetonide	>1000 - 2000	**>2000**
Flunisolide	>1000 - 2000	**>2000**
Fluticasone propionate	>250 - 500	**>500** - 1000
Fluticasone propionate HFA	>364 - 440	**>440**
Budesonide	>400 to 800	**>800** - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to 640	**>640** - 1280
Mometasone furoate	**≥400**	**≥800**

Reason for Amendment:

To correct editing error in previous table and to update table with new medications

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Appendix G Restricted and prohibited medications

Previous text:

Table 1 Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance of asthma controller medications (ICS-LABA)	Restricted	Changes in dose and regimen should not be done from enrolment and throughout the study treatment (unless there is a medical need as judged by the Investigator) Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home peak flow assessments (to be administered once assessments are completed)
Short acting beta-agonists (SABA)	Restricted	Rescue use of SABA administered via nebulisation is discouraged, except as urgent treatment during an asthma exacerbation. SABA should not be used within 6 hours prior to scheduled spirometry, ECG and home lung function assessments.
Additional Maintenance Controllers (eg LTRAs, tiotropium, cromone, theophylline **and oral corticosteroids**	Allowed with restriction	Stable dose for 2 weeks prior to **Visit 1** and stable dose during the treatment period)
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from enrollment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event May be used for managing an asthma exacerbation event.
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever	Prohibited	Not allowed from enrolment and throughout the study duration

Treatment)		
Zileuton	Prohibited	Not allowed within 30 days of Visit 1 and during treatment period.

– Other medication restrictions

Table 2 Other medication restrictions

Medication	**Prohibited/restricted**	**Details**
Live Attenuated Vaccines	Prohibited	Not allowed within 30 days of Visit 1;during treatment period and 4 months (5 half-lives) after the last dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	**Allowed provided they are not administered 1 week before or 1 week after any study visit**
Any immunomodulators or immunosuppressives	Prohibited	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF;during treatment period
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment

Medication	Prohibited/restricted	Details
		period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1 and during treatment period
Oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any oral or ophthalmic β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.

Revised text:

Table 3 Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance of asthma controller medications (ICS-LABA)	Restricted	Changes in dose and regimen should not be done from enrolment and throughout the study treatment (unless there is a medical need as judged by the Investigator) Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home peak flow assessments (to be administered once assessments are completed)
Short acting beta-agonists (SABA)	Restricted	Rescue use of SABA administered via nebulisation is discouraged, except as urgent treatment during an asthma exacerbation. SABA should not be used within 6 hours prior to scheduled spirometry, ECG and home lung function assessments.
Additional Maintenance Controllers (eg LTRAs, tiotropium, cromone,	Allowed with restriction	Stable dose for **2 weeks prior to randomisation** and stable dose during the treatment period **(except during**

theophylline		**the treatment of exacerbations)**
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from enrollment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event May be used for managing an asthma exacerbation event.
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Prohibited	Not allowed from enrolment and throughout the study duration
Zileuton	Prohibited	Not allowed within 30 days of Visit 1 and during treatment period.

– Other medication restrictions

Table 4 Other medication restrictions

Medication	**Prohibited/restricted**	**Details**
Live Attenuated Vaccines	Prohibited	Not allowed within 30 days of Visit 1;during treatment period and **within** 4 months (5 half-lives) after the last dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	**Not allowed within the 7 days before or within the 7 days after any study visit**
Any immunomodulators or immunosuppressives	Prohibited	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (eg omalizumab) or	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1;

Medication	Prohibited/restricted	Details
investigational biologic treatment		during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1 and, during treatment period
Oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any oral or **non-selective** ophthalmic β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.

Reason for Amendment:

Wording in the tables updated for clarity and to be consistent with wording present in other protocol sections, including inclusion and exclusion criteria

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of protocol affected:

Appendix H Estimate OCS Dose Therapy Equivalence

Additional text:

Estimated OCS Dose Therapy Equivalence

Asthma Therapy	Approximate equivalent Dose
OCS	
Oral Prednisone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Prednisolone	10 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Budesonide	2.25 mg
Deflazacort	12 mg

Reason for Amendment:

Oral corticosteroid equivalence table implemented to allow for OCS dose equivalence calculation when switching from other kinds of OCS during Visit 1

Person who initiated the Amendment:

AstraZeneca ZONDA Global Study Team

Section of Protocol affected:

All

Change:

Minor typographical and stylistic errors have been corrected throughout the Clinical Study Protocol. Redundant wording has been removed and replaced with a section reference.

Person who initiated Amendment:

AstraZeneca ZONDA Global Study Team

AstraZeneca
†

Clinical Study Protocol Amendment

Amendment Number	2
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
Date	10 February 2016
Protocol Dated	10 April 2015

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All

The protocol for the study is to be amended as follows:

Section of Protocol affected:

9.3: Study timetable and end of study

Previous text:

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q3 2016.

The study may be terminated at individual study centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

Revised text:

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study. The study is expected to start in Q2 2014 and to end by Q3 2016.

The study may be terminated at individual study centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

Database lock and unblinding for the CSR will occur after the last subject has completed the EOT or IPD visit. If, at this time, there are any patients who do not elect to continue in the separate extension study (D3250C00021), and have yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments are still to be conducted and the data will be listed separately in an addendum to the CSR.

Reason for the Amendments:

All data needed to assess the OCS sparing effect of benralizumab, and all efficacy and treatment-phase (on-treatment) safety data will have been obtained at the time the last subject completes the treatment period.

To date, over 95% of patients completing this trial have elected to enter the separate extension study. As such, at the time of the last patient completing the maintenance phase of the study

(Visit 14), it is expected that fewer than 5 patients will have yet to complete the 8-week follow-up, accounting for less than 1% of the planned on-study safety follow-up time. Therefore, database lock for the clinical study report will occur after the last patient completes the end of treatment (EOT) visit or investigational product discontinuation (IPD) visit, and data from any patients yet to complete final study-related assessments at the safety follow-up (Visit 15) will be listed separately in an addendum to the CSR.

Person who initiated Amendment:

AstraZeneca ZONDA Global Study Team

AstraZeneca

Statistical Analysis Plan

Study Code	D3250C00020
Edition Number	1.0
Date	29 Apr 2014

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Study Statistician T J Uryniak — Thomas Uryniak — 5 May 2014 — Date

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Global Product Statistician

Kelvin Shi, PhD

May 05, 2014
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma control questionnaire
ADA	Anti-drug antibodies
ANCOVA	Analysis of covariance
AQLQ	Asthma quality of life questionnaire
EOT	End of treatment
ER	Emergency room
ERV	Expiratory residual volume
FEV_1	Forced expiratory volume in one second
IC	Inspiratory capacity
ICS	Inhaled corticosteroid
IP	Investigational product
IRV	Inspiratory residual volume
ITT	Intent to treat
LABA	Long-acting beta-agonist
PEF	Peak expiratory flow
PK	Pharmacokinetic
SC	Subcutaneous
VCEX	Vital capacity - expiratory
VCIN	Vital capacity – inspiratory
VXMAX	Vital capacity - maximum

AMENDMENT HISTORY

Initial version

1. STUDY DETAILS

1.1 Study objectives

Primary Objective	Endpoint
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of OCS dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

Secondary Objectives	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	Proportion of patients with ≥1 asthma exacerbation after randomization Time to the first asthma exacerbation after randomization Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	Change from baseline in pre-bronchodilator FEV_1 Change from baseline in pre-bronchodilator Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)

To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	Change from baseline in asthma symptom score (total, daytime, and night time) Change from baseline in rescue medication use Change from baseline in home lung function (morning and evening PEF) Change from baseline in the number of nights with awakening due to asthma requiring rescue medication Change from baseline in ACQ-6
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	Change from baseline in AQLQ(S)+12
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	PK parameters ADA

Safety Objective	**Endpoint**
To assess the safety and tolerability of 2 dosing regimens of benralizumab	AE/SAE Laboratory variables ECG Physical Examination

Exploratory Objectives	**Endpoint**
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	Assessment of eosinophil progenitor cells
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	Sputum cell differential count Quantification of sputum cytokines and biomarkers Assessment of eosinophil progenitor cells
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	Serum biomarkers
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed thru body plethysmography (subset of patients)	TLC/RV/VC/IC/FRC

1.2 Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in 2 dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter) in patients with uncontrolled asthma receiving high-dose ICS-LABA and OCS with or without additional asthma controller(s).

The study will recruit approximately 120 patients (randomized 1:1:1) and stratified by region.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit on Week 28. The treatment period is divided into 3 phases:

- Induction (from Week 0 till Week 4; patients will remain on the optimized OCS dose)

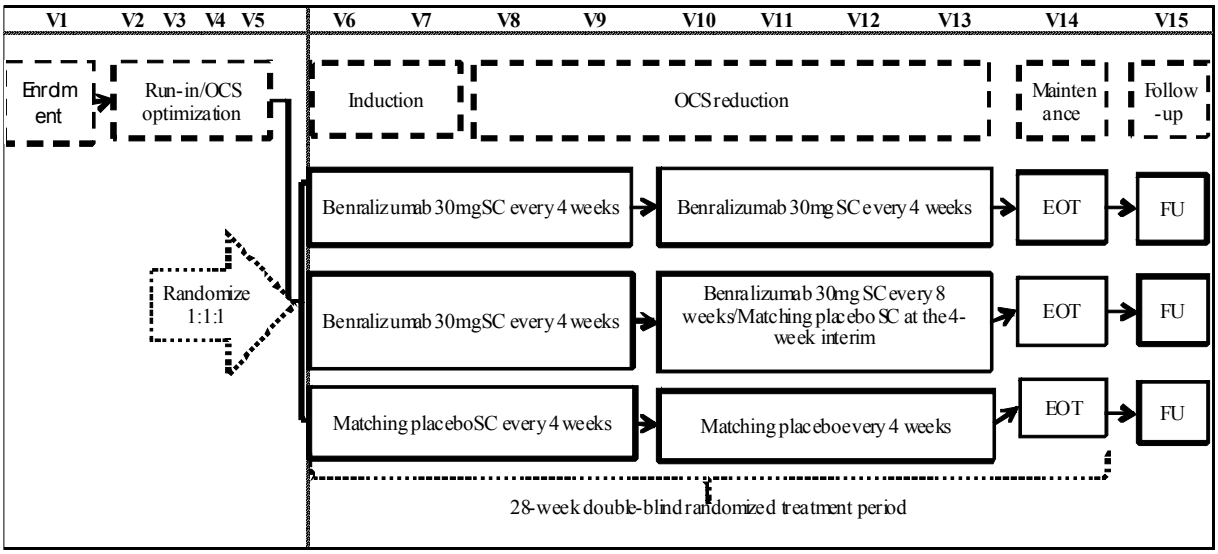
- Reduction (from Week 4 till Week 24, inclusively; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week interval)

- Maintenance (after Week 24 till Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate long-term safety extension study; all patients who complete Week 28 (Visit 14) in the current study will be eligible to enrol in the safety extension study.

The investigational product (IP) will be administered at the study centre every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS-LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Figure 1 Study flow chart



1.3 Number of subjects

For sample size estimation purposes, the targeted difference in the percentage reduction of the OCS dose between the active drug regimens and placebo is 60%. That is, the final OCS percentage reduction from baseline in the benralizumab group is targeted to be greater than the final OCS reduction from baseline in the placebo group (e.g. reduction from baseline for benralizumab is 80% and reduction from baseline for placebo is 20%). Based on previous studies of OCS reduction an estimate of 70% was used for the standard deviation. Assuming a Type I error rate of 5% and 90% power, the sample size required is 35 patients per treatment group. Estimates were based on data from studies by Nelson (Nelson H et al 1998, Nelson H et al 1999) and Ververelli (Ververelli K and C et al 2004).

2. ANALYSIS SETS

2.1 Definition of analysis sets

All efficacy analyzes will be performed using an Intent-to-Treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

2.1.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

All patients randomized and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

2.1.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen. All safety summaries will be based on this analysis set.

2.1.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

2.1.5 Anti-drug antibodies (ADA) analysis set

All patients in the safety analysis set who received at least 1 dose of benralizumab will be included in the ADA analysis set. Patients will be classified the same way as in the safety analysis set. All ADA summaries will be based on this analysis set. Both treatment induced and non-treatment induced (baseline) ADA responses will be summarized.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still randomized will be analyzed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Protocol deviations

This section summarizes protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

The final list of protocol deviations will be finalized and documented prior to unblinding the study data, and will include the following:

- Patients who do not meet the inclusion criteria
- Patients who do not meet the randomization criteria

- Patients who meet any of the exclusion criteria
- Concomitant use of disallowed medications (to be identified through programming). Patients who use one or more disallowed medication (for any reason, unless otherwise specified) during the randomized treatment period will be classed as protocol deviators.
- Patients who received the incorrect study treatment or study dose at any time during the 28-week double-blind treatment period
- Patients who developed withdrawal criteria during the study but were not withdrawn

Only important protocol deviations will be listed and tabulated in the CSR.

2.2.2 Visit window definitions

For the OCS dose reduction and exacerbation-related analyses, no windows will be applied. For the patient-report questionnaires collected by electronic patient-reported outcomes (ePRO), the variables will be summarized based on the protocol scheduled Days with ± 3-day window. For the other questionnaires, the window is the same as the protocol-defined visit windows. For local laboratory, and all vital signs, the visit recorded in web based data capture (WBDC) will be used. For the central laboratory results and other endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows are summarized below:

Table 1 Visit windows

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1
Week 4	29	15 ≤Study Days≤42
Week 8	57	43 ≤Study Days≤70
Week 12	85	71 ≤Study Days≤98
Week 16	113	99 ≤Study Days≤126
Week 20	141	127 ≤Study Days≤154
Week 24	169	155≤Study Days≤182
Week 28	197	183≤Study Days≤ 210
Week 36	253	239≤Study Days≤266

For assignment of data to timepoints using the visit windows, study day will be defined as follows:

(Date of assessment – first dose date) +1

By this definition, the day that the first dose of study medication is taken will be study day 1 (Visit 6) and the planned date of Visit 8 (week 4) will be study day 29 (=28+1) for example.

If multiple readings are recorded within a single visit window, please refer to the rules below.

- If there are two or more observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis.
- If two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If two observations are collected on the same day, then the non-missing one with the earlier collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

For overall analyses not based on any particular study visit, all data will be listed and/or analyzed, including any repeat or unscheduled visits, unless otherwise specified.

2.2.3 The definition of baseline

The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization.

For measurements of pulmonary function and lung capacity, the measurement recorded latest visit prior to randomization will be used as baseline. This will usually be Visit 6 unless the measurement is missing at that visit.

Baseline is defined as the last non-missing value before randomization for the asthma PROs and as the average of the last 10 days before randomization for the daily metrics.

For laboratory data, baseline will be defined as the latest non-missing assessment prior to first dose. Baseline will be defined as Visit 6 for the complete physical examination.

3. PRIMARY AND SECONDARY VARIABLES

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomized IP at Visit 6 and the conclusion of Visit 14, inclusive.

3.1 Primary variable

The primary variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

{(Baseline dose–final dose)/baseline dose}*100%

If a patient discontinues from the study during a given dose reduction period then the patient's final dose will be defined as the prior dose level. For example, suppose a patient had completed a previous dose reduction phase while receiving 10mg daily and was now in a subsequent dose reduction period receiving 5mg daily but withdrew before completing that period. In this case, the patient's final dose level would be defined as 10mg daily because the patient had not completed the period in which 5mg was used.

Note that during Weeks 24-28, the patients will be on a maintenance dose of OCS, that is, no reduction will be attempted. Should a patient's asthma deteriorate during that time to the point that the patient requires an increase in the daily dose of OCS during the maintenance period, that increased dose will be deemed as the patient's final dose for analysis purposes.

Also, should a patient be placed on an every other day regimen of OCS, their final dose will be defined as the average daily dose. For example, if a patient is placed on a regimen of 5mg every other day, their final dose is defined as 2.5mg/day.

3.2 Secondary variables

3.2.1 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation above results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in daily OCS dose. Patients with missing values will be considered as not having had a reduction. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

3.2.2 Proportion of patients with ≤5 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

3.2.3 Proportion of patients with average final OCS dose ≤5.0 mg daily

For each treatment group, the number of patients with average final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with average final OCS dose ≤5 mg daily at final visit / number of patients in treatment group

3.2.4 Forced expiratory volume in one second (FEV_1)

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-bronchodilator measurements recorded at Visit 6 will be used as baseline FEV_1.

3.2.5 Rate of exacerbations

Only exacerbations that result in ER visits or hospitalization will be analyzed. Additional bolus/burst of systemic corticosteroid, emergency room visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted for as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

Maximum follow-up time for a patient is approximately 28 weeks; defined as the time from randomization to the date of Visit 14. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed (i.e. the last contact date).

Exacerbations that occur after a patient has discontinued investigational product should still be accounted for when deriving the total number of exacerbations, and likewise the follow-up time will reflect the follow-up time regardless of whether or not the patient is still on investigational product.

In the statistical analysis, the number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. For the production of summary statistics, the annual exacerbation rate per patient is calculated and using the data from the 28-week double blind treatment period according to the formula described below.

Annual Exacerbation Rate = Number of Exacerbations*365.25 / (Follow-up date, up to & including visit 14 – Visit 6 date + 1)..

3.2.6 Proportion of patients with at least one exacerbation resulting in ER visit or hospitalization during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation resulting in an ER visit or hospitalization during the 28 weeks of treatment will also be analyzed. The proportion of such patients will be calculated for each treatment group as:

Number of patients with at least on exacerbation/number of patients in treatment group

3.2.7 Time to first exacerbation resulting in ER visit or hospitalization

Time from randomization to the first asthma exacerbation resulting in an ER visit or hospitalization will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation −Date of Randomization+1.

The time to first asthma exacerbation for patients who do not experience such an asthma exacerbation during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

3.2.8 Asthma symptom score

The outcome variable for asthma symptom score will be the change in mean asthma symptom scores from baseline to each of the post-randomization periods. Asthma symptom daytime scores, nighttime scores, and total scores will be calculated separately. Any missing data will be handled as follows: If a patient has completed assessments for fewer than half the days for a given post-randomization period, the assessment for that period will be recorded as missing. If not recorded as missing, the mean score for that period will be the average score of the non-missing daily scores in the period. Values missing for a period will not be imputed, and the observed data will be analyzed in the repeated measures analysis.

3.2.9 Rescue medication use

The outcome variable for rescue medication use (inhaler and/or nebulizer) will be the change in mean rescue medication use (puffs/day) from baseline to each of the post-randomization periods. Any missing data will be handled as follows: If a patient has completed values for fewer than half of the days for a given post-randomization period, the assessment for that period will be recorded as missing. If not recorded as missing, the mean score for that period will be the average score of the non-missing daily scores in the period. Values missing for a period will not be imputed, and the observed data will be analyzed in the repeated measures analysis.

3.2.10 Percentage of nights with awakenings due to asthma

The outcome variable for the percentage of nights with awakenings due to asthma will be the change in mean percentage from baseline to each of the post-randomization periods. Any missing data will be handled as follows: If a patient has completed fewer than half of the assessments for a given post-randomization period, the percentage for that period will be recorded as missing. If not recorded as missing, the mean score for that period will be the average score of the non-missing daily scores in the period. Values missing for a period will not be imputed, and the observed data will be analyzed in the repeated measures analysis.

3.2.11 Asthma Control Questionnaire (ACQ-6)

The outcome variable for ACQ-6 will be the change in mean score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (EOT – baseline) ≤-0.5 → Improvement
- -0.5 < ACQ-6 (EOT – baseline) <0.5 → No change
- ACQ-6 (EOT – baseline) ≥0.5 → Deterioration.

The number and percentage of patients achieving ACQ improvement, no change and deterioration as described above will be summarized by treatment.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ- 6 responder variable takes value 1 if change from baseline to EOT in ACQ-6 ≤-0.5 and 0 otherwise. Furthermore, patients will be categorized according to their ACQ-6 EOT score as follows (Juniper et al 2006):

- ACQ-6 (EOT) ≤0.75 → Well controlled
- 0.75< ACQ-6 (EOT) < 1.5 → Partly controlled
- ACQ-6 (EOT) ≥ 1.5 → not well controlled

The number and percentage of patients classified as well controlled, partly controlled and not well controlled as described above will be summarized by treatment.

3.2.12 Asthma Quality of Life Questionnaire for Patients 12 years or older (AQLQ(S)+12)

The AQLQ(S)+12 score will be summarized by domain (4 domains) and for overall. The outcome variable for the AQLQ(S)+12 will be the change in score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits:

- AQLQ(S)+12 (EOT – baseline) ≥0.5 → Improvement
- -0.5 < AQLQ(S)+12 (EOT – baseline) <0.5 → No change
- AQLQ(S)+12 (EOT – baseline) ≤-0.5 → Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to EOT in AQLQ(S)+12 ≥0.5 and 0 otherwise.

The number and percentage of patients achieving AQLQ(S) improvement, no change and deterioration as described above will be summarized by treatment.

3.3 Pharmacokinetic and Immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects at baseline prior to first benralizumab administration at Week 0 Day 1, at multiple time points before benralizumab administrations during the treatment, and during the follow-up phase of the study.

3.4 Exploratory variables

3.4.1 Sputum differential counts and biomarkers

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, CD34+ eosinophils by flow cytometry, the pharmacology of benralizumab, and eosinophils recruitment, activation and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients; in addition, in a sub-set of approximately 20 patients flow cytometry will be performed to assess CD34+ eosinophils and levels of ILC2 (CD45+I27+ST2+IL5+IL-13+) cells in the sputum expressed as absolute cell numbers and as a proportion of the total lin-CD45+I27+ST2+ cells.

3.4.2 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed in approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the investigator or qualified designee according to ATS/ERS guidelines (Wanger et al, 2005) according to the study schedule. Lung volumes will be determined by body plethysmography. Measurements using the body plethysmography will be conducted at Visits 6, 10 and 14. Variables measured include inspiratory capacity (IC), expiratory reserve volume (ERV), inspiratory reserve volume (IRV), inspiratory vital capacity (VCIN), expiratory vital capacity (VCEX), and maximum vital capacity (VCMAX).

3.5 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs (including SAEs).

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

3.5.1 Adverse events

Adverse events experienced by the patients will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data will be categorized according to their onset date into the following study periods:

- AEs occurring during run-in (onset date ≥ visit 1 and before the first dose of investigational product)
- AEs occurring during treatment (onset date ≥ the first day of study treatment and ≤ the last day of randomized treatment + 4 weeks, so effectively up to visit 15, week 28)
- AEs occurring during follow-up (onset date > week 28 and ≤ week 36)
- AEs occurring post-treatment (onset date > follow-up visit; this is only applicable for cases of early discontinuation of investigational product)

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on treatment AE.

3.5.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

3.5.3 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in Section 5.2.4, Tables 5 and 6 of the CSP will be collected. Laboratory data is to be reported in SI units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent on treatment assessment will be calculated. Baseline is defined as the last available value measured prior to the first dose of randomized treatment. The change from baseline is defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The AstraZeneca extended reference ranges will be used for laboratory variables (where they exist). All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each timepoint.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and on-treatment will be defined as the latest non-missing assessment whilst the patient is ongoing on treatment.

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase, GGT and total bilirubin (TBL), the multiple of the AstraZeneca upper limit of the normal (ULN)(not extended) range will be calculated for each data point.

Multiple = Value / ULN

I.e. if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Patients who meet any of the following criteria at any point during the study will be flagged:

- AST $\geq$ 3x ULN
- ALT $\geq$ 3x ULN
- TBL $\geq$ 2xULN

3.5.4 ECGs

Twelve-lead electrocardiogram (ECG) measurements will be recorded in accordance with the protocol, with the baseline visit being defined as visit 3.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.5.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in Section 4, Tables 1 and 2 of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.2 of the CSP. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

Each component of the baseline (visit 1) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.5.6 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate and body temperature) will be obtained in accordance with schedule provided in the protocol.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last value prior to the first dose of randomized treatment. The change from baseline is defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index (BMI) will be calculated from the height and weight as follows:

$$\text{BMI } (kg/m^2) = \text{weight } (kg) / (\text{height } (m))^2$$

4. ANALYSIS METHODS

4.1 General principles

The analysis of the primary and secondary endpoints will include all data captured during the 28- week treatment period, including follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

4.1.1 Testing strategy to account for multiplicity considerations

To account for multiplicity in testing the percentage change in oral corticosteroid dose, for the two dosing regimens a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Hochberg Y 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the two p-values is less than 0.05 then reject both null hypotheses. If the larger of the two p-values is greater than 0.05 then proceed to Step 2.

Step 2: If the smaller of the two p-values is less than 0.025 then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (i.e., unadjusted).

4.2 Analysis methods

4.2.1 Primary analysis method

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose while maintaining asthma control. Each benralizumab dose regimen will be compared with placebo.

For each of the two benralizumab dose regimens, the null hypothesis is that the percentage reduction in OCS on benralizumab is equal to the percentage reduction in OCS on placebo. The alternative hypothesis is that the percentage reduction in OCS on benralizumab is not equal to the percentage reduction in OCS on placebo, i.e.:

H_0: % reduction OCS (benralizumab vs Placebo)=0

H_a: % reduction OCS (benralizumab vs Placebo)≠0

The percentage reduction in OCS in each of the benralizumab dose regimen groups will be compared to the percentage reduction in OCS in the placebo group using an analysis of covariance (ANCOVA) model.

The response variable in the model is the percentage reduction in OCS dose from baseline to the final dose that the patient is receiving at Visit 14. The model will include covariates of treatment group, region, and baseline OCS dose.

The estimated treatment effect (ie, difference in mean percentage reduction of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the difference will be presented. In addition, the percentage reduction in OCS and the corresponding 95% CI within each treatment group will be presented.

In addition, the percentage reduction in OCS will also be summarized in patients with baseline blood eosinophil counts 300-449/μL, and >450/μL separately for descriptive purposes only.

4.2.2 Secondary analysis methods

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- PK and immunogenicity variables
- Proportion of patients with ≥1 asthma exacerbation associated with an emergency room visit or a hospitalization
- Time to the first asthma exacerbation associated with an emergency room visit or a hospitalization
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- Change from baseline in pre-bronchodilator FEV_1
- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom daytime/night time scores
- Change from baseline in rescue medication use
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- PK parameters

- ADA

The secondary efficacy endpoints will be analyzed in patients with baseline blood eosinophil counts 300-449/μL and >450/μL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-dose/pre-bronchodilator $FEV_1$and at least one post-randomization pre-dose/pre-bronchodilator FEV_1. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post baseline protocol-specified visits (up to the EOT visit).

Treatment group will be fitted as the explanatory variable, and region and baseline pre-bronchodilator FEV_1 will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in FEV1=Treatment group+baseline FEV_1+region+visit +treatment*visit

The following variables will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score and total rescue medication use, change from baseline in post-bronchodilator FEV_1 and change from baseline in morning and evening PEF.

For the following variables, the proportion in each of the two benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

The exacerbation rate in the benralizumab groups will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations requiring an ER visit or hospitalization over the 28-week treatment period. The model will include covariates of treatment group, region and starting OCS dose. The logarithm of the follow-up time will be used as an offset variable in the model. The estimated treatment effect (ie, the rate ratio of benralizumab to placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented.

Time to first asthma exacerbation associated with an emergency room visit or a hospitalization will be analyzed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, starting OCS dose, region and number of exacerbations in the year before the study.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot. The median time to event will be summarised by randomised treatment, if there is sufficient uncensored data available to calculate these median values.

The percentage of nights with awakening due to asthma and requiring rescue medication will be analyzed using a similar repeated measures model as described for the change from baseline in pre-dose/pre- bronchodilator FEV_1.

The change from baseline in ACQ-6 and AQLQ(s)+12 will be analyzed using a similar repeated measures model as described for the change from baseline in pre-dose/pre-bronchodilator FEV_1.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analyzed using a logistic regression model with factors of treatment, region and the baseline value as a covariate.

4.2.3 Pharmacokinetic and Immunogenicity variables

Descriptive statistics of benralizumab serum concentration data for each visit by treatment group will be provided. Potential impact of demographic covariates will be evaluated based on the steady-state trough (pre-dose) benralizumab concentrations. Serum concentration-time profiles of benralizumab by treatment group will be generated. Due to the sparse sampling schedule, non-compartmental PK data analysis is not planned. Serum concentrations of benralizumab, summary statistics, empirical demographic covariate analysis and PK profiles will be provided in a clinical PK report (an addendum to the CSR).

Empirical assessments of potential impact of ADA, body weight and other relevant demographic covariates on steady-state trough concentrations will be conducted.

To fully characterize the pharmacokinetic properties of benralizumab in adult patients, the PK data will be merged with those from other clinical studies for a population-based meta-analysis. Demographic covariate effects will also be evaluated.

The population modeling (meta-analysis) will be presented in a separate pharmacometrics report outside of the CSR.

All valid assay results from patients who receive any investigational product will be included in the ADA summaries. Empirical assessments of potential impact of ADA, body weight and other relevant demographic covariates on steady-state trough concentrations will be conducted.

Additional assessments on any potential association of ADA to safety events and efficacy will also be conducted. The association of ADA status (positive/negative) and titers > the median vs. ≤ the median titer to drug concentration levels and eosinophil levels will be investigated.

The neutralizing activity of the ADA response will be assessed at the end of treatment and also during the study follow up period. The association of nAb titer with ADA titer will be assessed. The kinetics of ADA development will also be summarized. The median time to positive result (including quartiles) will be presented for each treatment group. For each subject, the highest titer observed from all the post-dose time points up to the time point of interest will be used in median calculation within each treatment group.

In addition to the analyses mentioned above, an analysis will be conducted where patients will be considered ADA-positive if they have a positive reading at any time (includes baseline assessment, non-treatment emergent ADA) as a sensitivity analysis.

Additionally, the ADA-positive patients will also be divided into persistent versus transient positives. A patient will be considered as persistent positives if he/she has two scheduled (a visit not due to AE, early discontinuation etc.) positive ADA result a minimum of 16 weeks apart. Otherwise, the patient will be considered as transient ADA positive. The associations will be summarized for both persistent positive patients versus transient positives patients.

For ADA, all patients with titer information will be shown in the data listing.

4.2.4 Exploratory Objectives

4.2.4.1 Blood eosinophils

An important marker of the biological activity of benralizumab is the reduction in eosinophils in the peripheral blood. Absolute eosinophil counts along with their absolute changes from baseline, and percentage changes from baseline will be summarized using descriptive statistics by treatment and visit. Analysis of covariance with treatment group, region, number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no) as covariates will be used to compare the percentage changes from baseline between each benralizumab group and the placebo group. Results will be presented in terms of the adjusted means for each treatment group, and estimates of treatment difference, associated CI and p-value for each treatment comparison. Model assumptions will be checked, and if not met, appropriate data transformations may be applied or ANCOVA on ranks will be considered.

4.2.4.2 Serum biomarkers

Serum biomarker samples will be collected at weeks 0, 4, 12, EOT and follow-up. This will be done in order to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including periostin, IL-5, EDN, and eotaxin), and eosinophil- and inflammation-related biomarkers of asthma.

As collection of biological samples is an integral part of this study, no separate optional biomarker consent form was used, and so it is expected that all patients will have data available.

Results and methodological details for the serum biomarker analyses will be reported outside of the CSR.

4.2.5 Body plethysmography

Variables measured by body plethysmography are IC, ERV, IRV, VCIN, VCEX, and VCMAX. These will be measured at Visit 6 (baseline), Visit 10 (Week 12) and Visit 14 (Week 28 or EOT).

Change from baseline in these variables will be compared between each of the two benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline value at least one post-randomization value. The dependent variable will be the change from baseline in with the pre-bronchodilator measurement recorded at Visit 6 serving as the baseline.

Treatment group will be fitted as the explanatory variable, and region and baseline will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in Variable=Treatment group+baseline value+region+visit +treatment*visit

4.2.6 Sputum differential counts and biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. These variables include sputum cell differential counts, quantification of sputum cytokines and biomarkers, and assessment of eosinophil progenitor cells in sputum. Descriptive statistics will be provided for values at each visit and changes from baseline.

4.2.7 Safety variables

4.2.7.1 Adverse events (AEs)

AEs will be summarized separately for the treatment and follow-up periods, as defined in Section 3.5.1. AEs occurring during the run-in period, or occurring post-treatment (as per the definition above) will be listed, but not summarised.

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories; AEs, serious adverse events (SAEs), deaths due to AE, AEs causing discontinuation of investigational product (DAEs), and other significant adverse events (OAEs). The total number of AEs in the different AE categories in

terms of AE counts will also be presented (i.e., accounting for multiple occurrences of the same event in a patient).

AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least one occurrence will be presented i.e. for a patient multiple occurrences of an AE will only be counted once.

AEs (by PT) will be summarised by causality and maximum intensity. If a patient reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). SAEs, OAEs, DAEs, and deaths will also be summarized in separate tables.

The rate of AEs per person-years at risk, calculated as (number of patients reporting AE)/(total drug exposure with patients at risk of AE), will also be reported. Rates will typically be expressed in terms of events per 100 patient-years.

Separate listings of patients with AEs, SAEs, death due to AE, or discontinuations due to AEs will be presented.

4.2.7.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group.

AstraZeneca defined extended reference ranges will be used for the identification of individual clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum on-treatment value, as applicable for each parameter.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. A diagonal line indicating no change, and horizontal and vertical reference lines indicating the limits of the AstraZeneca defined reference ranges will also be displayed on the shift plots.

Data for patients who have treatment-emergent changes outside the predefined criteria will be presented. This data presentation will include all visits for this subset of patients.
The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (using AstraZeneca defined reference ranges) occurring during the clinical study will also be given.

In order to identify potential Hy's Law cases, maximum post baseline total bilirubin will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline total bilirubin against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for total bilirubin and at 3xULN for ALT/AST.

For all patients who meet the biochemical criteria for Hy's law (potential Hy's Law), a Patient Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these patients. Patients with elevated ALT or AST, and elevated total bilirubin, at any time may be explored further graphically using individual patient profile plots.

For urinalysis data, a shift table will be generated to present changes from baseline to EOT. The number of patients with treatment-emergent changes will also be summarized. Here, treatment-emergent changes are defined as 1) None/Trace at baseline to +, ++, +++, ++++ at any visit after baseline or 2) Increase of at least ++.

Any data outside the AstraZeneca normal and extended reference ranges will be explicitly noted on the listings that are produced.

4.2.7.3 ECGs

The Investigator's assessment of the 12-lead ECG (normal or abnormal) will be listed for all patients, along with detailing whether any abnormalities were clinically significant or not.

The number and percentage of patients with clinically significant abnormal ECGs will be summarised by treatment group and visit.

4.2.7.4 Physical examination

Shift tables (normal, abnormal) of baseline versus EOT will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

4.2.7.5 Vital signs

Vital signs data will be presented in the same way as described in Section 4.2.7.2 for the clinical laboratory data, and will be presented using AstraZeneca defined reference ranges, and clinically important change criteria.

All recorded vital signs data will be listed.

5. INTERIM ANALYSES

There is no interim analysis planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes from the protocol.

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AstraZeneca

Statistical Analysis Plan

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A Multicenter, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

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Study Statistician

Stephanie Sproule, MMath — 16 March 2016 (Date)

A Multicenter, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Global Product Statistician

Peter Barker, PhD

17 March 2016
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma control questionnaire
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AQLQ(S)+12	Standardised asthma quality of life questionnaire for 12 years and older
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
AZDD	AstraZeneca drug dictionary
BMI	Body mass index
CI	Confidence interval
CSP	Clinical study protocol
CSR	Clinical study report
DAE	AEs causing discontinuation of investigational product
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECL	Electrochemiluminescent
eCRF	Electronic case report form
EDN	Eosinophil-derived neurotoxin
EOT	End of treatment
ePRO	Electronic patient reported outcome
ER	Emergency room
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FU	Follow up
FVC	Forced vital capacity
GGT	Gamma-glutamyltransferase
IC	Inspiratory capacity

Abbreviation or special term	Explanation
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL-5	Interleukin-5
IP	Investigational product
IPD	Investigational product discontinuation
ITT	Intent to treat
LABA	Long-acting beta-agonist
LSMEANS	Least squares means
MACE	Major adverse cardiac events
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effects model for repeated measures
nAB	Neutralising antibodies
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PK	Pharmacokinetic
PN	Predicted normal
PRO	Patient reported outcome
PT	Preferred term
RV	Residual volume
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SI	Standard international
SOC	System organ class
TBL	Total bilirubin
TLC	Total lung capacity
ULN	Upper limit of normal
VC	Vital capacity
WBDC	Web-based data capture

AMENDMENT HISTORY

Date	Brief description of change
29 April 2014	Initial version
8 March 2016	Amended to reflect the following (editorial updates are not listed): • General updates to study design/endpoints/analyses to align with amended protocol, including: increase in sample size and addition of eosinophil stratification factor (≥150 to <300 vs ≥300 cells/μL), update to the sample size justification, addition of secondary efficacy endpoints (proportion of patients with 100% reduction in final OCS dose, proportion of patients with ≥ 1 exacerbation, annual rate of asthma exacerbations, time to first asthma exacerbation, number of days in hospital due to asthma, home lung function (PEF) and body plethysmography). Analysis methods were aligned with the protocol. • Removal of ADA analysis set (as analyses of ADA will be conducted in the safety set). • Clarification around the process for identifying and summarizing important protocol deviations. • Updates to visit window definitions, taking into account the way in which daily diary metrics are recorded (daytime assessments recorded in the evening and nighttime assessments recorded the morning of following calendar day) and ensuring that there are no gaps in visit windows. Update to definition of study day; relative to randomisation to align with the way in which study visits are scheduled. • Clarification provided on the definition of baseline for efficacy versus safety endpoints. • Clarification on the definition of prior and concomitant medications, as well as the addition of maintenance asthma medications at baseline. Additional detail provided regarding the summary of OCS at screening and baseline. • Clarification added around the primary endpoint definition. Addition of a sensitivity analysis to address cases when OCS dose down-titration was continued after the first exacerbation post-randomisation. • Addition of secondary endpoints; proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0mg daily, ACQ-5. • Analysis of ACQ-6 and AQLQ(S)+12 responders updated to evaluate patients with missing data at week 28 as non-responders. • Updated categorization of adverse events into the following study periods: on-study, on-treatment, and post-treatment. Appendix A added to provide detail around the handling of partial dates for AEs and prior/concomitant medications. • Removal of analysis of other adverse events. • Added reference to the separate Statistical Analysis Plan for Benralizumab Anti-Drug Antibody data. • Added reference to define when the database lock and unblinding for the

Date	Brief description of change
	CSR will occur, after the last subject has completed the EOT or IPD visit, as per CSP amendment 2.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective	Endpoint
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

1.1.2 Secondary objectives

Secondary Objectives	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

Secondary Objectives	**Endpoint**
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomisation • Annual rate of asthma exacerbations after randomisation • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalisation after randomisation • Time to the first asthma exacerbation after randomisation • Time to first exacerbation requiring hospitalisation • Time to first exacerbation requiring hospitalisation or emergency room (ER) visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and nighttime) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	Blood eosinophils

To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

1.1.3 Safety objectives

Objective	Endpoint
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

1.1.4 Exploratory objectives

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	Serum biomarkers

1.2 Study design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in 2 dosing regimens (every 4 weeks [Q4W] throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks [Q8W] thereafter) in patients with uncontrolled asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) and OCS with or without additional asthma controller(s).

The study was planned to recruit approximately 210 patients (randomised 1:1:1) with eosinophils ≥150 cells/μL, stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region. Approximately 60 patients were to be randomised into the lower eosinophil stratum (≥150 to <300 cells/μL) and approximately 150 patients were to be randomised into the higher eosinophil stratum (≥300 cells/μL). At the time recruitment was closed, a total of 220 patients were randomised, with 34 patients randomised in the lower eosinophil stratum due to slower than expected recruitment in this group.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimisation period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimised OCS dose). If the patient meets all of the criteria for OCS titration, his/her asthma will be considered stable and the patient will be eligible for further OCS dose reduction. All patients must be on either oral prednisone or prednisolone as their OCS. Patients who are on any other oral corticosteroid must switch over to an equivalent dose of either oral prednisone or prednisolone at Visit 1. Patients who meet eligibility criteria will be randomised to a 28-week treatment period, with the last dose of benralizumab/placebo administrated at Week 24, and end-of-treatment (EOT) visit at Week 28.

The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimised OCS dose)
- Reduction (from Week 4 to Week 24, inclusively; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)
- Maintenance (after Week 24 until Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained).

A follow-up visit will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on investigational product (IP) for the double-blind treatment period as defined in the protocol may be eligible to enrol in the follow-on extension study (these patients will not attend the follow-up visit at Week 36).

The IP will be administered at the study centre every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomised to the 8-week regimen will receive placebo at Week 12 (Dose 4) with active drug administered at Week 16 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

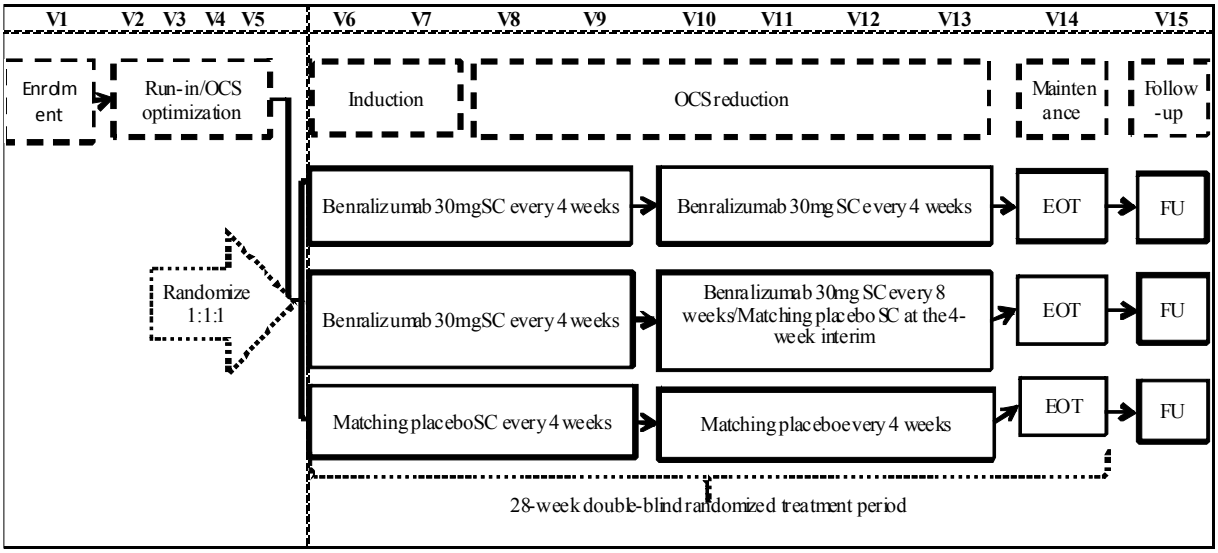
Patients will be maintained on their currently prescribed high-dose ICS/LABA therapy, without change, from enrolment throughout the run-in and treatment period.

All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation Visit (IPD) within 4 weeks (+7 days) after last IP administration. At that visit, patients should be encouraged to remain in the

study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

See CSP Section 4, Tables 1 and 2 for a detailed list of visits and assessments.

Figure 1 Study flow chart



Database lock and unblinding for the clinical study report will occur after the last subject has completed the EOT or IPD visit. If at this time there are any patients who do not elect to continue in the separate extension study, and have yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments will be listed separately in an addendum to the clinical study report.

1.3 Number of subjects

The study was planned to recruit a total of 210 patients with blood eosinophils ≥150 cells/µL. As the targeted patient population for the pivotal studies is ≥300 cells/µL, this study will be stratified by ≥150 to <300 cells/µL and ≥300 cells/µL. The ≥150 to <300 cells/µL stratum was planned to randomise approximately 60 patients and the ≥300 cells/µL stratum was planned to randomise approximately 150 patients. For sample size estimation, 70 patients per treatment arm are required to detect a difference in percent reduction of OCS dose between each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Four patient populations are defined below: all patients analysis set, full analysis set (FAS), safety analysis set and the PK analysis set. Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation), then the patient will be excluded from all analysis sets defined below.

2.1.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

All patients randomised and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat (ITT) principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

All efficacy analyses will be performed using an ITT approach based on the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS.

2.1.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on 1 or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen (ie, 30 mg dose of benralizumab every 4 weeks). All safety and ADA analyses will be based on this analysis set.

2.1.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (eg, disallowed medications) and who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still randomised will be analysed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Important protocol deviations

The important protocol deviations are important in that they may affect the assessments of the true treatment effect with respect to the primary efficacy endpoint, percent reduction in final OCS dose compared with baseline while maintaining asthma control. The important protocol deviations will include but may not be limited to:

- No proof of chronic oral corticosteroid therapy for at least 6 continuous months directly preceding Visit 1.
- No evidence of asthma as documented by the following:
    - Airway reversibility ($FEV_1 \geq 12\%$ and 200 mL) not demonstrated at Visit 1, Visit 2, and Visit 3 using the Maximum Post-bronchodilator Procedure AND;
    - No documented reversibility in the previous 24 months prior to Visit 1 AND;
    - Airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration $\leq$8mg/mL) not documented in the previous 12 months prior to planned date of randomisation AND;
    - Airflow variability in clinic FEV1 $\geq$20% between 2 consecutive clinic visits not documented in the 12 months prior to the planned date of randomisation (FEV_1 recorded during an exacerbation should not be considered for this criterion).
- No documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained.
- Optimized OCS dose not reached at least 2 weeks (± 3 days) prior to randomisation.
- Clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
- Asthma control reached at an OCS dose of $\leq$5mg during run-in/OCS optimization phase (Visit 2 to Visit 6).
- Concomitant use of disallowed medications for asthma (to be identified through programming). Patients who use 1 or more disallowed medication (for any reason, unless otherwise specified) during the randomised treatment period will be classed as protocol deviators.

- Patients who received the incorrect study treatment or dose at any time during the 28-week double-blind treatment period
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients for whom the protocol-defined post-baseline OCS dose titration procedures were not followed and which could have impacted the final OCS dose.

Only important protocol deviations will be tabulated in the CSR. Important protocol deviations will be reviewed and documented by the medical advisors and statisticians prior to unblinding.

Subjects for whom a significant protocol deviation was recorded that impacts the interpretation of the study safety outcomes will have a footnote added to applicable output to describe the deviation and its potential impact. Such subjects will be identified as part of the protocol deviation review process, prior to database lock.

2.2.2 Visit window definitions

For the OCS dose reduction and exacerbation-related analyses, no windows will be applied. For local laboratory, local ECG and all vital signs, the visit recorded in web-based data capture (WBDC) will be used. For endpoints that present visit-based data, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. No visit windows will be defined for enrolment and run-in/optimization phase visits.

The adjusted analysis-defined windows for assessments conducted every 4 weeks are summarised in Table 1, applicable to assessments conducted on or following randomisation (visit 6).

Table 1 Visit windows for assessments conducted every 4 weeks

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤Study Days≤42
Week 8	57	43 ≤Study Days≤70
Week 12	85	71 ≤Study Days≤98
Week 16	113	99 ≤Study Days≤126
Week 20	141	127 ≤Study Days≤154
Week 24	169	155≤Study Days≤182
Week 28	197	183≤Study Days≤ 210

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 36 (Follow-up)	253	211≤Study Days

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as follows:

(Date of assessment – date of randomisation) +1

By this definition, the day of randomisation will be study day 1 and the planned date of visit 8 (week 4) will be study day 29 (=28+1), for example.

If multiple assessments are recorded within a single adjusted visit window, please refer to the rules below.

- If there are 2 or more observations within the same visit window, then the non-missing 1 closest to the scheduled visit will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing 1 with the earlier collection time will be included in the analysis.

For patient reported outcomes collected twice daily, if 2 observations are collected on the same day during the same period (ie, am or pm) then the non-missing observation with the earlier collection time during the period will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

For endpoints which are not collected every 4 weeks, such as ACQ-6 which is assessed every 2 weeks, the above rules will be applied to derive adjusted analysis defined visit windows based on the protocol-defined visit schedule for that endpoint.

For pre-bronchodilator FEV_1 (L), the non-missing value with acceptable quality (acceptable or borderline quality grade) which is closest to the scheduled visit will be included in the analysis.

For daily diary and home PEF assessments, bi-weekly means will be calculated using daily diary entries between the scheduled study days contained in Table 2. As above, study days are relative to day of randomisation (visit 6). For daily diary assessments of rescue medication use and asthma symptom scores, the daytime measurement is captured in the evening and the nighttime measurement is captured the following morning. Nighttime awakenings are captured the following morning. Any observation recorded after the morning of Study Day 197 will not be included in the analysis but will be listed.

Table 2 Bi-weekly windows for daily diary and home PEF assessments

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum windows
Baseline	1	The last 14 days from evening of Study Day -14 to the morning of Study Day 1
Week 2	15	Evening of Study Day 1 to the morning of Study Day 15
Week 4	29	Evening of Study Day 15 to the morning of Study Day 29
Week 6	43	Evening of Study Day 29 to the morning of Study Day 43
Week 8	57	Evening of Study Day 43 to the morning of Study Day 57
Week 10	71	Evening of Study Day 57 to the morning of Study Day 71
Week 12	85	Evening of Study Day 71 to the morning of Study Day 85
Week 14	99	Evening of Study Day 85 to the morning of Study Day 99
Week 16	113	Evening of Study Day 99 to the morning of Study Day 113
Week 18	127	Evening of Study Day 113 to the morning of Study Day 127
Week 20	141	Evening of Study Day 127 to the morning of Study Day 141
Week 22	155	Evening of Study Day 141 to the morning of Study Day 155
Week 24	169	Evening of Study Day 155 to the morning of Study Day 169
Week 26	183	Evening of Study Day 169 to the morning of Study Day 183
Week 28	197	Evening of Study Day 183 to the morning of Study Day 197

For overall analyses not based on any particular study visit, all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For safety endpoints, all post-baseline results will be included in the overall analysis up to and including the follow-up visit. For efficacy endpoints, the post-baseline treatment period will be included up to and including the end of treatment (EOT) visit.

2.2.3 The definition of baseline

In general, the last recorded value on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints while the last recorded value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints. If there is no value prior to randomisation (or the first dose of study treatment, depending on the endpoint), then the baseline value will not be imputed and will be set to missing. No data known to be collected post first dose will be used in determining the baseline value, unless otherwise specified.

For categorical (yes/no) baseline respiratory disease characteristics, if ‘yes’ is indicated in any visit during enrollment or the run-in/OCS optimization phase (scheduled or unscheduled), ‘yes’ will be used.

The baseline OCS dose is defined as the dose upon which the patient is stabilised at randomisation.

For pre-bronchodilator FEV_1 (L), the last non-missing value with acceptable quality (acceptable or borderline quality grade) on or prior to the date of randomisation will be used as baseline. For post-bronchodilator spirometry assessments (including reversibility), the last non-missing value with acceptable quality on or prior to the date of randomisation will be used as baseline. It is expected that due to the planned visit schedule, the pre- and post-bronchodilator baseline assessments will not be from the same visit.

For asthma daily diary metrics and home PEF, baseline is defined as the mean from the last 14 days prior to the date of randomisation and will be derived from data collected on the evening of Study Day -14 to the morning of Study Day 1. The mean is calculated as the sum of all non-missing daily measures/scores over the 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within the baseline period are missing, then baseline is set to missing.

For summaries of central laboratory results by visit and in the calculation of change from baseline, the last non-missing result from the central laboratory prior to first dose of study treatment will be used as baseline.

For all data summaries and analyses by baseline blood eosinophil count strata (≥150 to <300/μL or ≥300/μL) or by baseline blood eosinophil count category (≥150-299/μL, 300-450/μL, >450/μL), the blood eosinophil count result from the local laboratory that was used to randomise the patient (ie, Visit 1) will be used. If the local laboratory result is not available, then the strata recorded in the IVRS system will be used to classify subjects into baseline blood eosinophil count strata (≥150 to <300/μL or ≥300/μL) and the other baseline blood eosinophil count categories will be set to missing.

2.2.4 Prior/concomitant medications

A medication will be classified as a maintenance asthma medication at baseline if it started prior to or on the date of randomisation and was ongoing after randomisation. Maintenance asthma medications with a stop date on the day of randomisation will be considered as prior medications. Inhaled corticosteroid (ICS) doses will be converted to their Fluticasone Propionate dry powder equivalent in micrograms. Oral corticosteroid (OCS) doses at screening (Visit 1) will be converted to their Prednisolone equivalent in milligrams, while OCS doses at baseline will not require conversion since all patients will have been switched to prednisone/prednisolone prior to starting the optimization phase.

A medication will be regarded as prior if it was stopped on or before the date of randomisation (medication stop date ≤ date of randomisation).

A medication will be regarded as concomitant if the start date is on or after the date of randomisation, or if it started prior to the date of randomisation and was ongoing after the date of randomisation. Medications with start date after the on-treatment period (as defined for adverse events in Section 3.4.1) will not be considered as concomitant.

3. PRIMARY AND SECONDARY VARIABLES

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomised IP at Week 0 (Visit 6) and the conclusion of Week 28 (Visit 14), inclusive.

3.1 Primary outcome variable

The primary variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The OCS dose titration schedule during the reduction phase (visits 8 to 13) is presented in Table 4 of the clinical study protocol.

The baseline OCS dose is defined as the dose upon which the patient is stabilised at randomisation (Week 0). Unless otherwise stated below, the final dose is generally defined as the dose at Week 28. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

If a patient discontinues from the study during a given dose reduction period then the patient's final dose will be defined as the prior dose level. For example, suppose a patient had completed a previous dose reduction phase while receiving 10mg daily and was now in a subsequent dose reduction period receiving 5mg daily but withdrew before completing that period. In this case, the patient's final dose level would be defined as 10mg daily because the patient had not completed the period in which 5mg was used.

Note that during Weeks 24-28 (between Visits 13 and 14) the patients will be on a maintenance dose of OCS, that is, no reduction will be attempted. Should a patient's asthma deteriorate during that time to the point that the patient requires an increase in the daily dose of OCS during the maintenance period, that increased dose will be deemed as the patient's final dose for analysis purposes. Also, should a patient be placed on an every other day regimen of OCS, their final dose will be defined as the average daily dose. For example, if a patient is placed on a regimen of 5mg every other day, their final dose is defined as 2.5mg/day.

For statistical analysis purposes, in the event that titration is terminated due to premature study discontinuation prior to Visit 13, a patient's final OCS dose will be recorded as 1 dose level higher than the dose at which termination occurred. Similarly if a patient experiences an exacerbation between Visits 13 and 14, or immediately before discontinuation, the final OCS dose will be 1 dose step higher than the dose at which the exacerbation started.

Following review of blinded preliminary data from the study database, instances were identified of patients who recorded an exacerbation following randomisation, but for whom, contrary to the process outlined in the protocol, the site appeared to continue down-titration of the OCS dose following the exacerbation. As a sensitivity assessment of the primary endpoint, change from baseline in OCS dose will also be calculated as follows:

For patients with no exacerbations recorded following Visit 6, the primary endpoint will be derived as outlined above. For those patients who do record an exacerbation on or after Visit 6, the final OCS dose used in the change from baseline calculation will be the OCS dose 1 step higher than the dose at which their first exacerbation started. Sensitivity analyses using this derivation of the change in OCS dose will be considered, following the same methods outlined for the primary endpoint.

The percentage reduction from baseline in OCS dose will also be derived for each scheduled post-baseline visit and is defined as follows:

*{(Baseline dose–dose at post-baseline visit)/baseline dose}*100%*

3.2 Secondary efficacy outcome variables

3.2.1 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the percent reduction from baseline in the final OCS dose while maintaining asthma control (Section 3.1), based on the primary definition, results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in OCS dose. Patients with missing values will be considered as not having had a reduction. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

Similarly, the proportion of patients with ≥25% reduction from baseline in the final OCS dose will also be derived.

3.2.2 Proportion of patients with 100% reduction from baseline in oral corticosteroid dose

For an individual patient, if the percent reduction from baseline in the final OCS dose while maintaining asthma control (Section 3.1), based on the primary definition, results in a value of 100% (ie, final dose is 0mg), that patient will be classified as having a 100% reduction in OCS dose. Patients with missing values will be considered as not having had a reduction. The proportion of such patients will be calculated for each treatment group as:

Number of patients with 100% reduction at final visit/number of patients in treatment group

Whether or not a patient can achieve a 100% reduction from baseline in OCS dose will depend on their optimized dose at baseline, such that patients with an OCS dose > 12.5mg/day at baseline will not be able to achieve a final OCS dose of 0mg according to the protocol-defined dose titration schedule (refer to Table 4 of the clinical study protocol). As a sensitivity analysis, the proportion of patients with 100% reduction from baseline in OCS dose will also be calculated using the number of patients with optimized OCS dose ≤12.5mg/day at baseline as the denominator (ie, patients eligible to meet this endpoint criteria).

3.2.3 Proportion of patients with ≤5.0 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5.0 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5.0 mg reduction at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.4 Proportion of patients with final OCS dose ≤5.0 mg daily

For each treatment group, the number of patients with final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with final OCS dose ≤5.0 mg daily at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.5 Proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily.

For each treatment group, the number of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥25% reduction from baseline and final OCS dose ≤5.0 mg daily at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.6 Asthma exacerbations

An asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step for at least 3 days to treat symptoms of asthma worsening,
- an emergency room (ER) visit due to asthma that required systemic corticosteroids, or
- an inpatient hospitalisation due to asthma.

In order to calculate the number of exacerbations experienced by a patient during the 28-week treatment period the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of an increased OCS dose that is used to treat an exacerbation, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of an increased OCS dose that is used to treat an exacerbation or the date of discharge from a hospital, whichever occurs later. In the primary analysis, the number of exacerbations observed for a patient during the 28-week double-blind treatment period will be used as response variable.

If the patient is not fulfilling criteria for down titration listed in Section 5.1.1.1 of the CSP and needs to be up-titrated, the patient should be titrated by 1 level and this up titration should not be considered the start of an exacerbation.

An additional bolus/burst of systemic corticosteroid, ER visit requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation, it must be preceded by at least 7 days in which neither criterion is fulfilled.

3.2.6.1 Proportion of patients with at least 1 exacerbation during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment will be analysed.

An exacerbation event will be defined in the same way as outlined in Section 3.2.6. In the statistical analysis, a binary variable taking on the value 1 if a patient has experienced 1 or more exacerbations during the 28-week double-blind treatment period and 0 otherwise, will be used as the response variable.

3.2.6.2 Annual rate of asthma exacerbations

Maximum follow-up time for calculation of the annual exacerbation rate is approximately 28 weeks; defined as the time from randomisation up to and including the date of Visit 14 (EOT visit at week 28). For patients who discontinue study treatment and remain in the study after the IPD visit, exacerbations will be counted from the time of randomisation up to and including the date of Visit 14. For a patient lost to follow-up before Visit 14, the follow-up time will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed. Exacerbations that start after Visit 14 will not be included in the efficacy assessments but will be listed. If a subject misses Visit 14, then any exacerbations that start after the scheduled Visit 14 date (ie, Study Day 197) will be excluded from efficacy assessments. If an exacerbation is ongoing at Visit 14, the exacerbation will be counted in the calculation of annual exacerbation rate, however the maximum follow-up time will be truncated at the date of Visit 14, as will the duration of the exacerbation. For the production of summary statistics, the annual exacerbation rate in each treatment group will be calculated using the time-based approach.

*Annual Exacerbation Rate = 365.25*Total Number of Exacerbations / (Total duration of follow-up within the treatment group (days)).*

3.2.6.3 Annual rate of asthma exacerbations that are associated with an ER visit or a hospitalisation

The annual rate of asthma exacerbations that are associated with an ER visit or hospitalisation will be analysed. Adjudication of hospitalisations and ER visits is not planned, therefore whether or not an exacerbation is associated with hospitalisation or an ER visit will be based on information recorded by the investigator in the eCRF.

The number of asthma exacerbations associated with an ER visit or hospitalisation experienced by a patient during the 28-week treatment period and maximum follow-up time used in the calculation of this annual exacerbation rate will be derived according to the rules described in Section 3.2.6.2.

Similarly, the annual rate of asthma exacerbations that are associated with a hospitalisation only and the annual rate of asthma exacerbations that are associated with an ER visit only will also be derived.

3.2.6.4 Time to first asthma exacerbation

Time from randomisation to the first asthma exacerbation will be analysed, and is calculated as follows:

Start date of first asthma exacerbation −Date of randomisation + 1.

An exacerbation event will be defined in the same way as outlined in Section 3.2.6. The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at visit 14 for patients who complete study treatment. Patients who discontinue study treatment or are lost to follow-up before visit 14 will be censored at the last visit date after which an exacerbation could not be assessed.

Time to first asthma exacerbation associated with an ER visit or hospitalisation, a hospitalisation only, or an ER visit only (as defined in Section 3.2.6.3) will be derived following the same approach as above.

3.2.6.5 Number of days in hospital due to asthma

The total number of days in hospital due to asthma during the 28 weeks of treatment will be calculated for each patient.

3.2.7 Pre-bronchodilator forced expiratory volume in 1 second

The change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1) (L) to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. Details regarding the definition of baseline for pre-bronchodilator FEV_1 are provided in Section 2.2.3.

3.2.8 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed in approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the investigator or qualified designee according to ATS/ERS guidelines (Wanger et al 2005) according to the study schedule.

The change from baseline to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated. Baseline is defined as the last non-missing value prior to randomisation.

3.2.9 Blood eosinophil levels

The baseline blood eosinophil count used to inform primary and secondary efficacy of benralizumab is defined in Section 2.2.3.

An important marker of the biological activity of benralizumab is the depletion in eosinophils in the peripheral blood. The blood eosinophil count change from baseline and percent change from baseline to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated using conventional units (cells/µL). Baseline is defined as the last non-missing value prior to the first dose of study treatment.

3.3 Patient reported outcome variables

Asthma patient reported outcomes (PROs) include asthma control questionnaire (ACQ-6), asthma quality of life questionnaire (AQLQ(S)+12), and daily metrics (asthma symptom scores, rescue medication use, peak flow and nights with awakenings due to asthma and requiring rescue medication), and will be derived from the data collected through the ePRO device. Daily diary metrics will be recorded in the asthma daily diary each day from the evening of Visit 1 to the morning of Visit 14.

Baseline is defined as the last non-missing value before randomisation for the asthma PROs and as the average of the last 14 days before randomisation for the daily metrics, as defined in Section 2.2.3. Post-randomisation periods for the daily metrics will be defined for the calculation of bi-weekly means using the analysis-defined study windows described in section 2.2.2 and listed in Table 2.

The post-randomisation bi-weekly means for daily diary metrics are calculated as the sum of all non-missing daily measures/scores over the 14 day window divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within that window are missing, then the mean daily measure/score for that period is set to missing. The change from baseline to each post-randomisation period will be used as secondary efficacy variables. No imputations will be made for missing values.

3.3.1 Asthma symptom score

Asthma symptoms during nighttime and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale of 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), nighttime score (recorded in the morning of the next calendar day), and total score will be calculated and presented separately. The daily asthma symptom total score will be calculated by taking the sum of the daytime score recorded in the evening and the nighttime score recorded the following morning. If a patient is missing a value for either the daytime or nighttime asthma symptom score on a given day, then the total score for that day will be set to missing.

Bi-weekly mean scores and change from baseline in bi-weekly mean scores will be calculated for total asthma symptom score, daytime asthma symptom score and nighttime asthma symptom score.

3.3.2 Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and nighttime use is recorded in the morning of the next calendar day. Inhaler usage will be reported as the number of puffs in a given period, whereas nebulizer use will be reported as the number of times. Rescue medication usage will be summarised as the number of puffs with 1 instance of nebulizer use converted to 2 puffs.

The number of rescue medication inhalations and nebulizer treatments captured in the Asthma Daily Diary each day will be calculated per patient. If a patient is missing a value for either daytime or nighttime rescue medication use on a given day, then the total rescue medication use for that day will be set to missing.

Total rescue medication use (inhaler and/or nebulizer), defined as number of puffs per day will be calculated as follows:

Number of daytime inhaler puffs (recorded in the evening) + 2 x [number of daytime nebulizer times (recorded in the evening)] + number of nighttime inhaler puffs (recorded the next morning)+ 2 x [number of nighttime nebulizer times (recorded the next morning)].

Total reliever inhaler puffs per day will be calculated as:

Number of daytime inhaler puffs (recorded in the evening diary) + number of nighttime inhaler puffs (recorded in the morning diary for next calendar day)

Total nebulizer use (number of times) per day will be calculated as:

Number of daytime nebulizer times (recorded in the evening diary) + number of nighttime nebulizer times (recorded in the morning diary for next calendar day)

Bi-weekly mean rescue medication use (average puffs/day) and change from baseline in the bi-weekly mean rescue medication use will be calculated.

3.3.3 Home lung function (morning and evening peak expiratory flow)

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Patients should perform 3 successive peak flow maneuvers while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening maneuvers.

Bi-weekly means and change from baseline in bi-weekly means will be calculated for morning PEF and evening PEF.

3.3.4 Nights with awakenings due to asthma

Nighttime awakenings due to asthma symptoms and requiring rescue medication use will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response, as well as the follow-up question whether he/she used rescue medication upon awakening during the night.

The bi-weekly proportion of nights with nocturnal awakenings due to asthma and requiring rescue medication use out of the nights with non-missing nighttime awakening data and the corresponding change from baseline for each post-randomisation period will be calculated.

3.3.5 Asthma Control Questionnaire-6

The Asthma Control Questionnaire-6 (ACQ-6) is a shortened version of the ACQ that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β2 agonist use) omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall the status of their asthma during the previous week and respond to the symptom and bronchodilator use questions of the ACQ-6, on a 7-point scale. The ACQ-6 questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is computed as the mean of the responses from all the items in the questionnaire.

The questionnaire will be completed by the patients using the ePRO device every 2 weeks post-randomisation throughout the 28-week treatment period.

The outcome variable for ACQ-6 will be the change in mean score from baseline to each of the post-randomisation periods. There will be no imputation for missing values.

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorised according to the following limits (Juniper et al 2005), where end of treatment is defined as week 28 (EOT visit):

- ACQ-6 (End of treatment – baseline) ≤-0.5 → Improvement
- -0.5 < ACQ-6 (End of treatment – baseline) <0.5 → No change
- ACQ-6 (End of treatment – baseline) ≥0.5 → Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ- 6 responder variable takes value 1 if change from baseline to end of treatment in ACQ-6 ≤-0.5 and 0 otherwise. Patients with missing or non-evaluable ACQ-6 score at week 28 will be considered non-responders.

Furthermore, patients will be categorised according to their ACQ-6 defined asthma control status at the end of treatment using the following score thresholds (Juniper et al 2006):

- ACQ-6 (End of treatment) ≤0.75 → Well controlled
- 0.75< ACQ-6 (End of treatment) < 1.5 → Partly controlled
- ACQ-6 (End of treatment) ≥ 1.5 → Not well controlled
- In addition to ACQ-6, the ACQ-5 score will be calculated by omitting the question related to rescue medication use. The change in mean score from baseline to each of the post-randomisation periods will be calculated and the asthma control responder status will be derived as defined above for ACQ-6. Patients will not be categorised as well controlled, partly controlled, and not well controlled based on ACQ-5.

3.3.6 Asthma quality of life questionnaire for 12 years and older

The Standardised asthma quality of life questionnaire for 12 years and older (AQLQ[S]+12) is a questionnaire that measures the health-related quality of life experienced by asthma patients. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥0.5 are considered clinically meaningful.

The questionnaire will be completed by the patients using the ePRO device every 4 weeks post-randomisation throughout the 28-week treatment period.

The AQLQ(S)+12 score will be summarised by domain (4 domains) and overall. The outcome variable for the AQLQ(S)+12 will be the change in mean score from baseline to each of the post-randomisation periods. There will be no imputation for missing values.

Patients will also be categorised according to the following limits, where end of treatment is defined as week 28 (EOT visit):

- AQLQ(S)+12 (End of treatment – baseline) ≥0.5 → Improvement
- -0.5 < AQLQ(S)+12 (End of treatment – baseline) <0.5 → No change
- AQLQ(S)+12 (End of treatment – baseline) ≤-0.5 → Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to end of treatment in AQLQ(S)+12 ≥0.5 and 0 otherwise. Patients with missing or non-evaluable AQLQ(S)+12 data at week 28 will be considered non-responders.

3.4 Safety outcome variables

The following safety data will be collected: reported AEs (including SAEs), haematology, clinical chemistry, urinalysis, 12-lead electrocardiogram (ECG), physical examination and vital signs.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarised by means of descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates for AEs and prior/concomitant medications is detailed in Appendix A.

3.4.1 Adverse events

Adverse events experienced by the patients will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) per the Data Management Plan.

Adverse event data will be categorised according to their onset date into the following study periods:

- AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the day of the scheduled follow-up visit, inclusive.
- AEs in the on-treatment period are defined as those with onset between day of first dose of study treatment and scheduled end of treatment (EOT) visit for patients who

complete study treatment or investigational product discontinuation visit (IPD) for patients who prematurely discontinue study treatment, inclusive. In the event that the EOT or IPD visit is beyond the protocol-defined visit window, AEs with onset after the last dose of study treatment date + 28 days + 7 days (visit window) will be excluded from the on-treatment period and instead assigned to the post-treatment period.

- AEs in the post-treatment period are defined as those with onset after the on-treatment period defined above.

For instances where a patient attends the safety follow-up visit only, but does not attend an earlier IPD visit (for patients who prematurely discontinue IP) or EOT visit (for patients who complete treatment with IP), adverse events occurring on or before the last dose of study treatment + 28 days will be assigned to the on-treatment period, while AEs with onset date after this time will be assigned to the post-treatment period.

If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered an on-treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE.

3.4.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the clinical study protocol (CSP), and will be assessed in a central laboratory. The parameters outlined in Section 5.2.4, Tables 5 and 6 of the CSP will be collected.

In summaries, listings and figures, lab results and normal ranges will be presented in the International System (SI) unit. Eosinophils data will be presented in both SI and conventional units (cells/μL) in summaries.

Changes in haematology and clinical chemistry variables between baseline and each post-baseline assessment will be calculated. Baseline is defined as the last available value measured prior to the first dose of randomised treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values. For values recorded with a leading greater than or less than (‘>’, ‘<’) symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each timepoint.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the last available non-missing value prior to first dose of randomised treatment, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the post-treatment period.

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), Gamma-GT (GGT) and total bilirubin (TBL), the multiple of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point.

Multiple = Value / ULN

That is, if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Patients who meet any of the following criteria at any point during the study will be flagged:

- AST ≥ 3x ULN
- ALT ≥ 3x ULN
- TBL ≥ 2xULN

3.4.3 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature) will be obtained in accordance with schedule provided in the protocol.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last value prior to the first dose of randomised treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values.

Absolute values will be compared to the reference ranges in Table 3 and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Table 3 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120

Parameter	Standard Units	Lower Limit	Upper Limit
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38
Weight	kg	40	200

Body mass index (BMI) will be calculated from the height and weight as follows:

$$BMI\ (kg/m^2) = weight\ (kg) / (height\ (m))^2$$

3.4.4 ECGs

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in Section 4, Tables 1 and 2 of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.2.1 of the CSP. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

Each component of the baseline (Week -10) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator or designee, will be reported as an AE.

3.5 Pharmacokinetic variables

Blood samples (processed to serum) for pharmacokinetic assessments will be collected from all subjects at baseline prior to first benralizumab administration at Day 1, at multiple time points before benralizumab administrations during the treatment, and at selected timepoints during the follow-up phase of the study. Serum concentrations of benralizumab will be determined using a validated electrochemiluminescent (ECL) immunoassay.

3.6 Immunogenicity variables

Immunogenicity assessments will be collected in a similar schedule as the pharmacokinetic assessments. In addition, serum samples for ADA assessments may be collected at unscheduled visits.

These will be handled using the visit windowing described in Section 2.2.2. If the scheduled visit is missing and the unscheduled visit is within the visit window, the unscheduled visit will be included in the by-visit summaries. Assessments at both scheduled and unscheduled visits

will be included in all the summaries of ADA results across visits. The proportions of patients with ADA results will be presented together with descriptive statistics of the ADA titers.

The presence of neutralising ADA (nAb) will be tested in ADA-positive samples and the proportions of patients with nAb results will be summarised.

4. ANALYSIS METHODS

4.1 General principles

The analysis of the primary and secondary efficacy endpoints will include all data captured during the 28-week double-blind treatment period, defined as the period after randomisation at Visit 6 (Week 0) and the conclusion of Visit 14 (Week 28), inclusive. This includes data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent to study participation. The statistical analyses will compare each dosing regimen of benralizumab to placebo. The analysis of secondary safety endpoints will include all data captured during the on-study period, defined as the period after first administration of randomised investigational product at Visit 6 and the conclusion of the scheduled post-treatment follow up visit (Week 36), inclusive. Any data collected after a patient is enrolled into the long-term extension study will not be included in the analyses described in this SAP.

All analyses and presentation of data by baseline blood eosinophil count, including the primary endpoint assessed in patients with baseline blood eosinophil count ≥300/μL, will be based on the local laboratory assessment at Visit 1 as described in Section 2.2.3.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards and validation procedures. Pharmacokinetic analyses will be performed using NONMEM or other appropriate software.

Summary data will be presented in tabular format by treatment group. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarised by descriptive statistics including N, mean, SD, median, and range. All data will be listed. Data listings will be sorted by treatment group and patient number.

All hypothesis testing will be reported using 2-sided tests. All p-values will be nominal (ie, not multiplicity adjusted) and will be rounded to 3 decimal places.

Statistical models will use stratification factors based on eCRF data for country (or region if there are model convergence issues). The local laboratory blood eosinophil count used for randomisation at Visit 1 will be used for determining subgroups (≥150-299/μL, ≥300/μL, 300-450/μL and >450/μL). If the local laboratory blood eosinophil count is not available, the baseline blood eosinophil count strata entered in IVRS will be used.

The absolute change from baseline is computed as (*visit value – baseline value*). Percent change from baseline is computed as ((*visit value – baseline value*)/*baseline value*) × 100%. If either a visit value or the baseline visit value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing. Additional details regarding the definition of baseline are provided in Section 2.2.3.

For analysis where region is used as a covariate, regions will be defined as

- South and Central America: Argentina, Chile
- Eastern Europe: Poland, Ukraine
- Europe: Germany, France, Spain, Turkey
- North America: USA, Canada
- ROW: Korea

4.1.1 Testing strategy to account for multiplicity considerations

To account for multiplicity in testing the primary endpoint, percentage reduction from baseline in OCS dose for the 2 dosing regimens, a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Bel et al 2014
Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371:1189-97.

Hochberg 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the 2 p-values is less than 0.05 then reject both null hypotheses. If the larger of the 2 p-values is greater than 0.05 then proceed to Step 2.

Step 2: If the smaller of the 2 p-values is less than 0.025 then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (ie, unadjusted).

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the all patients analysis set. The number of patients will be summarised for the following groups: those who enrolled, those who entered

run-in, and those who were not randomised (and reason). The number and percentage of patients within each treatment group will be presented by the following categories: randomised, received treatment with study drug, did not receive treatment with study drug (and reason), completed treatment with study drug, discontinued treatment with study drug (and reason), discontinued treatment with study drug but completed study follow-up, completed study, and withdrawn from study (and reason).

The number of patients randomised by country and centre will be summarised by treatment group in the full analysis set.

4.2.2 Demography data and patient characteristics

Demography data such as age, gender, race, and ethnicity will be summarised by treatment group for all patients in the full analysis set and for patients in the full analysis set with baseline blood eosinophil count ≥300/μL. Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For patients in countries where date of birth is not recorded the age as recorded in the electronic case report form (eCRF) will be used.

Various baseline characteristics will also be summarised by treatment for the full analysis set. These include smoking status, medical and surgical histories, FEV_1 (pre and post bronchodilator) at baseline and respiratory disease characteristics including asthma duration, age at onset of asthma, the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalisations in the previous 12 months.

The following will be summarised for patients in the full analysis set and repeated for patients with baseline blood eosinophil count ≥300/μL:

- Patient characteristics (weight, height and BMI, local eosinophil counts). The local laboratory eosinophil count results will be from the visit used to inform randomisation (Visit 1).

- Pre-bronchodilator lung function data (FEV_1 (L), FEV_1 (% PN), FVC (L), FVC (% PN), FEV_1/FVC, FEF 25-75% (L/S)). Repeated for post-bronchodilator lung function data, including reversibility. The post-bronchodilator lung function baseline results may not be from the same visit as the pre-bronchodilator lung function results, as detailed in Section 2.2.3.

- Home lung function (morning and evening PEF)

- ACQ-6 score

- Respiratory disease characteristics

Medical and surgical histories will be summarised by MedDRA PT within MedDRA SOC.

The number of patients remaining on treatment, patients discontinued IP but still in study follow-up and patients who withdraw from the study will be presented by treatment group and scheduled visit. The number of patients who performed follow-up visits will also be provided.

4.2.3 Prior and concomitant medications

The number and percentage of patients taking maintenance asthma medications, including ICS/LABA fixed dose combinations, at baseline will be summarised and for those subjects taking ICS at baseline, the converted dose will be summarised. The number of subjects treated with ICS at baseline will be summarised by ATC code and preferred term, with total daily dose (non-converted) at baseline summarised for each preferred term.

Total daily OCS dose at screening (Visit 1), baseline (optimized dose prior to randomisation), and at the end of the study (Visit 14 at week 28) will be summarised for all patients.

The number and percentage of patients who take prior medications, those who take allowed concomitant medications and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). The summary tables will present data by generic term within ATC code.

4.2.4 Study Treatments

4.2.4.1 Exposure

Exposure to investigational product will be calculated in days as:

Last dose date of IP-first dose date of IP+1

and will be summarised by treatment group for the safety analysis set.

4.2.4.2 Compliance

Study treatment compliance will be summarised descriptively for the full analysis set and will be calculated as:

(Total doses administered/total doses expected) x 100.

4.2.5 Primary outcome variable

4.2.5.1 Primary analysis

The primary efficacy variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control, as defined in Section 3.1. Each benralizumab dose regimen will be compared with placebo.

For each of the 2 benralizumab dose regimens, the null hypothesis is that the percentage reduction from baseline in the final OCS dose while maintaining asthma control on benralizumab is equal to the percentage reduction from baseline in the final OCS dose on placebo. The alternative hypothesis is that the percentage reduction from baseline in the final

OCS dose while maintaining asthma control on benralizumab is not equal to the percentage reduction from baseline in the final OCS dose on placebo, ie,:

H_0: % reduction in OCS dose (benralizumab vs Placebo) = 0

H_a: % reduction in OCS dose (benralizumab vs Placebo) ≠ 0

For each of the 2 benralizumab dose regimen groups the percentage reduction from baseline in final OCS dose while maintaining asthma control will be compared to the placebo group using a Wilcoxon rank-sum test. The median difference in the percentage reduction of OCS dose between each benralizumab dose regimen and placebo, along with the 95% CI and p-value will be presented. In addition, the median percentage reduction in OCS dose and the corresponding 95% CI within each treatment group will be presented.

The above analyses will also be performed for patients with baseline blood eosinophil counts ≥300/μL while the multiplicity will not be adjusted for these analyses.

The percentage reduction in OCS dose will be summarised by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL separately. The percentage reduction from baseline in OCS dose will also be summarised by visit.

4.2.5.2 Sensitivity analysis

As a sensitivity analysis to the primary endpoint analysis, the analyses described in Section 4.2.5.1 will be repeated, using the definition of percentage reduction from baseline in the final OCS dose while maintaining asthma control provided in Section 3.1 that is adjusted to take into account patients who experienced an exacerbation on or after Visit 6.

4.2.6 Secondary efficacy outcome variables

All secondary efficacy outcome variables will be summarised descriptively for the FAS and also by baseline blood eosinophil count categories (≥150-299/μL, ≥300/μL, 300-450/μL, and >450/μL). Formal statistical analyses will be conducted on the FAS.

4.2.6.1 Proportion of patients with ≥50% reduction from baseline in final OCS dose

The proportion of patients with ≥50% reduction in final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country/region.

The results of the analyses will be presented using odds ratios, together with associated 95% CI and 2-sided p-value for each active dose regimen versus placebo. The number and percentage of patients with ≥50% reduction in average daily OCS dose will also be summarised by treatment group.

The above analysis will be repeated for the proportion of patients with ≥25% reduction from baseline in final OCS dose.

4.2.6.2 Proportion of patients with 100% reduction from baseline in OCS dose

The proportion of patients with 100% reduction in final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

This analysis will be repeated for the proportion of patients with 100% reduction in final OCS dose in the subset of patients who are eligible to meet this endpoint criteria based on their optimized dose at baseline, as defined in Section 3.2.2.

4.2.6.3 Proportion of patients with ≤5.0 mg reduction from baseline in OCS dose

The proportion of patients with ≤5.0 mg reduction on final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.4 Proportion of patients with final OCS dose ≤5.0 mg daily

- The proportion of patients with final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.5 Proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily.

The proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.6 Proportion of patients with ≥1 asthma exacerbation

- The proportion of patients with ≥1 asthma exacerbation during the 28 week treatment period in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using using the same method, Cochran–Mantel–Haenszel

test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.7 Annual rate of asthma exacerbations

The annual exacerbation rate in each of the 2 benralizumab dose regimen groups will be compared to the annual exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a patient, over the 28-week double-blinded treatment period. The model will include covariates of treatment group, country/region and the number of exacerbations in the previous year. The logarithm of the patient's corresponding follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and 2-sided p-value for the rate ratio will be presented. In addition, the annual exacerbation rate and the corresponding 95% CI within each treatment group and the absolute difference between treatment groups with the corresponding 95% CI will be presented.

Asthma exacerbation summary statistics will be presented based on the full analysis set by treatment group and repeated by baseline blood eosinophil count categories (≥150-299/μL, ≥300/μL, 300-450/μL, and >450/μL).

4.2.6.8 Annual rate of asthma exacerbations associated with an ER visit or hospitalisation

The annual rate of asthma exacerbations that are associated with an ER visit or hospitalisation, ER visit only, and hospitalisation only will be analysed using the same method as described in Section 4.2.6.7. In the event that a patient was seen in the emergency room and was subsequently hospitalized, only the hospitalisation is considered.

4.2.6.9 Time to first asthma exacerbation

The time to first asthma exacerbation will be analysed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the previous year. This analysis will also be repeated for the time to first asthma exacerbation associated with an ER visit or hospitalisation, ER visit only, and hospitalisation only.

Results of these analyses will be summarised as hazard ratios, 95% confidence intervals and p-values for patients in the full analysis set.

- Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot, for patients in the full analysis set and repeated by baseline blood eosinophil count categories (≥150-299/μL, ≥300/μL, 300-450/μL, and >450/μL).

4.2.6.10 Number of days in hospital due to asthma

The number of days in hospital due to asthma will be summarised by treatment group for the full analysis set. No formal statistical comparisons are planned.

4.2.6.11 Pre-bronchodilator FEV_1 (L) measured at the study centre

- Change from baseline in pre-bronchodilator FEV_1 (L) will be compared between each of the 2 benralizumab treatment groups and the placebo group using a mixed-effect model for repeated measures (MMRM) analysis on patients with a baseline pre-bronchodilator FEV_1 and at least 1 post-randomisation pre-bronchodilator FEV_1 assessment for patients in the FAS.

- The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post-baseline protocol-specified visits (up to the EOT visit).Treatment group will be fitted as the explanatory variable, country/region, visit, and treatment*visit interaction as fixed effects and baseline pre-bronchodilator FEV_1 as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

- *Change from baseline in pre-bronchodilator FEV_1=Treatment group + baseline pre-bronchodilator FEV_1 + country/region + visit + treatment*visit*

Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% confidence intervals and p-values.

4.2.6.12 Change from baseline in morning and evening PEF

- Change from baseline in morning and evening PEF will be summarised and analysed separately using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.6.13 Body plethysmography

- The change from baseline in TLC, RV, VC, IC, and FRC will be summarised by treatment group for the subset of patients who are enrolled for sputum collection. No formal statistical comparisons are planned.

4.2.6.14 Blood eosinophils

The baseline blood eosinophil count used to inform primary and secondary efficacy of benralizumab is defined in Section 2.2.3.

An important marker of the biological activity of benralizumab is the depletion in eosinophils in the peripheral blood. Absolute eosinophil counts along with their absolute changes from baseline, and percentage changes from baseline will be summarised using descriptive statistics by treatment group and visit using conventional units (cells/μL). Baseline is defined as the last non-missing value prior to the first dose of study treatment. Percent change from baseline in eosinophil counts will be compared between each benralizumab group and the placebo

group using a repeated measures analysis, as defined for analysis of pre-bronchodilator FEV_1 in Section 4.2.6.11.

4.2.7 Patient reported outcome variables

4.2.7.1 Asthma symptom score

- Change from baseline in total asthma symptom score, daytime score, and nighttime score will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.2 Rescue medication use

- Change from baseline in total rescue medication use (average puffs/day) will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.3 Home lung function (morning and evening PEF)

- Change from baseline in morning and evening PEF will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.4 Nights with awakening due to asthma

- Change from baseline in the proportion of nights with nocturnal awakenings due to asthma requiring rescue medication will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.5 Asthma Control Questionnaire (ACQ-6 score)

- Change from baseline in ACQ-6 score will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

- Asthma control responder status based on ACQ-6 at EOT (week 28), as defined in Section 3.3.5, will be analysed using a logistic regression model with covariates of treatment, country/region, and baseline value. Patients with missing or non-evaluable ACQ-6 score at week 28 will be considered non-responders.

- The number and percentage of patients achieving an improvement, no change, or deterioration, and the number and percentage of patients achieving mean ACQ-6 ≤ 0.75 (Well controlled), >0.75 - < 1.5 (Partly controlled) and ≥ 1.5 (Not well controlled) at EOT (week 28) as defined in Section 3.3.5 will be summarised by treatment group.

- The above analyses will be repeated for ACQ-5, as defined in Section 3.3.5, excluding the summary of number and percentage of patients categorised as well controlled, partially controlled, and not well controlled.

4.2.7.6 Asthma quality of life questionnaire for 12 years and older (AQLQ(S) + 12 scores)

- Change from baseline in AQLQ(S)+12 (overall and by domain) will be summarised and analysed separately using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

- Asthma control responder status based on overall AQLQ(S)+12 score at EOT (week 28), as defined in Section 3.3.6, will be analysed using a logistic regression model with covariates of treatment, country/region, and baseline value. Patients with missing or non-evaluable total AQLQ(S)+12 score at week 28 will be considered non-responders.

- The number and percentage of patients achieving an improvement, no change, or deterioration at EOT (week 28) overall and by domain, as defined in Sections 3.3.6 will be summarised by treatment group.

4.2.8 Exploratory objectives

4.2.8.1 Eosinophil progenitor cells in blood

- Blood samples will be collected at weeks 0, 4, 12, EOT and follow-up to evaluate eosinophil progenitor cells by flow cytometry in a subset of patients.

- As collection of biological samples is an integral part of this study, no separate optional consent form was used, and so it is expected that all patients will have samples available

- The results from the investigation of such samples will not be reported in the CSR and are therefore outside the scope of this analysis plan.

4.2.8.2 Sputum differential cell counts and biomarkers

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, eosinophil progenitor cells by flow cytometry, the pharmacology of benralizumab, and eosinophils recruitment, activation and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients.

The samples will be analysed by a central laboratory and sputum biomarker samples will be retained for investigation of the pharmacology of benralizumab. The results from the investigation of such samples, including sputum biomarkers will not be reported in the CSR and are therefore outside the scope of this analysis plan.

4.2.8.3 Serum biomarkers

Serum biomarker samples will be collected at weeks 0, 4, 12, EOT and follow-up. This will be done in order to evaluate the pharmacology of benralizumab as well as biomarkers of

eosinophil recruitment, activation, and survival (including periostin, IL-5, EDN, and eotaxin), and eosinophil-, basophil-, and inflammation-related biomarkers of asthma.

As collection of biological samples is an integral part of this study, no separate optional biomarker consent form was used, and so it is expected that all patients will have samples available.

Results and methodological details for any serum biomarker analyses will be reported outside of the CSR.

4.2.9 Exposure

Duration of exposure to investigational product will be calculated in days as:

Last dose date of IP-first dose date of IP+1

and will be summarised by treatment group and repeated based on baseline blood eosinophil categories (≥150-299/μL, ≥300/μL, 300-450/μL, and >450/μL), for the safety analysis set.

4.2.10 Safety outcome variables

All safety variables will be summarised using the safety analysis set and data presented according to treatment received.

4.2.10.1 Adverse events

Adverse events (AEs) will be summarised separately for the on-study, on-treatment, and post-treatment periods, as defined in Section 3.4.1. All AEs will be listed for each subject, regardless of treatment period, with AEs during the run-in/optimization phase listed separately. All summaries will be presented by treatment group.

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories; AEs, serious adverse events (SAEs), AEs with outcome of death, and AEs leading to discontinuation of investigational product (DAEs). This summary will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods. The total number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a patient).

Adverse events, AEs with outcome of death, SAEs and DAEs will be summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least 1 occurrence will be presented, ie, for a patient multiple occurrences of an AE will only be counted once. SAEs causing discontinuation of the study treatment and SAEs causing discontinuation from the study will also be summarised. Presentations for AEs and SAEs will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods, and will also include the number and percentage of patients over both benralizumab treatment groups.

The rate of AEs per person-years at risk, calculated as (number of patients reporting AE)/(total period with patients at risk of AE), will also be reported for the on-study and on-treatment periods. The total period at risk for each patient will be defined as the period from first dose of study treatment to the date of the EOT (week 28) or IPD visit for the on-treatment period and as the period from first dose of study treatment to the follow-up visit (week 36) for the on-study period. Rates will be expressed in terms of events per 100 patient-years.

A summary of the most common (frequency of >5%) AEs will be presented by PT. Adverse events, SAEs and DAEs will be summarised by preferred term and investigator's causality assessment (related vs. not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). Summaries of AEs and SAEs by investigator's causality assessment will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods.

Adverse events of injection site reactions (high level term of administration and injection site) and hypersensitivity (standard MedDRA query of hypersensitivity) will be summarised by preferred term. The summary of injection site reactions will summarised by injection site location and number of IP administrations. The summary of AEs of hypersensitivity will be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods.

Adverse events related to device malfunction will be listed. Separate listings of patients with AEs, AEs with outcome of death, SAEs, or DAEs will be presented.

Adjudicated events (MACE and malignancies) will be summarised by treatment group and listed.

4.2.10.2 Laboratory data

All continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarised in SI units, with the exception of blood eosinophil counts which will be summarised in both SI and conventional units. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum post-baseline value, as applicable for each parameter and will include patients with both baseline and post-baseline data.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced.

Data for patients who have treatment-emergent changes outside central laboratory reference ranges will be presented. This data presentation will include all visits for this subset of patients.

Maximum post-baseline bilirubin elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. Bilirubin will be presented in multiples of the following ULN ≤1.5, >1.5-2, >2, and AST and ALT will be presented in multiples of the following ULN ≤1, >1-3, >3-5, >5-10, >10.

Maximum post-baseline total bilirubin will be presented (<2 and ≥2 x ULN) and plotted against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 x ULN), expressed as multiples of ULN. This will be repeated to show maximum post-baseline total bilirubin against maximum post-baseline AST.

Data for patients with ALT or AST ≥3 x ULN, and bilirubin ≥2 x ULN will be presented, which will include all visits for this subset of patients. A line plot of liver biochemistry test results (including ALP, ALT, AST, total bilirubin, and GGT) over time will also be presented for this subset of patients.

For all patients who meet the biochemical criteria for confirmed Hy's law, a SAE Narrative will be produced.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each parameter and will include patients with both baseline and post-baseline data.

Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced.

4.2.10.3 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented for each treatment group by visit. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data.

All recorded vital signs data will be listed.

4.2.10.4 Local electrocardiograms

The Investigator's assessment of the 12-lead electrocardiograms (ECG; normal, abnormal) will be listed for all patients, detailing whether any abnormalities were clinically significant or not.

A shift table will be produced for each ECG parameter to display normal, abnormal – not clinically significant, abnormal – clinically significant and not done. The shift table will present baseline and last observation post-baseline.

4.2.10.5 Physical examination

Shift tables (normal, abnormal, not done) of baseline versus the last observation post-baseline [normal, abnormal (same as baseline), abnormal (new or aggravated), not done] will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

4.2.11 Pharmacokinetic variables

The PK analyses will be performed at or under the guidance of AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarised using descriptive statistics at each visit by treatment group, and will be listed in the CSR.

4.2.12 Immunogenicity variables

The analysis of ADA to benralizumab is documented in the Benralizumab ADA statistical analysis plan but the scope of the study ADA analysis will be modified as follows.

The demographics and patient characteristics will be presented by ADA status (positive, negative) and further by ADA positive subgroups; ADA positive with titer greater than median of maximum titer.

The ADA responses and nAb responses at any timepoint and at each specific timepoint will be summarised. ADA cumulative response will also be summarised at each timepoint. Summary of ADA titer will be presented by descriptive statistics.

Association between ADA and safety will be explored.

Due to the short study period (ie, 28 weeks), the subgroup analyses for patients who are persistently or transiently ADA positive will not be evaluated. The association between ADA and efficacy will not be evaluated either for the same reason. In addition, summaries will not be produced by baseline blood eosinophils count categories due to the limited sample size in the subgroups.

5. INTERIM ANALYSES

There is no interim analysis planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The definition of the PK analysis set was updated to ensure consistency with the definition used for other benralizumab studies. The following underlined text was added; all patients

who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations(eg, disallowed medication) and who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis set.

The protocol states that the anti-drug antibodies analysis set will be used for all ADA summaries, however the definition of the ADA analysis set is equivalent to the definition of the safety analysis set. The safety analysis set will be used for all ADA summaries.

The mean number of days with oral corticosteroids taken for exacerbations is described in the study protocol as a secondary endpoint, however this endpoint was excluded from analysis. The study design incorporates changes in OCS dose throughout the study such that the outcome of this endpoint would be difficult to interpret.

The name and description of OCS dose-related endpoints was updated to remove the term 'average'. Text is included in the SAP to address how to handle the situation when a patient is dosed every 2 days (ie, divide the dose by 2 to get the daily dose). The final OCS dose is not intended to be an average dose, therefore terminology is updated to avoid confusion.

Following discussion with the AstraZeneca patient safety physician, Other Adverse Events (OAEs) will not be defined for this study, and as such, reference to OAEs has been omitted from this SAP.

7. REFERENCES

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Appendix A Partial dates for adverse events and prior/concomitant medication

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify treatment-emergent AEs and to classify prior/concomitant medications:

Adverse events

The missing day of onset of an AE will be set to:

- First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
- The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
- The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.

The missing day of resolution of an AE will be set to:

- The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.

If the onset date of an AE is missing both the day and month, the onset date will be set to:

- January 1 of the year of onset, if the onset year is after the year of the first study treatment
- The date of the first treatment, if the onset year is the same as the year of the first study treatment
- The date of informed consent, if the onset year is before the year of the first treatment

If the resolution date of an AE or end date of a IP is missing both the day and month, the date will be set to:

- December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

The missing day of start date of a therapy will be set to the first day of the month that the event occurred.

The missing day of end date of a therapy will be set to the last day of the month of the occurrence.

If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.

If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.

If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the date of the first study visit.

If the start date of a therapy is null and the end date is a complete date

- and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
- otherwise the start date will be set to the end date of the therapy.

If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the date of the last study visit.

If the end date of a therapy is null and the start date is a complete date

- and the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit.
- otherwise, the end date will be set to the start date of the therapy.

AstraZeneca

Statistical Analysis Plan

Study Code	D3250C00020
Edition Number	3.0
Date	15 August 2016

A Multicenter, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

A Multicenter, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Study Statistician

Stephanie Sproule, MMath

16 Aug 2016
Date

A Multicenter, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Global Product Statistician

Peter Barker, PhD

16 Aug 2016
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma control questionnaire
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AQLQ(S)+12	Standardised asthma quality of life questionnaire for 12 years and older
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
AZDD	AstraZeneca drug dictionary
BDR	Blinded data review
BMI	Body mass index
CI	Confidence interval
CSP	Clinical study protocol
CSR	Clinical study report
DAE	AEs causing discontinuation of investigational product
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECL	Electrochemiluminescent
eCRF	Electronic case report form
EDN	Eosinophil-derived neurotoxin
EOT	End of treatment
ePRO	Electronic patient reported outcome
ER	Emergency room
FAS	Full analysis set
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GGT	Gamma-glutamyltransferase
IC	Inspiratory capacity

Abbreviation or special term	Explanation
ICS	Inhaled corticosteroid
IL-5	Interleukin-5
IP	Investigational product
IPD	Investigational product discontinuation
ITT	Intent to treat
IVRS	Interactive voice response system
LABA	Long-acting beta-agonist
LSMEANS	Least squares means
MACE	Major adverse cardiac events
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effects model for repeated measures
nAB	Neutralizing antibodies
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PK	Pharmacokinetic
PN	Predicted normal
PRO	Patient reported outcome
PT	Preferred term
RV	Residual volume
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SI	Standard international
SOC	System organ class
TBL	Total bilirubin
TLC	Total lung capacity
ULN	Upper limit of normal
VC	Vital capacity
WBDC	Web-based data capture

AMENDMENT HISTORY

Date	Brief description of change
29 April 2014	Initial version
8 March 2016	Amended to reflect the following (editorial updates are not listed): • General updates to study design/endpoints/analyses to align with amended protocol, including: increase in sample size and addition of eosinophil stratification factor (≥150 to <300 vs ≥300 cells/μL), update to the sample size justification, addition of secondary efficacy endpoints (proportion of patients with 100% reduction in final OCS dose, proportion of patients with ≥ 1 exacerbation, annual rate of asthma exacerbations, time to first asthma exacerbation, number of days in hospital due to asthma, home lung function (PEF) and body plethysmography). Analysis methods were aligned with the protocol. • Removal of ADA analysis set (as analyses of ADA will be conducted in the safety set). • Clarification around the process for identifying and summarizing important protocol deviations. • Updates to visit window definitions, taking into account the way in which daily diary metrics are recorded (daytime assessments recorded in the evening and nighttime assessments recorded the morning of following calendar day) and ensuring that there are no gaps in visit windows. Update to definition of study day; relative to randomisation to align with the way in which study visits are scheduled. • Clarification provided on the definition of baseline for efficacy versus safety endpoints. • Clarification on the definition of prior and concomitant medications, as well as the addition of maintenance asthma medications at baseline. Additional detail provided regarding the summary of OCS at screening and baseline. • Clarification added around the primary endpoint definition. Addition of a sensitivity analysis to address cases when OCS dose down-titration was continued after the first exacerbation post-randomization. • Addition of secondary endpoints; proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0mg daily, ACQ-5. • Analysis of ACQ-6 and AQLQ(S)+12 responders updated to evaluate patients with missing data at week 28 as non-responders. • Updated categorization of adverse events into the following study periods: on-study, on-treatment, and post-treatment. Appendix added to provide detail around the handling of partial dates for AEs and prior/concomitant medications. • Removal of analysis of other adverse events. • Added reference to the separate Statistical Analysis Plan for Benralizumab Anti-Drug Antibody data. • Added reference to define when the database lock and unblinding for the

Date	Brief description of change
	CSR will occur, after the last subject has completed the EOT or IPD visit, as per CSP amendment 2.
15 August 2016	Amended to reflect the following: • Updated list of important protocol deviations, added text regarding the detection of IP treatment deviations and assignment of actual treatment arm for safety analysis population. • Removal of requirement to convert maintenance OCS dose at baseline to prednisone/prednisolone equivalent since all patients are on prednisone/prednisolone by Visit 1. • Added clarification for the definition of final OCS dose. If a patient discontinues from the study prior to Visit 13, the final dose will be 1 step higher than the dose at the time of the withdrawal. • Added clarification that asymptotic Hodges-Lehmann estimation will be used to estimate median differences and corresponding 95% confidence intervals for the primary efficacy endpoint, percent reduction in final OCS dose from baseline. • Removal of secondary endpoint summaries by baseline blood eosinophil count categories. • Removal of annual rate of asthma exacerbations that are associated with an ER visit only and hospitalisation only and time to first asthma exacerbation associated with an ER visit only and hospitalisation only endpoints. • Updated all statistical model definitions to replace country/region with region and updated region categories to match what was done for other pivotal benra studies. • Added overall post-baseline mean score and overall change from baseline to the summary of PRO endpoints asthma symptom score, ACQ-6, ACQ-5, and AQLQ(S)+12 by visit. • Added sensitivity analysis of primary endpoint using proportion odds model for categorised percentage reduction from baseline in final OCS dose. • Added details for calculation and summary of OCS compliance. • Added summary of total corticosteroid exposure during the treatment period. • Added summary of primary endpoint by the following subgroup factors: age category (≥18-65 and ≥65 years), gender, BMI (≤35 kg/m^2, >35 kg/m^2), number of exacerbations in the previous year (1, 2, ≥3), region (Asia, Eastern Europe, Europe, European Union, North America, and rest of world), and OCS dose at baseline (≤10mg, >10mg). • Added optional sensitivity logistic regression using hybrid LOCF approach for ACQ-6 and AQLQ responder analysis if issues with missing data at end of study are observed. • Added marginal standardization method for annual asthma exacerbation rate to be done as an additional presentation to further characterize the primary analysis results. • Added shift table from baseline to maximum CTCAE grade and a summary

Date	Brief description of change
	of shift from baseline to minimum post-baseline value for certain white blood cells.

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective	Endpoint
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

1.1.2 Secondary objectives

Secondary Objectives	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

Secondary Objectives	**Endpoint**
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomisation • Annual rate of asthma exacerbations after randomisation • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalisation after randomisation • Time to the first asthma exacerbation after randomisation • Time to first exacerbation requiring hospitalisation • Time to first exacerbation requiring hospitalisation or emergency room (ER) visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and nighttime) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	Blood eosinophils

To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

1.1.3 Safety objectives

Objective	Endpoint
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

1.1.4 Exploratory objectives

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	Serum biomarkers

1.2 Study design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in 2 dosing regimens (every 4 weeks [Q4W] throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks [Q8W] thereafter) in patients with uncontrolled asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) and OCS with or without additional asthma controller(s).

The study was planned to recruit approximately 210 patients (randomised 1:1:1) with eosinophils ≥150 cells/μL, stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region. Approximately 60 patients were to be randomised into the lower eosinophil stratum (≥150 to <300 cells/μL) and approximately 150 patients were to be randomised into the higher eosinophil stratum (≥300 cells/μL). At the time recruitment was closed, a total of 220 patients were randomised, with 34 patients randomised in the lower eosinophil stratum due to slower than expected recruitment in this group.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimisation period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimised OCS dose). If the patient meets all of the criteria for OCS titration, his/her asthma will be considered stable and the patient will be eligible for further OCS dose reduction. All patients must be on either oral prednisone or prednisolone as their OCS. Patients who are on any other oral corticosteroid must switch over to an equivalent dose of either oral prednisone or prednisolone at Visit 1. Patients who meet eligibility criteria will be randomised to a 28-week treatment period, with the last dose of benralizumab/placebo administered at Week 24, and end-of-treatment (EOT) visit at Week 28.

The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimised OCS dose)
- Reduction (from Week 4 to Week 24, inclusively; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)
- Maintenance (after Week 24 until Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained).

A follow-up visit will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on investigational product (IP) for the double-blind treatment period as defined in the protocol may be eligible to enrol in the follow-on extension study (these patients will not attend the follow-up visit at Week 36).

The IP will be administered at the study centre every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomised to the 8-week regimen will receive placebo at Week 12 (Dose 4) with active drug administered at Week 16 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

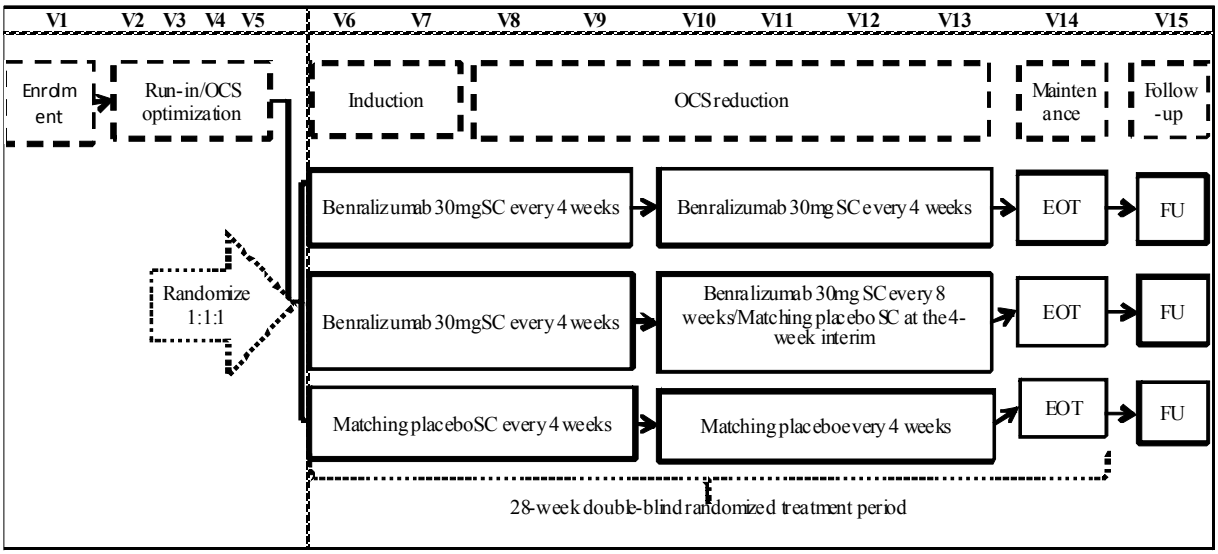
Patients will be maintained on their currently prescribed high-dose ICS/LABA therapy, without change, from enrolment throughout the run-in and treatment period.

All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation Visit (IPD) within 4 weeks (+7 days) after last IP administration. At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively

agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre one last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

See CSP Section 4, Tables 1 and 2 for a detailed list of visits and assessments.

Figure 1 Study flow chart



Database lock and unblinding for the clinical study report will occur after the last subject has completed the EOT or IPD visit. If at this time there are any patients who do not elect to continue in the separate extension study, and have yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments will be listed separately in an addendum to the clinical study report.

1.3 Number of subjects

The study was planned to recruit a total of 210 patients with blood eosinophils ≥150 cells/μL. As the targeted patient population for the pivotal studies is ≥300 cells/μL, this study will be stratified by ≥150 to <300 cells/μL and ≥300 cells/μL. The ≥150 to <300 cells/μL stratum was planned to randomise approximately 60 patients and the ≥300 cells/μL stratum was planned to randomise approximately 150 patients. For sample size estimation, 70 patients per treatment arm are required to detect a difference in percent reduction of OCS dose between each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Four patient populations are defined below: all patients analysis set, full analysis set (FAS), safety analysis set and the PK analysis set. Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation), then the patient will be excluded from all analysis sets defined below.

2.1.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

All patients randomised and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat (ITT) principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

All efficacy analyses will be performed using an ITT approach based on the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS.

2.1.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen (ie, 30 mg dose of benralizumab every 4 weeks). All safety and ADA analyses will be based on this analysis set.

2.1.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (eg, disallowed medications) and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still randomised will be analysed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Important Protocol deviations

The important protocol deviations are important in that they may affect the assessments of the true treatment effect with respect to the primary efficacy endpoint, percent reduction in final OCS dose compared with baseline while maintaining asthma control. The important protocol deviations will include but may not be limited to:

- No proof of chronic oral corticosteroid therapy for at least 6 continuous months directly preceding Visit 1.
- Optimised OCS dose not reached at least 2 weeks (± 3 days) prior to randomization.
- Clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
- Asthma control reached at an OCS dose of ≤5mg during run-in/OCS optimization phase (Visit 2 to Visit 6).
- Patients who received the incorrect study treatment or dose at any time during the 28-week double-blind treatment period
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients for whom the protocol-defined post-baseline OCS dose titration procedures were not followed and which could have impacted the final OCS dose. These deviations will be sub-categorised as:
  - Patients who experienced an asthma exacerbation after Visit 6 and were not maintained at the protocol-specified final OCS dose level after resolution of the exacerbation (ie, one dose level higher than the dose at the time the exacerbation started)
  - Patients who were down-titrated but did not meet the down-titration criteria
  - Patients who were not down-titrated but met the down-titration criteria

Only important protocol deviations will be tabulated in the CSR. Important protocol deviations will be reviewed and documented by the medical advisors and statisticians prior to unblinding.

Patients who received incorrect study treatment will be identified after database lock and unblinding. Patients will be classified according to the treatment they actually received for the safety analysis set according to the following criteria, based on the unblinded data from the IVRS system:

- Subjects assigned to the placebo group who receive one or more doses of benralizumab will be assigned to the benralizumab q.8 weeks group, unless they received 2 or more consecutive doses of benralizumab after week 8, in which case they will be assigned to the benralizumab q.4 weeks group.

- Subjects assigned to either benralizumab treatment regimen who receive only placebo will be assigned to the placebo group.

- Subjects assigned to the placebo or benralizumab q.8 weeks group who receive 2 or more consecutive doses of benralizumab after week 8 will be assigned to the benralizumab q.4 weeks group.

Subjects for whom a significant protocol deviation was recorded that impacts the interpretation of the study safety outcomes will have a footnote added to applicable output to describe the deviation and its potential impact. Such subjects will be identified as part of the protocol deviation review process, prior to database lock.

2.2.2 Visit window definitions

For the OCS dose reduction and exacerbation-related analyses, no windows will be applied. For local laboratory, local ECG and all vital signs, the visit recorded in web-based data capture (WBDC) will be used. For endpoints that present visit-based data, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. No visit windows will be defined for enrolment and run-in/optimization phase visits.

The adjusted analysis-defined windows for assessments conducted every 4 weeks are summarised in Table 1, applicable to assessments conducted on or following randomization (Visit 6).

Table 1 Visit windows for assessments conducted every 4 weeks

Adjusted defined windows visit	Scheduled Study Day	Maximum windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤Study Days≤42
Week 8	57	43 ≤Study Days≤70
Week 12	85	71 ≤Study Days≤98
Week 16	113	99 ≤Study Days≤126
Week 20	141	127 ≤Study Days≤154
Week 24	169	155≤Study Days≤182

Table 1 Visit windows for assessments conducted every 4 weeks

Adjusted defined windows visit	Scheduled Study Day	Maximum windows
Week 28	197	183≤Study Days≤224
Week 36 (Follow-up)	253	225≤Study Days

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as follows:

(Date of assessment–date of randomisation)+1

By this definition, the day of randomisation will be study day 1 and the planned date of Visit 8 (Week 4) will be Study Day 29 (=28+1), for example.

If multiple assessments are recorded within a single adjusted visit window, please refer to the rules below.

- If there are 2 or more observations within the same visit window, then the non-missing 1 closest to the scheduled visit will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing 1 with the earlier collection time will be included in the analysis.

For patient reported outcomes collected twice daily, if 2 observations are collected on the same day during the same period (ie, am or pm) then the non-missing observation with the earlier collection time during the period will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

For endpoints which are not collected every 4 weeks, such as ACQ-6 which is assessed every 2 weeks, the above rules will be applied to derive adjusted analysis defined visit windows based on the protocol-defined visit schedule for that endpoint.

For pre-bronchodilator FEV_1 (L), the non-missing value with acceptable quality (acceptable or borderline quality grade) which is closest to the scheduled visit will be included in the analysis.

For daily diary and home PEF assessments, bi-weekly means will be calculated using daily diary entries between the scheduled study days contained in Table 2. As above, study days are relative to day of randomization (Visit 6). For daily diary assessments of rescue medication use and asthma symptom scores, the daytime measurement is captured in the evening and the nighttime measurement is captured the following morning. Nighttime awakenings are captured the following morning.

Table 2 Bi-weekly windows for daily diary and home PEF assessments

Adjusted defined windows visit	Scheduled Study Day	Maximum windows
Baseline	1	The last 14 days from evening of Study Day -14 to the morning of Study Day 1
Week 2	15	Evening of Study Day 1 to the morning of Study Day 15
Week 4	29	Evening of Study Day 15 to the morning of Study Day 29
Week 6	43	Evening of Study Day 29 to the morning of Study Day 43
Week 8	57	Evening of Study Day 43 to the morning of Study Day 57
Week 10	71	Evening of Study Day 57 to the morning of Study Day 71
Week 12	85	Evening of Study Day 71 to the morning of Study Day 85
Week 14	99	Evening of Study Day 85 to the morning of Study Day 99
Week 16	113	Evening of Study Day 99 to the morning of Study Day 113
Week 18	127	Evening of Study Day 113 to the morning of Study Day 127
Week 20	141	Evening of Study Day 127 to the morning of Study Day 141
Week 22	155	Evening of Study Day 141 to the morning of Study Day 155
Week 24	169	Evening of Study Day 155 to the morning of Study Day 169
Week 26	183	Evening of Study Day 169 to the morning of Study Day 183
Week 28	197	Evening of Study Day 183 to the morning of Study Day 197

For overall analyses not based on any particular study visit, all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For safety endpoints, all post-baseline results will be included in the overall analysis up to and including the follow-up visit. For efficacy endpoints, the post-baseline treatment period will be included up to and including the end of treatment (EOT) visit.

2.2.3 The definition of baseline

In general, the last recorded value on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints while the last recorded value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints. If there is no value prior to randomisation (or the first dose of study treatment, depending on the endpoint), then the baseline value will not be imputed and will be set to missing. No data known to be collected post first dose will be used in determining the baseline value, unless otherwise specified.

For categorical (yes/no) baseline respiratory disease characteristics, if ‘yes’ is indicated in any visit during enrollment or the run-in/OCS optimization phase (scheduled or unscheduled), ‘yes’ will be used.

The baseline OCS dose is defined as the dose upon which the patient is stabilised at randomisation.

For pre-bronchodilator FEV_1 (L), the last non-missing value with acceptable quality (acceptable or borderline quality grade) on or prior to the date of randomisation will be used as baseline. For post-bronchodilator spirometry assessments (including reversibility), the last non-missing value with acceptable or borderline quality on or prior to the date of randomisation will be used as baseline. It is expected that due to the planned visit schedule, the pre- and post-bronchodilator baseline assessments will not be from the same visit.

For asthma daily diary metrics and home PEF, baseline is defined as the mean from the last 14 days prior to the date of randomisation and will be derived from data collected on the evening of Study Day -14 to the morning of Study Day 1. The mean is calculated as the sum of all non-missing daily measures/scores over the 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within the baseline period are missing, then baseline is set to missing.

For summaries of central laboratory results by visit and in the calculation of change from baseline, the last non-missing result from the central laboratory prior to first dose of study treatment will be used as baseline.

For all data summaries and analyses by baseline blood eosinophil count strata (≥150 to <300/μL or ≥300/μL) or by baseline blood eosinophil count category (≥150-299/μL, 300-450/μL, >450/μL), the blood eosinophil count result from the local laboratory that was used to randomise the patient (ie, Visit 1) will be used. If the local laboratory result is not available, then the strata recorded in the IVRS system will be used to classify subjects into baseline blood eosinophil count stratum (≥150 to <300/μL or ≥300/μL) and the other baseline blood eosinophil count categories will be set to missing.

2.2.4 Prior/concomitant medications

A medication will be classified as a maintenance asthma medication at baseline if it started prior to or on the date of randomisation and was ongoing after randomisation. Maintenance asthma medications with a stop date on the day of randomisation will be considered as prior medications. Inhaled corticosteroid (ICS) doses will be converted to their Fluticasone Propionate dry powder equivalent in micrograms. Oral corticosteroid (OCS) doses will not be converted since all patients will have been switched to prednisone/prednisolone prior to starting the optimization phase at Visit 1, with the exception of OCS other than prednisone/prednisolone taken as a result of an adverse event or asthma exacerbation.

A medication will be regarded as prior if it was stopped on or before the date of randomisation (medication stop date ≤date of randomisation).

A medication will be regarded as concomitant if the start date is after the date of randomisation, or if it started on or prior to the date of randomisation and was ongoing after

the date of randomisation. Medications with start date after the on-treatment period (as defined for adverse events in Section 3.4.1) will not be considered as concomitant.

3. PRIMARY AND SECONDARY VARIABLES

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomised IP at Week 0 (Visit 6) and the conclusion of Week 28 (Visit 14), inclusive.

3.1 Primary outcome variable

The primary variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The OCS dose titration schedule during the reduction phase (Visits 8 to 13) is presented in Table 4 of the clinical study protocol.

The baseline OCS dose is defined as the dose upon which the patient is stabilised at randomisation (Week 0). Unless otherwise stated below, the final dose is generally defined as the dose at Week 28. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

If a patient discontinues from the study during a given dose reduction period prior to Visit 14 then the patient's final OCS dose will be defined as 1 dose level higher than the dose at which the discontinuation occurred. For example, suppose a patient had completed a previous dose reduction phase while receiving 10mg daily and was now in a subsequent dose reduction period receiving 5mg daily but withdrew before completing that period. In this case, the patient's final dose level would be defined as 10mg daily because the patient had not completed the period in which 5mg was used. If a patient experiences an asthma exacerbation immediately prior to discontinuation, the final OCS dose will be 1 dose level higher than the dose at which the exacerbation started.

Note that during Weeks 24-28 (between Visits 13 and 14), the patients will be on a maintenance dose of OCS, that is, no reduction will be attempted. Should a patient's asthma deteriorate during that time to the point that the patient requires an increase in the daily dose of OCS during the maintenance period, or if the patient experiences an asthma exacerbation, the final dose will be deemed as 1 dose level higher than the dose at which the asthma exacerbation or deterioration started. Any increase in the daily dose of OCS that is not associated with an exacerbation will be treated as an asthma deterioration for analysis purposes, regardless of whether the reason for treatment was due to an AE that is unrelated to the patient's asthma.

Should a patient be placed on an every other day regimen of OCS, their final dose will be defined as the average daily dose. For example, if a patient is placed on a regimen of 5mg every other day, their final dose is defined as 2.5mg/day.

Following review of blinded preliminary data from the study database, instances were identified of patients who recorded an exacerbation following randomisation, but for whom, contrary to the process outlined in the protocol, the site appeared to continue down-titration of the OCS dose following the exacerbation. As a sensitivity assessment of the primary endpoint, percent reduction from baseline in OCS dose will also be calculated as follows:

For patients with no exacerbations recorded following Visit 6, the primary endpoint will be derived as outlined above. For those patients who do record an exacerbation on or after Visit 6, the final OCS dose used in the percent reduction from baseline calculation will be the OCS dose 1 step higher than the dose at which their first exacerbation started. Sensitivity analyses using this derivation of the percent reduction in OCS dose will be considered, following the same methods outlined for the primary endpoint.

The percentage reduction from baseline in final OCS dose, using the primary definition of final OCS dose, will also be derived for each scheduled post-baseline visit and is defined as follows:

*{(Baseline dose–dose at post-baseline visit)/baseline dose}*100%*

The percentage reduction from baseline in OCS dose, using the primary definition of final OCS dose, will be categorised as follows:

- 90 – 100% reduction
- 75 - <90% reduction
- 50 - <75% reduction
- >0 - <50% reduction
- No change or any increase

The total corticosteroid exposure over the treatment period will be calculated as the total daily dose, regardless of route or reason for administration, summed over the period from baseline to Week 28 (the end of the on-treatment period).

3.2 Secondary efficacy outcome variables

3.2.1 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the percent reduction from baseline in the final OCS dose while maintaining asthma control (Section 3.1), based on the primary definition, results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in OCS dose. Patients with missing values will be considered as not having had a reduction. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

Similarly, the proportion of patients with ≥25% reduction from baseline in the final OCS dose will also be derived.

3.2.2 Proportion of patients with 100% reduction from baseline in oral corticosteroid dose

For an individual patient, if the percent reduction from baseline in the final OCS dose while maintaining asthma control (Section 3.1), based on the primary definition, results in a value of 100% (ie, final dose is 0mg), that patient will be classified as having a 100% reduction in OCS dose. Patients with missing values will be considered as not having had a reduction. The proportion of such patients will be calculated for each treatment group as:

Number of patients with 100% reduction at final visit/number of patients in treatment group

Whether or not a patient can achieve a 100% reduction from baseline in OCS dose will depend on their optimised dose at baseline, such that patients with an OCS dose > 12.5mg/day at baseline will not be able to achieve a final OCS dose of 0 mg according to the protocol-defined dose titration schedule (refer to Table 4 of the clinical study protocol). As a sensitivity analysis, the proportion of patients with 100% reduction from baseline in OCS dose will also be calculated using the number of patients with optimized OCS dose ≤12.5 mg/day at baseline as the denominator (ie, patients eligible to meet this endpoint criteria).

3.2.3 Proportion of patients with ≤5.0 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5.0 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5.0 mg reduction at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.4 Proportion of patients with final OCS dose ≤5.0 mg daily

For each treatment group, the number of patients with final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with final OCS dose ≤5.0 mg daily at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.5 Proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily.

For each treatment group, the number of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥25% reduction from baseline and final OCS dose ≤5.0 mg daily at final visit / number of patients in treatment group

Details for determination of the final OCS dose are provided in Section 3.1.

3.2.6 Asthma exacerbations

An asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step) for at least 3 days to treat symptoms of asthma worsening,
- an emergency room (ER) visit due to asthma that required systemic corticosteroids, or
- an inpatient hospitalisation due to asthma.

In order to calculate the number of exacerbations experienced by a patient during the 28-week treatment period the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of an increased OCS dose that is used to treat an exacerbation, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of an increased OCS dose that is used to treat an exacerbation or the date of discharge from a hospital, whichever occurs later. In the primary analysis, the number of exacerbations observed for a patient during the 28-week double-blind treatment period will be used as response variable.

If the patient is not fulfilling criteria for down titration listed in Section 5.1.1.1 of the CSP and needs to be up-titrated, the patient should be titrated by 1 level and this up titration should not be considered the start of an exacerbation.

An additional bolus/burst of systemic corticosteroid, ER visit requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation, it must be preceded by at least 7 days in which neither criterion is fulfilled.

3.2.6.1 Proportion of patients with at least 1 exacerbation during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment will be analysed.

An exacerbation event will be defined in the same way as outlined in Section 3.2.6. In the statistical analysis, a binary variable taking on the value 1 if a patient has experienced 1 or more exacerbations during the 28-week double-blind treatment period and 0 otherwise, will be used as the response variable.

3.2.6.2 Annual rate of asthma exacerbations

Maximum follow-up time for calculation of the annual exacerbation rate is approximately 28 weeks; defined as the time from randomisation up to and including the date of Visit 14 (EOT visit at week 28). For patients who discontinue study treatment and remain in the study after the IPD visit, exacerbations will be counted from the time of randomisation up to and including the date of Visit 14. For a patient lost to follow-up before Visit 14, the follow-up time will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed. Exacerbations that start after Visit 14 will not be included in the efficacy assessments but will be listed. If a subject misses Visit 14, then any exacerbations that start after the scheduled Visit 14 date (ie, Study Day 197) will be excluded from efficacy assessments. If an exacerbation is ongoing at Visit 14, the exacerbation will be counted in the calculation of annual exacerbation rate; however, the maximum follow-up time will be truncated at the date of Visit 14, as will the duration of the exacerbation. For the production of summary statistics, the annual exacerbation rate in each treatment group will be calculated using the time-based approach.

*Annual Exacerbation Rate = 365.25*Total Number of Exacerbations / (Total duration of follow-up within the treatment group (days)).*

3.2.6.3 Annual rate of asthma exacerbations that are associated with an ER visit or a hospitalisation

The annual rate of asthma exacerbations that are associated with an ER visit or hospitalisation will be analysed. Adjudication of hospitalisations and ER visits is not planned; therefore, whether or not an exacerbation is associated with hospitalisation or an ER visit will be based on information recorded by the Investigator in the eCRF.

The number of asthma exacerbations associated with an ER visit or hospitalisation experienced by a patient during the 28-week treatment period and maximum follow-up time used in the calculation of this annual exacerbation rate will be derived according to the rules described in Section 3.2.6.2.

3.2.6.4 Time to first asthma exacerbation

Time from randomisation to the first asthma exacerbation will be analysed and is calculated as follows:

Start date of first asthma exacerbation −Date of randomization+1.

An exacerbation event will be defined in the same way as outlined in Section 3.2.6. The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at Visit 14 for patients who complete study treatment. Patients who discontinue study treatment or are lost to follow-up before Visit 14 will be censored at the last visit date after which an exacerbation could not be assessed.

Time to first asthma exacerbation associated with an ER visit or hospitalisation (as defined in Section 3.2.6.3) will be derived following the same approach as above.

3.2.6.5 Number of days in hospital due to asthma

The total number of days in hospital due to asthma during the 28 weeks of treatment will be calculated for each patient.

3.2.7 Pre-bronchodilator forced expiratory volume in 1 second (FEV_1)

The change from baseline in pre-bronchodilator FEV_1 (L) to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. Details regarding the definition of baseline for pre-bronchodilator FEV_1 are provided in Section 2.2.3.

3.2.8 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed in approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the Investigator or qualified designee according to ATS/ERS guidelines (Wanger et al 2005) according to the study schedule.

The change from baseline to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated. Baseline is defined as the last non-missing value prior to randomisation.

3.2.9 Blood eosinophil levels

The baseline blood eosinophil count used to inform primary and secondary efficacy of benralizumab is defined in Section 2.2.3.

An important marker of the biological activity of benralizumab is the depletion in eosinophils in the peripheral blood. The blood eosinophil count change from baseline and percent change from baseline to each of the post-randomisation visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated using conventional

units (cells/µL). Baseline is defined as the last non-missing value prior to the first dose of study treatment.

3.3 Patient reported outcome variables

Asthma patient reported outcomes (PROs) include asthma control questionnaire (ACQ-6), asthma quality of life questionnaire (AQLQ(S)+12), and daily metrics (asthma symptom scores, rescue medication use, peak flow and nights with awakenings due to asthma and requiring rescue medication), and will be derived from the data collected through the ePRO device. Daily diary metrics will be recorded in the asthma daily diary each day from the evening of Visit 1 to the morning of Visit 14.

Baseline is defined as the last non-missing value before randomisation for the non-daily asthma PROs and as the average of the last 14 days before randomisation for the daily metrics, as defined in Section 2.2.3. Post-randomisation periods for the daily metrics will be defined for the calculation of bi-weekly means using the analysis-defined study windows described in Section 2.2.2 and listed in Table 2.

The post-randomisation bi-weekly means for daily diary metrics are calculated as the sum of all non-missing daily measures/scores over the 14 day window divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within that window are missing, then the mean daily measure/score for that period is set to missing. The change from baseline to each post-randomisation period will be used as secondary efficacy variables. No imputations will be made for missing values.

3.3.1 Asthma symptom score

Asthma symptoms during nighttime and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale of 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), nighttime score (recorded in the morning of the next calendar day), and total score will be calculated and presented separately. The daily asthma symptom total score will be calculated by taking the sum of the daytime score recorded in the evening and the nighttime score recorded the following morning. If a patient is missing a value for either the daytime or nighttime asthma symptom score on a given day, then the total score for that day will be set to missing.

Bi-weekly mean scores and change from baseline in bi-weekly mean scores will be calculated for total asthma symptom score, daytime asthma symptom score and nighttime asthma symptom score. Additionally, the overall post-baseline score and overall change from baseline will be evaluated for the total asthma symptom score, with the overall mean defined as the mean across all post-baseline visits for each patient.

3.3.2 Rescue medication use

The number of rescue medication inhalations and nebuliser treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and nighttime use is recorded in the morning of the next calendar day. Inhaler usage will be

reported as the number of puffs in a given period, whereas nebuliser use will be reported as the number of times. Rescue medication usage will be summarised as the number of puffs with 1 instance of nebuliser use converted to 2 puffs.

The number of rescue medication inhalations and nebuliser treatments captured in the Asthma Daily Diary each day will be calculated per patient. If a patient is missing a value for either daytime or nighttime rescue medication use on a given day, then the total rescue medication use for that day will be set to missing.

Total rescue medication use (inhaler and/or nebuliser), defined as number of puffs per day will be calculated as follows:

Number of daytime inhaler puffs (recorded in the evening)+2x [number of daytime nebuliser times (recorded in the evening)] +number of nighttime inhaler puffs (recorded the next morning)+ 2x [number of nighttime nebuliser times (recorded the next morning)].

Total reliever inhaler puffs per day will be calculated as:

Number of daytime inhaler puffs (recorded in the evening diary)+number of nighttime inhaler puffs (recorded in the morning diary for next calendar day)

Total nebuliser use (number of times) per day will be calculated as:

Number of daytime nebuliser times (recorded in the evening diary)+number of nighttime nebuliser times (recorded in the morning diary for next calendar day)

Bi-weekly mean rescue medication use (average puffs/day) and change from baseline in the bi-weekly mean rescue medication use will be calculated.

3.3.3 Home lung function (morning and evening PEF)

Home PEF testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Patients should perform 3 successive peak flow maneuvers while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening maneuvers.

Bi-weekly means and change from baseline in bi-weekly means will be calculated for morning PEF and evening PEF.

3.3.4 Nights with awakenings due to asthma

Nighttime awakenings due to asthma symptoms and requiring rescue medication use will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response, as well as the follow-up question whether he/she used rescue medication upon awakening during the night.

The bi-weekly proportion of nights with nocturnal awakenings due to asthma and requiring rescue medication use out of the nights with non-missing nighttime awakening data and the corresponding change from baseline for each post-randomisation period will be calculated.

3.3.5 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β2 agonist use) omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall the status of their asthma during the previous week and respond to the symptom and bronchodilator use questions of the ACQ-6, on a 7-point scale. The ACQ-6 questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is computed as the mean of the responses from all the items in the questionnaire.

The questionnaire will be completed by the patients using the ePRO device every 2 weeks post-randomisation throughout the 28-week treatment period.

The outcome variable for ACQ-6 will be the change in mean score from baseline to each of the post-randomisation periods. There will be no imputation for missing values. Additionally, the overall post-baseline mean score and overall change from baseline will be calculated, with the overall mean defined as the mean across all post-baseline visits for each patient.

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorised according to the following limits (Juniper et al 2005), where end of treatment is defined as Week 28 (EOT visit):

ACQ-6 (End of treatment–baseline) $\leq$-0.5 $\rightarrow$ Improvement

-0.5 < ACQ-6 (End of treatment–baseline) <0.5 $\rightarrow$ No change

ACQ-6 (End of treatment–baseline) $\geq$0.5 $\rightarrow$ Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ- 6 responder variable takes value 1 if change from baseline to end of treatment in ACQ-6 $\leq$-0.5 and 0 otherwise. Patients with missing or non-evaluable ACQ-6 score at Week 28 will be considered non-responders.

Furthermore, patients will be categorised according to their ACQ-6 defined asthma control status at the end of treatment using the following score thresholds (Juniper et al 2006):

ACQ-6 (End of treatment) $\leq$0.75 $\rightarrow$ Well controlled

0.75<ACQ-6 (End of treatment) < 1.5 $\rightarrow$ Partly controlled

ACQ-6 (End of treatment) ≥1.5 → Not well controlled

In addition to ACQ-6, the ACQ-5 score will be calculated by omitting the question related to rescue medication use. The change in mean score from baseline to each of the post-randomisation periods will be calculated and the asthma control responder status will be derived as defined above for ACQ-6. Patients will not be categorised as well controlled, partly controlled, and not well controlled based on ACQ-5.

3.3.6 Asthma quality of life questionnaire for 12 years and older (AQLQ(S) + 12)

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma patients. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥0.5 are considered clinically meaningful.

The questionnaire will be completed by the patients using the ePRO device every 4 weeks post-randomisation throughout the 28-week treatment period.

The AQLQ(S)+12 score will be summarised by domain (4 domains) and overall. The outcome variable for the AQLQ(S)+12 will be the change in mean score from baseline to each of the post-randomisation periods. There will be no imputation for missing values. Additionally, the overall post-baseline mean score and overall change from baseline will be calculated, with the overall mean defined as the mean across all post-baseline visits for each patient.

Patients will also be categorised according to the following limits, where end of treatment is defined as week 28 (EOT visit):

AQLQ(S)+12 (End of treatment–baseline) ≥0.5 → Improvement

-0.5 < AQLQ(S)+12 (End of treatment–baseline) <0.5 → No change

AQLQ(S)+12 (End of treatment–baseline) ≤-0.5 → Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to end of treatment in AQLQ(S)+12 ≥0.5 and 0 otherwise. Patients with missing or non-evaluable AQLQ(S)+12 data at week 28 will be considered non-responders.

3.4 Safety outcome variables

The following safety data will be collected: reported AEs (including SAEs), haematology, clinical chemistry, urinalysis, 12-lead electrocardiogram (ECG), physical examination, and vital signs.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarised by means of descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates for AEs and prior/concomitant medications is detailed in Appendix A.

3.4.1 Adverse events

Adverse events (AEs) experienced by the patients will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) per the Data Management Plan.

Adverse event data will be categorised according to their onset date into the following study periods:

- Adverse events in the on-study period are defined as those with onset between day of first dose of study treatment and the day of the scheduled follow-up visit, inclusive.
- Adverse events in the on-treatment period are defined as those with onset between day of first dose of study treatment and scheduled end of treatment (EOT) visit for patients who complete study treatment or investigational product discontinuation visit (IPD) for patients who prematurely discontinue study treatment, inclusive. In the event that the EOT or IPD visit is beyond the protocol-defined visit window, AEs with onset after the last dose of study treatment date + 28 days + 7 days (visit window) will be excluded from the on-treatment period and instead assigned to the post-treatment period.
- Adverse events in the post-treatment period are defined as those with onset after the on-treatment period defined above.

For instances where a patient attends the safety follow-up visit only, but does not attend an earlier IPD visit (for patients who prematurely discontinue IP) or EOT visit (for patients who complete treatment with IP), AEs occurring on or after the day of first dose of study treatment and on or before the last dose of study treatment + 28 days will be assigned to the on-treatment period, while AEs with onset date after this time will be assigned to the post-treatment period.

If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered an on-treatment event. Similarly, if an AE has a partial onset date, then

unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE.

3.4.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the clinical study protocol (CSP), and will be assessed in a central laboratory. The parameters outlined in Section 5.2.4, Tables 5 and 6 of the CSP will be collected.

In summaries, listings and figures, lab results and normal ranges will be presented in the International System (SI) unit. Eosinophils data will be presented in both SI and conventional units (cells/µL) in summaries.

Changes in haematology and clinical chemistry variables between baseline and each post-baseline assessment will be calculated. Baseline is defined as the last available value measured prior to the first dose of randomised treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values. For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each timepoint.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the last available non-missing value prior to first dose of randomised treatment, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the post-treatment period.

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), Gamma-GT (GGT) and total bilirubin (TBL), the multiple of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point.

Multiple=Value / ULN

That is, if the ALT value was 72 IU/L (ULN 36), then the multiple would be 2.

Patients who meet any of the following criteria at any point during the study will be flagged:

- AST ≥3x ULN
- ALT ≥3x ULN
- TBL ≥2xULN

3.4.3 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature) will be obtained in accordance with schedule provided in the protocol.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last value prior to the first dose of randomised treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values.

Absolute values will be compared to the reference ranges in Table 3 and classified as low (below range), normal (within range or on limits), or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Table 3 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38
Weight	kg	40	200

Body mass index (BMI) will be calculated from the height and weight as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / (\text{height (m)})^2$$

3.4.4 ECGs

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in Section 4, Tables 1 and 2 of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.2.1 of the CSP. For

the brief physical examination only information on whether the assessment was performed or not is to be recorded.

Each component of the baseline (Week -10) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator or designee, will be reported as an AE.

3.5 Pharmacokinetic variables

Blood samples (processed to serum) for pharmacokinetic assessments will be collected from all subjects at baseline prior to first benralizumab administration at Day 1, at multiple time points before benralizumab administrations during the treatment, and at selected timepoints during the follow-up phase of the study. Serum concentrations of benralizumab will be determined using a validated electrochemiluminescent (ECL) immunoassay.

3.6 Immunogenicity variables

Immunogenicity assessments will be collected in a similar schedule as the pharmacokinetic assessments. In addition, serum samples for ADA assessments may be collected at unscheduled visits.

These will be handled using the visit windowing described in Section 2.2.2. If the scheduled visit is missing and the unscheduled visit is within the visit window, the unscheduled visit will be included in the by-visit summaries. Assessments at both scheduled and unscheduled visits will be included in all the summaries of ADA results across visits. The proportions of patients with ADA results will be presented together with descriptive statistics of the ADA titers.

The presence of neutralizing ADA (nAb) will be tested in ADA-positive samples and the proportions of patients with nAb results will be summarised.

4. ANALYSIS METHODS

4.1 General principles

The analysis of the primary and secondary efficacy endpoints will include all data captured during the 28-week double-blind treatment period, defined as the period after randomisation at Visit 6 (Week 0) and the conclusion of Visit 14 (Week 28), inclusive. This includes data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent to study participation. The statistical analyses will compare each dosing regimen of benralizumab to placebo. The analysis of secondary safety endpoints will include all data captured during the on-study period, defined as the period after first administration of randomised IP at Visit 6 and the conclusion of the scheduled post-treatment follow up visit (Week 36), inclusive. Any data

collected after a patient is enrolled into the long-term extension study will not be included in the analyses described in this SAP.

All analyses and presentation of data by baseline blood eosinophil count, including the primary endpoint assessed in patients with baseline blood eosinophil count ≥300/μL, will be based on the local laboratory assessment at Visit 1 as described in Section 2.2.3.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards and validation procedures. Pharmacokinetic analyses will be performed using NONMEM or other appropriate software.

Summary data will be presented in tabular format by treatment group. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarised by descriptive statistics including N, mean, SD, median, and range. All data will be listed. Data listings will be sorted by treatment group and patient number.

All hypothesis testing will be reported using 2-sided tests. All p-values will be nominal (ie, not multiplicity adjusted) and will be rounded to 3 decimal places.

Statistical models will use stratification factors based on eCRF data for region. The local laboratory blood eosinophil count used for randomisation at Visit 1 will be used for determining subgroups (≥150-299/μL, ≥300/μL, 300-450/μL and >450/μL). If the local laboratory blood eosinophil count is not available, the baseline blood eosinophil count strata entered in IVRS will be used.

The absolute change from baseline is computed as (*visit value–baseline value*). Percent change from baseline is computed as ([*visit value–baseline value*]/*baseline value*)×100%. If either a visit value or the baseline visit value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing. Additional details regarding the definition of baseline are provided in Section 2.2.3.

For analysis where region is used as a covariate, regions will be defined as:

- Asia: Korea
- Eastern Europe: Poland, Ukraine
- Europe: Germany, France, Spain, Turkey
- North America: USA, Canada
- ROW: Argentina, Chile

4.1.1 Testing strategy to account for multiplicity considerations

To account for multiplicity in testing the primary endpoint, percentage reduction from baseline in OCS dose for the 2 dosing regimens, a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Hochberg 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the 2 p-values is less than 0.05 then reject both null hypotheses. If the larger of the 2 p-values is greater than 0.05 then proceed to Step 2.

Step 2: If the smaller of the 2 p-values is less than 0.025 then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (ie, unadjusted).

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the all patients analysis set. The number of patients will be summarised for the following groups: those who enrolled, those who entered run-in, and those who were not randomised (and reason). The number and percentage of patients within each treatment group will be presented by the following categories: randomised, received treatment with study drug, did not receive treatment with study drug (and reason), completed treatment with study drug, discontinued treatment with study drug (and reason), discontinued treatment with study drug but completed study follow-up, completed study, and withdrawn from study (and reason).

The number of patients randomised by country and centre will be summarised by treatment group in the full analysis set.

4.2.2 Demography data and patient characteristics

Demography data such as age, gender, race, and ethnicity will be summarised by treatment group for all patients in the full analysis set and for patients in the full analysis set with baseline blood eosinophil count ≥300/μL. Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For patients in countries where date of birth is not recorded the age as recorded in the electronic case report form (eCRF) will be used.

Various baseline characteristics will also be summarised by treatment for the full analysis set. These include smoking status, medical and surgical histories, FEV_1 (pre and post bronchodilator) at baseline and respiratory disease characteristics including asthma duration,

age at onset of asthma, the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalisations in the previous 12 months.

The following will be summarised for patients in the full analysis set and repeated for patients with baseline blood eosinophil count ≥300/μL:

- Patient characteristics (weight, height and BMI, local eosinophil counts). The local laboratory eosinophil count results will be from the visit used to inform randomisation (Visit 1).
- Pre-bronchodilator lung function data (FEV_1 (L), FEV_1 (% PN), FVC (L), FVC (% PN), FEV_1/FVC, FEF 25-75% (L/S)). Repeated for post-bronchodilator lung function data, including reversibility. The post-bronchodilator lung function baseline results may not be from the same visit as the pre-bronchodilator lung function results, as detailed in Section 2.2.3.
- Home lung function (morning and evening PEF)
- ACQ-6 score
- Respiratory disease characteristics

Medical and surgical histories will be summarised by MedDRA PT within MedDRA SOC. Cardiovascular medical and surgical history, as collected on the CRF, will be summarised separately.

The number of patients remaining on treatment, patients discontinued IP but still in study follow-up and patients who withdraw from the study will be presented by treatment group and scheduled visit. The number of patients who performed follow-up visits will also be provided.

4.2.3 Prior and concomitant medications

The number and percentage of patients taking maintenance asthma medications, including ICS/LABA fixed dose combinations, at baseline will be summarised, and for those subjects taking ICS at baseline, the converted dose will be summarised. The number of subjects treated with ICS at baseline will be summarised by ATC code and preferred term (PT), with total daily dose (non-converted) at baseline summarised for each PT.

Total daily OCS dose at study entry (Visit 1) and baseline (optimised dose prior to randomisation) will be summarised for all patients. Given that all patients were required to be on or switch to prednisone/prednisolone at Visit 1, dose conversions are required for this summary only for OCS taken due to an exacerbation or adverse event.

The number and percentage of patients who take prior medications, those who take allowed concomitant medications and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). The summary tables will present data by generic term within ATC code.

4.2.4 Study Treatments

4.2.4.1 Exposure

Exposure to IP will be calculated in days as:

Last dose date of IP-first dose date of IP+1

and will be summarised by treatment group for the safety analysis set.

4.2.4.2 Compliance

Study treatment compliance will be summarised descriptively for the full analysis set and will be calculated as:

(Total doses administered/total doses expected) x 100.

OCS compliance will be summarised descriptively for the full analysis set by study phase (OCS optimisation and on-treatment) and will be calculated as:

OCS compliance = (total days compliant/total days with completed data) x 100.

A patient is considered compliant with OCS if they took their OCS dose, OCS dose was not scheduled, or their OCS dose was reduced to zero on that day, as recorded in their daily e-diary.

4.2.5 Primary outcome variable

4.2.5.1 Primary analysis

The primary efficacy variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control, as defined in Section 3.1. Each benralizumab dose regimen will be compared with placebo.

For each of the 2 benralizumab dose regimens, the null hypothesis is that the percentage reduction from baseline in the final OCS dose while maintaining asthma control on benralizumab is equal to the percentage reduction from baseline in the final OCS dose on placebo. The alternative hypothesis is that the percentage reduction from baseline in the final OCS dose while maintaining asthma control on benralizumab is not equal to the percentage reduction from baseline in the final OCS dose on placebo, ie:

H_0: % reduction in OCS dose (benralizumab vs Placebo)=0

H_a: % reduction in OCS dose (benralizumab vs Placebo)≠0

For each of the 2 benralizumab dose regimen groups the percentage reduction from baseline in final OCS dose while maintaining asthma control will be compared to the placebo group using a Wilcoxon rank-sum test. The median difference in the percentage reduction of OCS dose between each benralizumab dose regimen and placebo, along with the 95% CI and p-value will be presented. The median differences and corresponding confidence intervals will be

derived using asymptotic Hodges-Lehmann estimation. In addition, the median percentage reduction in OCS dose and the corresponding 95% CI within each treatment group will be presented.

The above analyses will also be performed for patients with baseline blood eosinophil counts ≥300/μL while the multiplicity will not be adjusted for these analyses.

The percentage reduction in OCS dose will be summarised by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL separately. The percentage reduction from baseline in OCS dose will also be summarised by visit.

4.2.5.2 Sensitivity analyses

As a sensitivity analysis to the primary endpoint analysis, the analyses described in Section 4.2.5.1 will be repeated, using the definition of percentage reduction from baseline in the final OCS dose while maintaining asthma control provided in Section 3.1 that is adjusted to take into account patients who experienced an exacerbation on or after Visit 6.

Additionally, a sensitivity analysis will be performed to evaluate the percentage reduction in OCS dose categories, as defined in Section 3.1, using a proportional odds model and controlling for treatment group, region, and baseline (optimised) OCS dose. The results of this analysis will be presented using proportional odds ratios, together with 95% CI and two-sided p-value for each active dose regimen versus placebo.

The total corticosteroid exposure, regardless of route or reason for administration, over the treatment period will be summarised.

4.2.5.3 Subgroup analyses

To explore the uniformity of the overall percentage reduction from baseline in final OCS dose, summaries of the primary endpoint by subgroups will be provided for the following factors; age category (≥18-65 and ≥65 years) , gender, BMI (≤35 kg/m^2, >35 kg/m^2), number of exacerbations in the previous year (1, 2, ≥3), region (Asia, Eastern Europe, Europe, European Union, North America, and rest of world), and OCS dose at baseline (≤10mg, >10mg). The region category of European Union includes all European countries except Ukraine and Turkey. Categories of percent reduction from baseline in final OCS dose, as defined in Section 3.1, will also be summarised by these subgroup factors.

4.2.6 No formal statistical comparisons will be performed by subgroup.Secondary efficacy outcome variables

All secondary efficacy outcome variables will be summarised descriptively and will have formal statistical analyses conducted on the FAS.

4.2.6.1 Proportion of patients with ≥50% reduction from baseline in final OCS dose

The proportion of patients with ≥50% reduction in final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive

variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for region.

The results of the analyses will be presented using odds ratios, together with associated 95% CI and 2-sided p-value for each active dose regimen versus placebo. The number and percentage of patients with ≥50% reduction in average daily OCS dose will also be summarised by treatment group.

The above analysis will be repeated for the proportion of patients with ≥25% reduction from baseline in final OCS dose.

4.2.6.2 Proportion of patients with 100% reduction from baseline in OCS dose

The proportion of patients with 100% reduction in final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

This analysis will be repeated for the proportion of patients with 100% reduction in final OCS dose in the subset of patients who are eligible to meet this endpoint criteria based on their optimised dose at baseline, as defined in Section 3.2.2.

4.2.6.3 Proportion of patients with ≤5.0 mg reduction from baseline in OCS dose

The proportion of patients with ≤5.0 mg reduction on final OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.4 Proportion of patients with final OCS dose ≤5.0 mg daily

The proportion of patients with final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control will be addressed as a supportive variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.5 Proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily.

The proportion of patients with ≥25% reduction from baseline and with final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control will be addressed as a supportive

variable to the primary objective for the full analysis set. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.6 Proportion of patients with ≥1 asthma exacerbation

The proportion of patients with ≥1 asthma exacerbation during the 28 week treatment period in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using the same method, Cochran–Mantel–Haenszel test, as for the proportion of patients with ≥50% reduction in average daily OCS dose as described in Section 4.2.6.1.

4.2.6.7 Annual rate of asthma exacerbations

The annual exacerbation rate in each of the 2 benralizumab dose regimen groups will be compared to the annual exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a patient, over the 28-week double-blinded treatment period. The model will include covariates of treatment group, region and the number of exacerbations in the previous year. The logarithm of the patient's corresponding follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the annual exacerbation rate and the corresponding 95% CI within each treatment group and the absolute difference between treatment groups with the corresponding 95% CI will be presented.

The annual exacerbation rate estimates in the individual treatment groups will be estimated using the OBSMARGINS option in LSMEANS statement in SAS. This option provides predicted estimates of rates under the assumption of mean levels for baseline covariates (observed proportions for categorical variables). It is noted that in regression models such as the negative binomial, that transform the linear predictor, estimation of response evaluated at the mean covariate levels may not closely approximate the overall mean population response, especially if any covariate has a strong association with the outcome, even when the model provides an appropriate fit to the data (Muller and MacLehose 2014). As such, the model estimated difference in exacerbation rates will be used to provide further context on the treatment effect evaluated as an absolute difference in rates based on a patient with a mean covariate level, but the model estimated rates themselves should not be interpreted as representing the population average. Marginal standardization method will be done as an additional presentation to further characterize the primary analysis results.Asthma exacerbation summary statistics will be presented based on the full analysis set by treatment group.

4.2.6.8 Annual rate of asthma exacerbations associated with an ER visit or hospitalisation

The annual rate of asthma exacerbations that are associated with an ER visit or hospitalisation will be analysed using the same method as described in Section 4.2.6.7. In the event that a patient was seen in the emergency room and was subsequently hospitalised, only the hospitalisation is considered. Baseline covariates will be treatment group, region and whether the subject had an exacerbation in the previous year that was associated with a hospitalization or ER visit.

4.2.6.9 Time to first asthma exacerbation

The time to first asthma exacerbation will be analysed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, region and number of exacerbations in the previous year. This analysis will also be repeated for the time to first asthma exacerbation associated with an ER visit or hospitalisation.

Results of these analyses will be summarised as hazard ratios, 95% confidence intervals and p-values for patients in the full analysis set.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot, for patients in the full analysis set.

4.2.6.10 Number of days in hospital due to asthma

The number of days in hospital due to asthma will be summarised by treatment group for the full analysis set. No formal statistical comparisons are planned.

4.2.6.11 Pre-bronchodilator FEV_1 (L) measured at the study centre

Change from baseline in pre-bronchodilator FEV_1 (L) will be compared between each of the 2 benralizumab treatment groups and the placebo group using a mixed-effect model for repeated measures (MMRM) analysis on patients with a baseline pre-bronchodilator FEV_1 and at least 1 post-randomisation pre-bronchodilator FEV_1 assessment for patients in the FAS.

The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post-baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, region, visit, and treatment*visit interaction as fixed effects and baseline pre-bronchodilator FEV_1 as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

$$\textit{Change from baseline in pre-bronchodilator } FEV_1 = \textit{Treatment group} + \textit{baseline pre-bronchodilator } FEV_1 + \textit{region} + \textit{visit} + \textit{treatment*visit}$$

Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% confidence intervals and p-values.

4.2.6.12 Change from baseline in morning and evening PEF

Change from baseline in morning and evening PEF will be summarised and analysed separately using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.6.13 Body plethysmography

The change from baseline in TLC, RV, VC, IC, and FRC will be summarised by treatment group for the subset of patients who are enrolled for sputum collection. No formal statistical comparisons are planned.

4.2.6.14 Blood eosinophils

The baseline blood eosinophil count used to inform primary and secondary efficacy of benralizumab is defined in Section 2.2.3.

An important marker of the biological activity of benralizumab is the depletion in eosinophils in the peripheral blood. Absolute eosinophil counts along with their absolute changes from baseline, and percentage changes from baseline will be summarised using descriptive statistics by treatment group and visit using conventional units (cells/μL). Baseline is defined as the last non-missing value prior to the first dose of study treatment. Percent change from baseline in eosinophil counts will be compared between each benralizumab group and the placebo group using a repeated measures analysis, as defined for analysis of pre-bronchodilator FEV_1 in Section 4.2.6.11.

4.2.7 Patient reported outcome variables

4.2.7.1 Asthma symptom score

Change from baseline in total asthma symptom score, daytime score, and nighttime score will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.2 Rescue medication use

Change from baseline in total rescue medication use (average puffs/day) will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.3 Home lung function (morning and evening PEF)

Change from baseline in morning and evening PEF will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.4 Nights with awakening due to asthma

Change from baseline in the proportion of nights with nocturnal awakenings due to asthma requiring rescue medication will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

4.2.7.5 Asthma Control Questionnaire (ACQ-6 score)

Change from baseline in ACQ-6 score will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

Asthma control responder status based on ACQ-6 at EOT (Week 28), as defined in Section 3.3.5, will be analysed using a logistic regression model with covariates of treatment, region, and baseline value. Patients with missing or non-evaluable ACQ-6 score at Week 28 will be considered non-responders. In the event that there is a differential proportion of patients with missing results at Week 28, based on review of an ACQ-6 compliance summary, a sensitivity logistic regression analysis will be performed using a hybrid LOCF approach. For this analysis, patients who complete the study and have missing ACQ-6 score at Week 28 will have their last non-missing score carried forward. Patients who did not complete the study will be treated as non-responders.

The number and percentage of patients achieving an improvement, no change, or deterioration, and the number and percentage of patients achieving mean ACQ-6 ≤ 0.75 (Well controlled), >0.75 - < 1.5 (Partly controlled) and ≥ 1.5 (Not well controlled) at EOT (Week 28) as defined in Section 3.3.5 will be summarised by treatment group.

The above analyses will be repeated for ACQ-5, as defined in Section 3.3.5, excluding the summary of number and percentage of patients categorised as well controlled, partially controlled, and not well controlled.

4.2.7.6 Asthma quality of life questionnaire for 12 years and older (AQLQ(S) + 12 scores)

Change from baseline in AQLQ(S)+12 (overall and by domain) will be summarised and analysed separately using the same method, MMRM, as for pre-bronchodilator FEV_1 (L) described in Section 4.2.6.11.

Asthma control responder status based on overall AQLQ(S)+12 score at EOT (week 28), as defined in Section 3.3.6, will be analysed using a logistic regression model with covariates of treatment, region, and baseline value. Patients with missing or non-evaluable total AQLQ(S)+12 score at week 28 will be considered non-responders. In the event that there is a differential proportion of patients with missing results at week 28, based on review of an AQLQ(S)+12 compliance summary, a sensitivity logistic regression analysis will be performed using a hybrid LOCF approach. For this analysis, patients who complete the study and have missing AQLQ(S)+12 score at Week 28 will have their last non-missing score carried forward. Patients who did not complete the study will be treated as nonresponders.

The number and percentage of patients achieving an improvement, no change, or deterioration at EOT (week 28) overall and by domain, as defined in Sections 3.3.6 will be summarised by treatment group.

4.2.8 Exploratory Objectives

4.2.8.1 Eosinophil progenitor cells in blood

Blood samples will be collected at Weeks 0, 4, 12, EOT and follow-up to evaluate eosinophil progenitor cells by flow cytometry in a subset of patients.

As collection of biological samples is an integral part of this study, no separate optional consent form was used, and so it is expected that all patients will have samples available

The results from the investigation of such samples will not be reported in the CSR and are therefore outside the scope of this analysis plan.

4.2.8.2 Sputum differential cell counts and biomarkers

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, eosinophil progenitor cells by flow cytometry, the pharmacology of benralizumab, and eosinophils recruitment, activation and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients.

The samples will be analysed by a central laboratory and sputum biomarker samples will be retained for investigation of the pharmacology of benralizumab. The results from the investigation of such samples, including sputum biomarkers will not be reported in the CSR and are therefore outside the scope of this analysis plan.

4.2.8.3 Serum biomarkers

Serum biomarker samples will be collected at weeks 0, 4, 12, EOT and follow-up. This will be done in order to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (including periostin, IL-5, EDN, and eotaxin), and eosinophil-, basophil-, and inflammation-related biomarkers of asthma.

As collection of biological samples is an integral part of this study, no separate optional biomarker consent form was used, and so it is expected that all patients will have samples available.

Results and methodological details for any serum biomarker analyses will be reported outside of the CSR.

4.2.9 Exposure

Duration of exposure to investigational product will be calculated in days as:

Last dose date of IP-first dose date of IP+1

and will be summarised by treatment group and repeated based on baseline blood eosinophil categories (≥150-299/μL, ≥300/μL, 300-450/μL, and >450/μL), for the safety analysis set.

4.2.10 Safety outcome variables

All safety variables will be summarised using the safety analysis set and data presented according to treatment received.

4.2.10.1 Adverse events

Adverse events will be summarised separately for the on-study, on-treatment, and post-treatment periods, as defined in Section 3.4.1. All AEs will be listed for each subject, regardless of treatment period, with AEs during the run-in/optimisation phase listed separately. All summaries will be presented by treatment group.

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories; AEs, serious adverse events (SAEs), AEs with outcome of death, and AEs leading to discontinuation of IP (DAEs). This summary will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods. The total number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a patient).

Adverse events, AEs with outcome of death, SAEs and DAEs will be summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least 1 occurrence will be presented, ie, for a patient multiple occurrences of an AE will only be counted once. SAEs causing discontinuation of the study treatment and SAEs causing discontinuation from the study will also be summarised. Presentations for AEs and SAEs will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods, and will also include the number and percentage of patients over both benralizumab treatment groups.

The rate of AEs per person-years at risk, calculated as (number of patients reporting AE)/(total period with patients at risk of AE), will also be reported for the on-study and on-treatment periods. The total period at risk for each patient will be defined as the period from first dose of study treatment to the date of the EOT (week 28) or IPD visit for the on-treatment period and as the period from first dose of study treatment to the follow-up visit (Week 36) for the on-study period. Rates will be expressed in terms of events per 100 patient-years.

A summary of the most common (frequency of ≥3%) AEs will be presented by PT. Adverse events, SAEs, and DAEs will be summarised by PT and Investigator's causality assessment (related vs. not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). Summaries of AEs and SAEs by Investigator's causality assessment will also be repeated for patients with baseline blood eosinophil count ≥300/μL, for the on-study and on-treatment periods.

Adverse events of injection site reactions (high level term of administration and injection site) and hypersensitivity (standard MedDRA query of hypersensitivity) will be summarised by PT. The summary of injection site reactions will summarised by injection site location and number of IP administrations. The summary of AEs of hypersensitivity will be repeated for patients with baseline blood eosinophil count ≥300/µL, for the on-study and on-treatment periods.

Adverse events related to device malfunction will be listed. Separate listings of patients with AEs, AEs with outcome of death, SAEs, or DAEs will be presented.

Adjudicated events (MACE and malignancies) will be summarised by treatment group and listed.

4.2.10.2 Laboratory data

All continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarised in SI units, with the exception of blood eosinophil counts which will be summarised in both SI and conventional units. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum post-baseline value, as applicable for each parameter and will include patients with both baseline and post-baseline data. In addition, shift tables from baseline to maximum CTCAE grade will be presented for CD4+T-cells, leukocytes, lymphocytes, neutrophils and B-cells. A separate table summarizing the shift from baseline to minimum post-baseline value will be presented for CD4+T-cells, CD8+T-cells, B-cells, and NK cells flow cytometry.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced.

Data for patients who have treatment-emergent changes outside central laboratory reference ranges will be presented. This data presentation will include all visits for this subset of patients.

Maximum post-baseline bilirubin elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. Bilirubin will be presented in multiples of the following ULN ≤1.5, >1.5-2, >2, and AST and ALT will be presented in multiples of the following ULN ≤1, >1-3, >3-5, >5-10, >10.

Maximum post-baseline total bilirubin will be presented (<2 and ≥2 x ULN) and plotted against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 x ULN), expressed as multiples of ULN. This will be repeated to show maximum post-baseline total bilirubin against maximum post-baseline AST.

Data for patients with ALT or AST ≥3 x ULN, and bilirubin ≥2 x ULN will be presented, which will include all visits for this subset of patients. A line plot of liver biochemistry test results (including ALP, ALT, AST, total bilirubin, and GGT) over time will also be presented for this subset of patients.

For all patients who meet the biochemical criteria for confirmed Hy's law, an SAE narrative will be produced.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each parameter and will include patients with both baseline and post-baseline data.

Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced.

4.2.10.3 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented for each treatment group by visit. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data.

All recorded vital signs data will be listed.

4.2.10.4 Local ECGs

The Investigator's assessment of the 12-lead ECG (normal, abnormal) will be listed for all patients, detailing whether any abnormalities were clinically significant or not.

A shift table will be produced for each ECG parameter to display normal, abnormal – not clinically significant, abnormal – clinically significant and not done. The shift table will present baseline and last observation post-baseline.

4.2.10.5 Physical examination

Shift tables (normal, abnormal, not done) of baseline versus the last observation post-baseline [normal, abnormal (same as baseline), abnormal (new or aggravated), not done] will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

4.2.11 Pharmacokinetic variables

The PK analyses will be performed at or under the guidance of AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarised using descriptive statistics at each visit by treatment group and will be listed in the CSR. The population modeling will be presented in a separate pharmacometrics report.

4.2.12 Immunogenicity variables

The analysis of anti-drug antibodies (ADA) to benralizumab is documented in the benralizumab ADA SAP but the scope of the study ADA analysis will be modified as follows.

The demographics and patient characteristics will be presented by ADA status (positive, negative).

The ADA responses and nAb responses at any timepoint and at each specific timepoint will be summarised. ADA cumulative response will also be summarised at each timepoint. Summary of ADA titer will be presented by descriptive statistics.

Association between ADA and safety will be explored.

Due to the short study period (ie, 28 weeks) and small sample size, the subgroup analyses for patients who are ADA positive with titer greater than the median of maximum titer, persistently or transiently ADA positive will not be evaluated except for the eosinophil count over time. The eosinophil counts will be summarised over time for patients who are ADA positive with titer >median. The association between ADA and efficacy will not be evaluated either for the same reason. In addition, summaries will not be produced by baseline blood eosinophils count categories due to the limited sample size in the subgroups.

5. INTERIM ANALYSES

There is no interim analysis planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The protocol states that all secondary efficacy endpoints will be summarised by baseline blood eosinophil count categories (≥150-299/μL, 300-450/μL, and >450/μL). Given that the planned sample size of the study is 210 patients and only 34, 71 and 115 patients were randomised to the ≥150-299/μL, 300-450/μL, and >450/μL categories respectively, summary results by eosinophil count categories are not easily interpretable and therefore will only be provided for the primary efficacy endpoint and the secondary endpoints related to OCS dose reduction. All other efficacy endpoints will be summarised for the full analysis set.

Based on review of blinded data, analysis of the time to first asthma exacerbation requiring hospitalisation will not be performed due to the small observed number of asthma exacerbations recorded during the study. The time to first asthma exacerbation after randomisation and time to first asthma exacerbation requiring hospitalisation or ER visit will be analysed as planned.

The definition of the PK analysis set was updated to ensure consistency with the definition used for other benralizumab studies. The following underlined text was added; all patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations(eg, disallowed medication) and who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis set.

The protocol states that the ADA analysis set will be used for all ADA summaries; however, the definition of the ADA analysis set is equivalent to the definition of the safety analysis set. The safety analysis set will be used for all ADA summaries.

The mean number of days with OCS taken for exacerbations is described in the study protocol as a secondary endpoint; however, this endpoint was excluded from analysis. The study design incorporates changes in OCS dose throughout the study such that the outcome of this endpoint would be difficult to interpret.

The name and description of OCS dose-related endpoints was updated to remove the term 'average'. Text is included in the SAP to address how to handle the situation when a patient is dosed every 2 days (ie, divide the dose by 2 to get the daily dose). The final OCS dose is not intended to be an average dose; therefore, terminology is updated to avoid confusion.

Following discussion with the AstraZeneca patient safety physician, Other Adverse Events (OAEs) will not be defined for this study, and as such, reference to OAEs has been omitted from this SAP.

The protocol indicated that country/region would be among the baseline covariates adjusted for in formal statistical models. Following the blinded data review of the Phase 3 asthma exacerbation studies, where convergence issues were encountered for some of the statistical models, the decision was made to replace the country/region covariate effect with region in all analyses where this effect is included.

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Appendix A Partial dates for AEs and prior/concomitant medication

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify treatment-emergent AEs and to classify prior/concomitant medications:

Adverse events

The missing day of onset of an AE will be set to:

- First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
- The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
- The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.

The missing day of resolution of an AE will be set to:

- The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.

If the onset date of an AE is missing both the day and month, the onset date will be set to:

- January 1 of the year of onset, if the onset year is after the year of the first study treatment
- The date of the first treatment, if the onset year is the same as the year of the first study treatment
- The date of informed consent, if the onset year is before the year of the first treatment

If the resolution date of an AE or end date of an IP is missing both the day and month, the date will be set to:

- December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

The missing day of start date of a therapy will be set to the first day of the month that the event occurred.

The missing day of end date of a therapy will be set to the last day of the month of the occurrence.

If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.

If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.

If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the date of the first study visit.

If the start date of a therapy is null and the end date is a complete date

- and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
- otherwise the start date will be set to the end date of the therapy.

If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the date of the last study visit.

If the end date of a therapy is null then the end date will be set to the date of the last study visit or the final disposition date, whichever is greater.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. DOI: 10.1056/NEJMoa1703501

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

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1. Participating Investigators

- A total of 369 patients were enrolled at 89 centers from April 28, 2014, to November 12, 2015. The last patient completed the study on August 8, 2016.
- Investigators at 64 of the centers that enrolled patients in 12 countries randomized at least one patient (numbers of patients randomized in each country are given in parentheses):
  - ***Argentina (10 patients):*** Cristina De Salvo, Mariano Fernandez Acquier, Fernando Scherbovsky, Alberto Tolcachier.
  - ***Bulgaria (8 patients):*** Dimitar Kostadinov, Hristo Metev, Kostadinka Sotirova, Mariyana Stoyanova, Oleg Yakov.
  - ***Canada (23 patients):*** Louis-Philippe Boulet, Delbert Dorscheid, James Martin, Parameswaran Nair, William Yang.
  - ***Chile (9 patients):*** Susana Munoz, Juana Pavie, Patricia Rivas.
  - ***France (10 patients):*** Arnaud Bourdin, Gilles Devouassoux, Alain Didier, Christophe Leroyer.
  - ***Germany (45 patients):*** Regina Deckelmann, Joachim Kirschner, Stephanie Korn, Klaus-Friedrich Rabe, Tobias Welte.
  - ***South Korea (11 patients):*** Sang-Heon Cho, Byung-Jae Lee, Sang-Haak Lee, Sook Young Lee, Jung-Won Park.
  - ***Poland (45 patients):*** Renata Bijata-Bronisz, Andrzej Dyczek, Tomasz Fijolek, Grazyna Jasieniak-Pinis, Piotr Kuna, Artur Kwasniewski, Ewa Pisarczyk-Bogacka, Malgorzata Zurowska-Gebala.
  - ***Spain (3 patients):*** Eva Martinez, José Luis Velasco.

- ***Turkey (11 patients):*** Sevim Bavbek, Dane Ediger, Bilun Gemicioglu, Ismail Hanta.
- ***Ukraine (28 patients):*** Viktor Blazhko, Yevgenya Dytyatkovs'ka, Volodymyr Gavrysyuk, Olena Krakhmalova, Lesia Kuryk, Yuriy Mostovoy, Mykola Ostrovskyy, Liliia Romaniuk.
- ***United States (17 patients):*** David Bernstein, Eugene Bleecker, Gonzalo Gonzalez, Rohit Katial, Joel Kline, Njira Lugogo, Mark Moss, John Panuto, Kartik Shenoy, Manuel Villareal, Sally Wenzel.

2. Eligibility Criteria

2.1 Inclusion Criteria

For inclusion in the study, patients must have fulfilled all of the following criteria:

- Provision of informed consent prior to any study specific procedures.
- Female and male aged from 18 to 75 years, inclusively.
- Women of childbearing potential must have used a highly effective form of birth control (confirmed by the investigator) from enrollment, throughout the study duration, and to within 16 weeks after the last dose of study drug. In addition, they must have had a negative serum pregnancy test result at enrollment (visit 1, week –10).
    - Highly effective forms of birth control included: true sexual abstinence, a vasectomized sexual partner, Implanon®, female sterilization by tubal occlusion, any effective intrauterine device/levonorgestrel intrauterine system, Depo-Provera® injections, oral contraceptive, and Evra Patch™ or Nuvaring®.
- Women not of childbearing potential were defined as women who were either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who were postmenopausal.
- All male patients who were sexually active must have agreed to use a double barrier method of contraception (condom with spermicide) from the first dose of study drug until 16 weeks after their last dose.
- Weight of ≥40 kg.
- Peripheral blood eosinophil count of ≥150 cells/µl assessed by local laboratory at enrollment.

- History of physician-diagnosed asthma requiring treatment with medium- to high-dose inhaled glucocorticoid (total daily dose equivalent to >250 μg fluticasone dry powder formulation) and a long-acting β_2-agonist (LABA) for ≥12 months prior to enrollment.
- Documented treatment with high-dose inhaled glucocorticoid total daily dose equivalent to >500 μg fluticasone dry powder formulation) and LABA for ≥ 6 months prior to enrollment.
  - For inhaled glucocorticoid/LABA combination preparations, the highest approved maintenance dose in the local country met this criterion.
- Chronic oral glucocorticoid therapy for ≥6 continuous months directly preceding enrollment.
  - Patients must have been receiving doses equivalent to 7.5–40 mg/d of prednisolone/prednisone at visit 1 and must have been on a stable dose for ≥2 weeks before randomization.
  - Patients must have agreed to switch to study-required prednisone/prednisolone as their oral glucocorticoid for the duration of the study.
- Patients with documented failures of oral glucocorticoid reduction within 6 months prior to enrollment were not required to proceed through the dose optimization phase during run in.
  - Failed attempts at oral glucocorticoid dose reduction were those that resulted in documented clinical deterioration or reduced lung function attributed to asthma, defined as:
    - Prebronchodilator forced expiratory volume in 1 second (FEV_1) <80% of personal baseline.
    - Morning peak expiratory flow (PEF) <80% of personal baseline.
    - Night-time awakenings increase of >50% of mean personal baseline.
    - Albuterol or salbutamol use >4 puffs/day above mean personal baseline.

        - Requirement for a prednisone or prednisolone burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction.

- Additional maintenance asthma controller medications (e.g., leukotriene receptor antagonists, tiotropium, cromone, and theophylline) were permitted.
    - 5-Lipoxygenase inhibitors (e.g., zileuton and roflumilast) were prohibited.
- Morning prebronchodilator FEV_1 of <80% predicted at visit 2 (week 8).
- Evidence of asthma as documented by:
    - Airway reversibility (FEV_1 ≥12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3 (week –10, –8, or –6) using the Maximum Post-bronchodilator Procedure, *or*
    - Documented reversibility in the previous 24 months prior to enrollment, *or*
    - Airway hyper-responsiveness (provocative concentration of methacholine causing a 20% drop in FEV_1 methacholine concentration ≤8 mg/ml) documented in the previous 12 months prior to planned date of randomization, *or*
    - Airflow variability in clinic FEV_1 ≥20% between two consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV_1 recorded during an exacerbation were considered for this criterion).
- All patients must have had reversibility testing performed before randomization to establish a baseline characteristic.
    - If patients did not demonstrate airway reversibility at either visit 1 or visit 2 (week –10 or –8) and this was needed to qualify the patient for randomization, the site should have reiterated the need to withhold short- and long-acting bronchodilators prior to visit 3 (week 6) in an effort to meet this inclusion criterion.

- At least one documented asthma exacerbation in the 12 months prior to the date informed consent was obtained.

2.2 Inclusion criteria at randomization

- Negative urine pregnancy test at randomization (visit 6, week 0).
- Optimized oral glucocorticoid dose reached ≥2 weeks prior to randomization.
- Additional asthma controller medication must not have been initiated during the run-in/oral glucocorticoid optimization phase (not applicable for management of exacerbations during screening/run-in/oral glucocorticoid optimization phase).
- At least 70% compliance with oral glucocorticoid use from visits 1 to 6 (weeks –10 to 0) based on the Asthma Daily Diary.
- At least 70% compliance with usual asthma controller inhaled glucocorticoid and LABA from visits 1 to 6 (weeks –10 to 0) based on Asthma Daily Diary.
- Minimum 70% (i.e., 10 of 14 days) compliance with the Asthma Daily Diary (morning and evening diary) for the period between each study visit from visits 1 to 6 (weeks –10 to 0).

2.3 Exclusion criteria

Patients must not have entered the study if any of the following exclusion criteria were fulfilled:

- Clinically important pulmonary disease other than asthma (e.g., active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, α1 antitrypsin deficiency, and primary ciliary dyskinesia) or had ever been diagnosed with pulmonary or systemic disease (other than asthma) that was associated with elevated peripheral eosinophil counts

(e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, or hypereosinophilic syndrome).

- Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that was not stable in the opinion of the investigator and could have:
  - Affected the safety of the patient throughout the study.
  - Influenced the findings of the studies or their interpretations.
  - Impeded the patient's ability to complete the entire duration of study.
- Known history of allergy or reaction to the study drugs.
- History of anaphylaxis to any biologic therapy.
- A helminth parasitic infection diagnosed within 24 weeks prior to enrollment that had not been treated with, or had failed to respond to, standard-of-care therapy.
- Acute upper or lower respiratory infections requiring antibiotics or antiviral medications within 30 days prior to enrollment or during the run-in/oral glucocorticoid optimization phase.
- Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during the run-in/oral glucocorticoid optimization phase, which in the opinion of the investigator, may have put the patient at risk because of his/her participation in the study, or may have influenced the results of the study, or the patient's ability to complete entire duration of the study.

- Any clinically significant cardiac disease or any electrocardiogram abnormality obtained during the run-in/oral glucocorticoid optimization phase, which in the opinion of the investigator, may have put the patient at risk or interfered with study assessments.
- History of alcohol or drug abuse within 12 months prior to enrollment.
- Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C.
    - Patients with a history of hepatitis B vaccination without history of hepatitis B were allowed to enroll.
- A history of known immunodeficiency disorder, including a positive human immunodeficiency virus test.
- Current smokers or former smokers with a smoking history of ≥10 pack-years.
- History of cancer:
    - Patients who had basal cell carcinoma, localized squamous cell carcinoma of the skin, or *in-situ* carcinoma of the cervix were eligible provided that the patient was in remission and curative therapy was completed ≥12 months prior to enrollment
    - Patients who had other malignancies were eligible provided that the patient was in remission and curative therapy was completed ≥5 years prior to enrollment.
- Use of immunosuppressive medication (including methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot glucocorticoid, or any experimental anti-inflammatory therapy) within 3 months prior to enrollment.
    - Chronic maintenance oral glucocorticoid for the treatment of asthma were allowed.

- Clinically significant asthma exacerbation, in the opinion of the investigator, including those requiring use of systemic glucocorticoid, or an increase in maintenance dose of oral glucocorticoid 2 weeks prior to enrollment.
- History of life-threatening asthma.
- Asthma control reached at an oral glucocorticoid dose of ≤5 mg/d during run-in/oral glucocorticoid optimization phase.
- Patient qualified for three consecutive dose reductions at visits 2–4 (weeks –8 to –4) and continued to meet oral glucocorticoid dose reduction criteria at visit 5 (week –2).
- Receipt of oral glucocorticoid, other than prednisone or prednisolone, as the maintenance oral glucocorticoid controller for asthma symptoms from enrollment and throughout the study.
- Receipt of immunoglobulin or blood products within 30 days prior to enrollment.
- Receipt of any marketed (e.g., omalizumab) or investigational biologic within 4 months or 5 half-lives prior to enrollment, whichever was longer.
- Receipt of live attenuated vaccines 30 days prior to enrollment:
    - Receipt of inactive/killed vaccinations (e.g., inactive influenza) were allowed provided they were not administered within 1 week before/after any study visit.
- Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to enrollment, whichever was longer.
- Patients previously randomized and dosed in any benralizumab clinical trial.
- Initiation of new allergen immunotherapy was not allowed within 30 days prior to enrollment.

  - Immunotherapy initiated prior to this period, or as a routine part of the patient's seasonal treatment, was allowed.
  - If the immunotherapy was delivered as an injection, there was to be a gap of 7 days between the immunotherapy and study drug administration.
- Current use of any oral or ophthalmic non-selective β-adrenergic antagonist (e.g., propranolol).
- Planned surgical procedures during the conduct of the study.
- Currently breastfeeding or lactating women.
- Previous randomization in the present study.
- Concurrent enrollment in another clinical trial.
- AstraZeneca staff involved in the planning and/or conduct of the study.
- Employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
- Alanine aminotransferase or aspartate aminotransferase concentration ≥2.5 times the upper limit of normal confirmed during screening period.

3. Study Procedures

- Data were collected from all patients at:
  - Enrollment (week –10).
  - Two-weekly intervals during run-in/oral glucocorticoid optimization phase (weeks –8 to –2).
  - Randomization (week 0) and during the induction phase (week 2).
  - Four-weekly intervals during the reduction and maintenance phases (weeks 4–28).
  - Follow up (week 36, completed by only those patients not entering an extension study [NCT02258542]).

3.1 Spirometry

- Patients received prebronchodilator spirometry at enrollment, at 2-weekly intervals during run-in/oral glucocorticoid optimization phase, and at 4-weekly intervals during the treatment period.
- Patients also received post-bronchodilator spirometry at enrollment, then at weeks –8, –6, 0, 12, 28, and 36.
- Spirometry was conducted by study investigators or authorized delegates according to American Thoracic Society/European Respiratory Society guidelines.[1]

3.2 Asthma Daily Diary

- Patients completed the Asthma Daily Diary[2,3] using an electronic patient-reported outcomes device (ePRO) every day from enrollment (week –10) to the end of the treatment period (week 28).
- The Asthma Daily Diary included the following daily recordings: home PEF data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, and background medication compliance.
- Patients completed assessments of their symptoms in the Asthma Daily Diary twice daily (morning, upon waking, and evening, prior to going to bed).
    - The morning diary included one item pertaining to asthma symptoms that occurred in the night, scored on a 4-point response scale (0 – No asthma symptoms to 3 – You were unable to sleep because of your asthma).
        - The morning diary also captured night-time awakenings (yes/no) and the use of rescue medication during these awakenings (yes/no).
    - The evening diary contained one item pertaining to asthma symptoms, scored on a 4-point response scale (0 – No asthma symptoms to 3 – You were unable to do your normal activities because of your asthma).
- The total daily symptom score was the sum of the morning and evening responses.
    - The total daily symptom score was calculated only when both morning and evening scores were available, otherwise it was set to missing.
- Patients' ePRO devices were programmed to alert both the patient and the study center when certain prespecified asthma worsening thresholds were crossed, including:

  - A decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline.
  - An increase in rescue medication use of ≥4 puffs, or use of one new or additional nebulized β_2-agonist on ≥2 consecutive days compared with average use during baseline.
  - An increase of two nocturnal awakenings because of asthma over a 7-day period compared with average during baseline.
  - An increase in total asthma symptom score (the sum of day time [evening assessment] and night-time [morning assessment] of ≥2 units above the baseline average or the greatest possible score [daily score of 6]), on ≥2 consecutive days.
- Study investigators confirmed patients' adherence to their daily diaries at each visit.

3.3 Asthma Control Questionnaire 6

- The Asthma Control Questionnaire 6 (ACQ-6) is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and short-acting β_2-agonist use, while omitting the FEV_1 measurement from the original ACQ score.[4]
- The ACQ-6 was completed using the ePRO device.
- Patients were asked to recall their experiences during the previous week and score each of the questions on a 7-point scale, ranging from 0 (totally controlled) to 6 (severely uncontrolled).
  - The overall score was calculated as the mean response to all questions.
- Individual ACQ-6 total score changes of ≥0.5 were considered clinically meaningful.

- Study investigators checked patients' adherence to questionnaires at each visit.

3.4 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older

- The Asthma Quality of Life Questionnaire (standardized) for ≥12 years [AQLQ(S)+12] is a questionnaire that measures the health-related quality of life experienced by patients aged ≥12 years with asthma.[5]
    - The questionnaire comprises four separate domains: symptoms, activity limitations, emotional function, and environmental stimuli.
    - The questionnaire was completed using the ePRO device.
- Patients were asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale, ranging from 7 (no impairment) to 1 (severe impairment).
    - The overall score was calculated as mean response to all questions.
    - The four individual domain scores were the means of responses to questions in each domain.
- Individual AQLQ(S)+12 total or domain score changes of ≥0.5 were considered clinically meaningful.
- Study investigators checked patients' adherence to questionnaires at each visit.

3.5 Assessment of Sputum Eosinophils

- Sputum samples were collected for a subset of patients to assess sputum total cell and differential counts, quantify sputum cytokines and biomarkers, and evaluate eosinophil progenitor cells in sputum.
    - The sputum assessment aimed to collect samples from approximately 60 patients.

- Sputum collection was conducted at randomization (week 0), during treatment (week 12), and at the end of treatment (week 28).
- Sputum was induced by the inhalation of hypertonic saline, and post-bronchodilator spirometry was conducted as part of the sputum induction procedure.

3.6 Safety

- An independent data monitoring board evaluated cumulative safety and other clinical trial data.
- Major adverse cardiac events and malignancies were assessed by an independent adjudication committee.

4. Oral Glucocorticoid Dose Reduction Criteria

- Patients without documented failures of oral glucocorticoid dose reduction within 6 months before enrollment entered the optimization phase.
    - Patients with documented failures of oral glucocorticoid dose reduction (i.e., attempts that resulted in clinical deterioration or reduced lung function attributed to asthma) were considered to have been historically optimized.
        - These patients did not proceed through the optimization phase and maintained their current oral glucocorticoid dose until randomization.
- Patients who met all of the following criteria were eligible for oral glucocorticoid dose reduction during the optimization and reduction phases:
    - Prebronchodilator FEV_1 ≥80% of baseline.
    - Morning PEF ≥80% of mean morning measures over the 14-day period prior to the scheduled study visit, as compared with baseline.
    - Mean night-time awakenings ≤50% increase over the 14-day period prior to the scheduled study visit, as compared with baseline.
    - Short-acting β_2-agonist rescue medication use of ≤4 inhalations per day above the mean value over the 14-day period prior to the scheduled study visit, as compared with baseline, or <12 inhalations per day.
    - No requirement to increase the dose of oral glucocorticoid for asthma symptoms since the last visit.

- If the criteria for dose reduction were not met, or if asthma symptoms worsened between visits, oral glucocorticoid dose was uptitrated to the previous effective dose and maintained without further adjustment until randomization.

5. Statistical Models

5.1 Primary Outcome

- Benralizumab was compared with placebo via a Wilcoxon rank sum test.
    - To control the overall type I error rate, we accounted for multiplicity through the Hochberg procedure.
- A sensitivity analysis for the primary outcome assessment was conducted with a proportional odds model, with controls for treatment group, region (Asia, Central and Eastern Europe, Western Europe and Turkey, North America, and rest of world), and baseline oral glucocorticoid dose.
    - The proportional odds model was not multiplicity protected.

5.2 Secondary Outcomes

- For secondary analyses of reductions in oral glucocorticoid doses, we used a Cochran–Mantel–Haenszel test, with adjustment for region,
- Annual rates of asthma exacerbations were analyzed using a negative binomial model.
    - The number of asthma exacerbations experienced by a patient during the 28-week double-blind treatment period was used as response variable, and the logarithm of the patient's corresponding follow-up time was used as an offset in the analysis to adjust for patients having different exposure times during which the events occurred.
    - The model included covariates of treatment group, region, and number of exacerbations in the year before the study.

- Annual rates of asthma exacerbations that were associated with an emergency department visit or a hospitalization were analyzed using as method similar to that used to assess annual rates of asthma exacerbations.
    - Baseline covariates were treatment group, region, and whether the patient had an exacerbation in the previous year that was associated with emergency department visit or a hospitalization.
- To assess time to first asthma exacerbation, a Cox proportional hazard model was fitted to data with the covariates of treatment, region, and number of exacerbations in the year before the study.
    - Time to first asthma exacerbation that was associated with emergency department visit or a hospitalization was analyzed using a similar model, with the covariates of treatment, region, and number of exacerbations exacerbation that were associated with emergency department visit or a hospitalization in the year before the study.
- Change from baseline in prebronchodilator FEV_1 was compared between each of the benralizumab dose regimen groups and the placebo group using a mixed-effect model for repeated measures analysis for patients with a baseline prebronchodilator FEV_1 and $\geq$1 post-randomization prebronchodilator FEV_1.
    - The dependent variable was the change from baseline in prebronchodilator FEV_1 at post-baseline, protocol-specified visits, up to the end of therapy visit.
    - Treatment group was fitted as the explanatory variable; region and baseline prebronchodilator FEV_1 were used as covariates.
    - Visit was fitted as a categorical variable, and the variance-covariance matrix was assumed to be unstructured.

  - For this type of analysis missing data were assumed to be missing at random.

- Change from baseline in total asthma symptom score, ACQ-6 score, and AQLQ(S)+12 score was analyzed using a mixed-effect model for repeated measures analysis that was similar to the model used to analyze prebronchodilator FEV_1.

5.3 Exploratory Outcomes

- Absolute eosinophil counts, as well as their absolute changes from baseline and percentage changes from baseline were summarized using descriptive statistics by treatment group and visit.
- Percentage change from baseline in eosinophil counts was compared between each benralizumab group and the placebo group using a mixed-effect model for repeated measures analysis that was similar to the model used to analyze prebronchodilator FEV_1.

6. Summaries of Patient Deaths

6.1 Acute Cardiac Failure

The patient died following an adverse event of cardiac failure acute 23 days after the first dose of benralizumab 30 mg. The patient had a medical history of hypertension and coronary artery disease at study entry, for which this patient was already being treated with lisinopril and acetylsalicylic acid, respectively. The patient received two doses of salbutamol because the patient was feeling mild general weakness, dyspnea, chest pain, and dizziness, before lying down. This patient was found later to have died during sleep.

6.2 Pneumonia

The patient died following an adverse event of pneumonia 20 days after the third dose of benralizumab 30 mg. The patient was hospitalized, and the diagnosis was right-sided community-acquired pneumonia with middle-lobe syndrome and severe, worsening bronchial asthma. The patient developed atrial fibrillation (with a rapid ventricular rate of 133 beats per minute). The event persisted despite treatment with amiodarone. The patient had hypercholesterolemia, hypertension, angina pectoris, and congestive heart failure at the time of death, as well as dyslipidemia and past atrial fibrillation at study entry. The causes of death were reported as pneumonia and pulmonary insufficiency.

7. Tables and Figures

Table S1. Oral Glucocorticoid Dose Titration Schedule During Optimization Phase

Enrollment Visit	Run-in/Optimization Phase (Oral Glucocorticoid Dose in mg/d)			
Visit 1 **Week –10**	**Visit 2** **Week –8**	**Visit 3** **Week –6**	**Visit 4** **Week –4**	**Visit 5** **Week –2**
40	35	30	25	*
37.5	32.5	27.5	22.5	*
35	30	25	20	*
32.5	27.5	22.5	17.5	*
30	25	20	15	*
27.5	22.5	17.5	12.5	*
25	20	15	10	*
22.5	17.5	12.5	7.5	*
20	15	10	7.5	*
17.5	12.5	7.5	5	†
15	10	7.5	5	†
12.5	7.5	5	†	
10	7.5	5	†	
7.5	5	†		

*Patients who qualified for three consecutive dose reductions at visits 2 to 4 and continued to meet the oral glucocorticoid dose reduction criteria at visit 5 were excluded from the study.

†Patients who qualified for three consecutive dose reductions at visits 2 to 4, and continued to meet the oral glucocorticoid dose reduction criteria at visit 5, *or* who had reached an oral glucocorticoid dose ≤5.0 mg/d during the optimization phase, were excluded from the study.

Table S2. Oral Glucocorticoid Dose Titration Schedule During Reduction Phase

Optimized Dose at Visit 6 (mg/d)	Visit 8 Week 4	Visit 9 Week 8	Visit 10 Week 12	Visit 11 Week 16	Visit 12 Week 20	Visit 13 Week 24
40	35	30	25	20	15	10
37.5	32.5	27.5	22.5	17.5	12.5	7.5
35	30	25	20	15	10	7.5
32.5	27.5	22.5	17.5	12.5	7.5	5
30	25	20	15	10	7.5	5
27.5	22.5	17.5	12.5	7.5	5	5
25	20	15	10	7.5	5	5
22.5	17.5	12.5	7.5	5	5	5
20	15	10	7.5	5	5	5
17.5	12.5	7.5	5	5	5	2.5
15	10	7.5	5	5	2.5*	1.25*
12.5	7.5	5	2.5	1.25*	0	0
10	7.5	5	2.5	1.25*	0	0
7.5	5	2.5	1.25*	0	0	0

*It was permitted to administer a daily dose of 1.25 mg as 2.5 mg every other day.

Table S3. Demographics and Clinical Characteristics of Patients at Baseline*

Characteristic	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Age group — no. (%)			
≥18 to <50 yr	36 (48)	33 (46)	29 (40)
≥50 to <65 yr	31 (41)	31 (43)	32 (44)
≥65 to 75 yr	8 (11)	8 (11)	12 (16)
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Race — no. (%)			
White	70 (93)	69 (96)	66 (90)
Black or African-American	1 (1)	0	1 (1)
Asian	4 (5)	3 (4)	5 (7)
Other†	0	0	1 (1)
Body mass index‡	28.73±5.24	29.79±6.79	30.24±6.53
Median smoking history (range) — pack-years	6.0 (1–9)	5.5 (2–9)	5.0 (1–8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1–54.5)	13.3 (1.2–52.3)	16.3 (1.3–53.0)
Median oral glucocorticoid dose (range) — mg/d			
At study entry§	10.0 (7.5–40.0)	10.0 (7.5–40.0)	10.0 (7.5–40.0)
At end of optimization phase	10.0 (7.5–40.0)	10.0 (7.5–40.0)	10.0 (7.5–40.0)
Mean inhaled glucocorticoid dose (range) — µg/d¶	1232 (250–5000)	1033 (250–3750)	1192 (100–3250)
Leukotriene-receptor antagonists — no. (%)	25 (33)	28 (39)	29 (40)
Exacerbations in the previous 12 months — no./patient			
Total	2.5±1.8	2.8±2.0	3.1±2.8
Resulting in emergency department visit	0.3±0.8	0.4±1.1	0.2±0.7

Characteristic	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Resulting in hospitalization	0.5±0.7	0.4±1.0	0.5±1.1
Patients with ≥1 exacerbations in the previous 12 months			
Resulting in emergency department visit	11 (15)	13 (18)	7 (10)
Resulting in hospitalization	26 (35)	16 (22)	20 (27)
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median reversibility (range) — %‖	16.4 (–5.4 to 93.4)	18.2 (–3.0 to 126.0)	22.6 (–3.4 to 88.0)
Total asthma symptom score**	2.43±0.99	2.47±0.99	2.34±1.09
ACQ-6 score††	2.68±0.95	2.59±1.13	2.42±1.21
AQLQ(S)+12 score‡‡	4.11±1.07	4.25±1.09	4.44±1.25
Median blood eosinophils (range) — cells/μl	535 (160–4550)	462 (160–1740)	437 (154–2140)
≥150 to <300 cells/μl — no. (%)	11 (15)	10 (14)	12 (16)
≥300 cells/μl — no. (%)	64 (85)	62 (86)	61 (84)
Median sputum eosinophils (range) — %§§	4.90 (0.5–63.0)	4.80 (0.3–30.2)	17.00 (0.0–59.0)
Allergic rhinitis — no. (%)	30 (40)	42 (58)	40 (55)
Atopy — no. (%)	37 (49)	29 (40)	29 (40)
Nasal polyps — no. (%)	28 (37)	22 (31)	20 (27)
History of omalizumab treatment — no. (%)	8 (11)	14 (19)	9 (12)

*Plus–minus values are means±standard deviation unless otherwise stated. Patient demographics, postbronchodilator lung function parameters, asthma (including smoking) history, and local blood eosinophil counts were collected at visit 1. Other clinical characteristics were collected at multiple time points from visits 1 to 6. The

last recorded value prior to randomization served as the baseline measurement. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, Q4W every 4 weeks, and Q8W every 8 weeks.

†Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other.

‡The body mass index is the weight in kilograms divided by the square of the height in meters.

§Patients were transitioned to equivalent doses of prednisone/prednisolone at study entry.

¶Expressed in their fluticasone propionate dry powder equivalent doses.

‖Percentage reversibility was calculated using pre- and postbronchodilator FEV_1 values at baseline: ([postbronchodilator FEV_1 – prebronchodilator FEV_1] ÷ prebronchodilator FEV_1) x 100.

**The total asthma symptom score is a composite of morning assessments of asthma symptoms, night-time awakenings, and rescue medication use, and an evening assessment of activity impairment, scored on a 0–6 scale. A greater score indicates a greater symptom burden.

††The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale. Low numbers represent better control.

‡‡The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale. Greater scores indicate better asthma-related quality of life.

§§Sputum eosinophil counts at baseline available for a subset of patients who received placebo (n = 8), benralizumab Q4W (n = 9), or benralizumab Q8W (n = 9).

Table S4. Median Reduction from Baseline in Final Oral Glucocorticoid Dose Stratified by Baseline Oral Glucocorticoid Dose

	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Baseline oral glucocorticoid dose ≤10 mg/d subgroup			
Patients — no.	39	37	38
Baseline oral glucocorticoid dose (range) — mg/d*	10.0 (7.5–10.0)	10.0 (7.5–10.0)	10.0 (7.5–10.0)
Median final oral glucocorticoid dose (range) — mg/d*	7.5 (0.0–25.0)	0.0 (0.0–20.0)	0.0 (0.0–15.0)
Median reduction in final oral glucocorticoid dose compared with baseline (range) — %†	25.0 (–150 to 100)	100 (–100 to 100)	100 (–50 to 100)
Baseline oral glucocorticoid dose >10 mg/d subgroup			
Patients — no.	36	35	35
Baseline oral glucocorticoid dose (range) — mg/d*	20.0 (12.5–40.0)	20.0 (11.5–40.0)	20.0 (12.5–40.0)
Median final oral glucocorticoid dose (range) — mg/d*	15.0 (1.25–40.0)	7.5 (0.0–45.0)	7.5 (0.0–30.0)
Median reduction in final oral glucocorticoid dose compared with baseline (range) — %†	20.0 (–25.0 to 91.7)	62.5 (–33.3 to 100)	62.5 (–25.0 to 100)

*Baseline oral glucocorticoid dose was the daily dose on which the patient was stabilized at randomization, and the final oral glucocorticoid dose was the final daily dose at week 28. Q4W denotes every 4 weeks, and Q8W every 8 weeks.

†Negative values denote an increase in the final oral glucocorticoid dose from baseline.

Table S5. Efficacy Endpoints for Asthma Exacerbations*

	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Percentage of patients with ≥1 asthma exacerbation after randomization†			
Patients — no. (%)	39 (52)	19 (26)	17 (23)
Odds ratio (95% CI)*	—	0.32 (0.16–0.65)	0.28 (0.14–0.56)
P value	—	0.001	<0.001
Annual asthma exacerbation rate ratio‡			
Crude rate	1.80	0.82	0.55
Marginal rate estimate (95% CI)	1.83 (1.33–2.50)	0.83 (0.55–1.26)	0.54 (0.34–0.88)
Marginal absolute difference estimate (95% CI)		–0.99 (–1.66 to –0.33)	–1.28 (–1.92 to –0.64)
Rate ratio (95% CI)	—	0.45 (0.27–0.76)	0.30 (0.17–0.53)
P value	—	0.003	<0.001
Time to first exacerbation§			
Hazard ratio (95% CI)	—	0.39 (0.22–0.66)	0.32 (0.17–0.57)
P value	—	<0.001	<0.001
Annual exacerbation rate ratio associated with an emergency department visit or hospitalization¶			
Marginal rate estimate (95% CI)	0.32 (0.16–0.65)	0.14 (0.05–0.38)	0.02 (0.00–0.18)
Marginal absolute difference estimate (95% CI)	—	–0.18 (–0.45 to 0.09)	–0.30 (–0.53 to –0.07)
Rate ratio (95% CI)	—	0.44 (0.13–1.49)	0.07 (0.01–0.63)
P value	—	0.187	0.018
Time to first exacerbation associated with an emergency department visit or hospitalization‖			
Hazard ratio (95% CI)	—	0.53 (0.14–1.64)	0.12 (0.01–0.63)
P value	—	0.291	0.042

*P values reported are nominal (i.e., not multiplicity protected).

†The odds ratio estimate was determined from the Cochran–Mantel–Haenszel test, with control for region.

‡The annual exacerbation rate ratios were calculated with the use of a negative binomial model with a log-link function and an offset term of log–follow-up time. The model included covariates of treatment group, region, and number of exacerbations in the previous year.

§The hazard ratio estimate was determined using a Cox proportional hazards model, which included covariates of treatment group, region, and number of exacerbations in the previous year.

¶The annual exacerbation rate ratios were calculated with the use of a negative binomial model with a log-link function and an offset term of log–follow-up time. The model included covariates of treatment group, region, and number of exacerbations that required an emergency department visit or hospitalization in the previous year. Confidence intervals for marginal rates and absolute differences were estimated via the delta method. Rate ratios, confidence intervals, and P values were estimated directly from SAS GENMOD procedure.

‖The hazard ratio estimate was determined using a Cox proportional hazards model, including covariates of treatment group, region, and number of exacerbations that required an emergency department visit or hospitalization in the previous year.

Table S6. Change from Baseline in Oral Glucocorticoid Dose by Baseline Blood Eosinophil Counts

Outcome	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Blood eosinophil count ≥150 to <300 cells/µl			
No. of patients	11	10	12
Median final oral glucocorticoid dose (range) — mg/d*	5.0 (0.0–15.0)	7.50 (0.0–35.0)	6.25 (0.0–30.0)
Median reduction in final oral glucocorticoid dose compared with baseline (range) — %	50.0 (0.0–100)	37.5 (–16.7 to 100)	57.5 (–50.0 to 100)
Blood eosinophil count ≥300 cells/µl			
No. of patients	64	62	61
Median final oral glucocorticoid dose (range) — mg/d*	10.0 (0.0–40.0)	5.0 (0.0–45.0)	5.0 (0.0–25.0)
Median reduction in final oral glucocorticoid dose compared with baseline (range) — %	0.0 (–150 to 100)	75.0 (–100 to 100)	75.0 (–50.0 to 100)

*The final oral glucocorticoid dose was the final daily dose at week 28 (the baseline oral glucocorticoid dose was the daily dose on which the patient was stabilized at randomization). Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

Table S7. Demographics and Clinical Characteristics of the Patients with Sputum Eosinophil Counts*

Characteristic	Placebo (N = 9)	Benralizumab Q4W (N = 12)	Benralizumab Q8W (N = 12)
Age — yr	54.1±9.7	49.5±11.5	52.7±9.7
Female sex — no. (%)	7 (78)	5 (42)	7 (58)
Body mass index†	32.3±7.6	31.6±4.4	29.9±6.7
Mean time since asthma diagnosis (range) — yr	4.2 (1.1–43.0)	14.9 (1.3–52.3)	6.9 (1.6–40.3)
Median oral glucocorticoid dose (range) — mg/d			
At end of optimization phase	15.0 (7.5–30.0)	10.0 (10.0–40.0)	11.3 (7.5–30.0)
Mean inhaled glucocorticoid dose (range) — µg/d‡	1396 (750–2000)	1656 (500–3000)	1365 (500–2250)
Exacerbations in the previous 12 months — no./patient	2.4±1.1	2.8±1.7	2.7±1.2
Patients with ≥1 exacerbations in the previous 12 months resulting in hospitalization — no. (%)	2 (22)	0 (0)	1 (8)
FEV_1 before bronchodilation			
Value — liters	1.952±0.795	2.273±0.848	2.083±0.218
Percent of predicted normal	66.8±15.7	64.9±19.2	68.5±11.8
FEV_1:FVC ratio before bronchodilation — %	66±12	60±13	65±6
Mean reversibility (range) — %§	24.3 (8.6–93.4)	18.0 (7.0–40.2)	18.8 (5.4–48.1)
ACQ-6 score¶	2.56±0.92	2.49±1.26	1.97±1.28
Mean blood eosinophils (range) — cells/µl	513 (200–840)	456 (170–800)	619 (300–2140)
Median sputum eosinophils (range) — %‖	4.90 (0.5–63.0)	4.80 (0.3–30.2)	17.00 (0.0–59.0)

*Plus–minus values are means ±SD unless otherwise stated. Patient demographics, postbronchodilator lung function parameters, asthma (including smoking) history and local blood eosinophil counts were collected at visit 1. Other clinical characteristics were collected at multiple time points from visits 1 to 6. The last recorded value prior to randomization served as the baseline measurement. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, Q4W every 4 weeks regimen, and Q8W every 8 weeks regimen.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

‡Expressed in their fluticasone propionate dry powder equivalent doses.

§Percentage reversibility was calculated using pre- and post-bronchodilator FEV_1 values at baseline: ([post-bronchodilator FEV_1 – prebronchodilator FEV_1] ÷ prebronchodilator FEV_1) x 100.

¶The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale. Low numbers represent better control.

‖Median sputum eosinophils available for a subset of patients who received placebo (n = 8), benralizumab Q4W (n = 9), or benralizumab Q8W (n = 9).

Table S8. Summary of Adverse Events

Event — no. of patients (%)	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
Adverse event	62 (83)	49 (68)	55 (75)
Adverse event leading to treatment discontinuation	2 (3)	0	3 (4)
Adverse events with frequency ≥3%*			
Nasopharyngitis	15 (20)	11 (15)	11 (15)
Asthma	18 (24)	8 (11)	2 (3)
Bronchitis	12 (16)	4 (6)	7 (10)
Sinusitis	8 (11)	5 (7)	4 (5)
Headache	4 (5)	5 (7)	6 (8)
Upper respiratory tract infection	5 (7)	4 (6)	5 (7)
Rhinitis	2 (3)	2 (3)	6 (8)
Influenza	5 (7)	3 (4)	1 (1)
Back pain	4 (5)	2 (3)	2 (3)
Cough	4 (5)	2 (3)	1 (1)
Dyspnea	4 (5)	2 (3)	1 (1)
Hypertension	2 (3)	2 (3)	3 (4)
Pneumonia	3 (4)	0	3 (4)
Vertigo	2 (3)	1 (1)	3 (4)
Nausea	3 (4)	1 (1)	0
Oral candidiasis	4 (5)	0	0
Presyncope	0	0	3 (4)
Status asthmaticus	3 (4)	0	0
Serious adverse event†	14 (19)	7 (10)	7 (10)
Serious adverse event unrelated to	11 (15)	6 (8)	6 (8)

Event — no. of patients (%)	Placebo (N = 75)	Benralizumab Q4W (N = 72)	Benralizumab Q8W (N = 73)
asthma exacerbation‡			
Deaths§	0	0	2 (3)†
Injection-site reactions	2 (3)	2 (3)	0
Hypersensitivity	1 (1)	1 (1)	2 (3)
Urticaria	1 (1)	0	1 (1)

Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

*Medical Dictionary for Regulatory Activities version 18.1.

†Worsening asthma was reported for two, one, and four patients in the benralizumab Q4W, benralizumab Q8W, and placebo groups, respectively.

‡Patients who only had serious adverse events of worsening asthma or status asthmaticus were excluded from these totals.

§The causes of death were acute cardiac failure (patient had hypertension and coronary artery disease at study entry) and pneumonia (patient developed atrial fibrillation while in hospital; this patient had hypercholesterolemia, hypertension, angina pectoris, congestive heart failure, and past atrial fibrillation at study entry).

Table S9. Anti-Drug Antibody Responses

ADA Category — no. of patients (%)*	Placebo	Benralizumab Q4W	Benralizumab Q8W
Positive at any visit (baseline and/or post baseline)	6/75 (8)	5/72 (7)	7/73 (10)
Both baseline and post-baseline positive	3/75 (4)	0/68 (0)	0/69 (0)
Only post-baseline positive	3/75 (4)	5/71 (7)	6/70 (9)
Only baseline positive	0/75 (0)	0/69 (0)	1/72 (1)
ADA persistently positive†	5/75 (7)	4/71 (6)	6/70 (9)
ADA transiently positive‡	1/75 (1)	1/71 (1)	0/70 (0)
ADA-positive patients who were neutralizing antibody positive	3/75 (4)	4/72 (6)	6/73 (8)

Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

*Denominators denote the numbers of patients with one or more valid anti-drug antibody result for the category; numerators denote the numbers of patients with a positive result in that category.

†Persistent was defined as positive at two or more post-baseline assessments (with ≥16 weeks between first and last positive) or positive at the last post-baseline assessment.

‡Transient was defined as having at least one post-baseline ADA-positive assessment and not fulfilling the conditions of persistently positive.

Table S10. Pharmacodynamic Effects of Anti-Drug Antibody Responses

	Blood eosinophil counts (cells/μl)											
	Benralizumab Q4W					Benralizumab Q8W						
Patient*	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**
Baseline	110	550	340	110	420	380	690	750	540	440	200	320
Week 12	10	40	0	10	10	—	0	0	60	20	0	0
Week 24	0	1,070†	10	0	0	580‡	0	50	130	3,610‡	0	50
Week 28	0	560	20	0	—	0	0	0	440‡	90	10	0

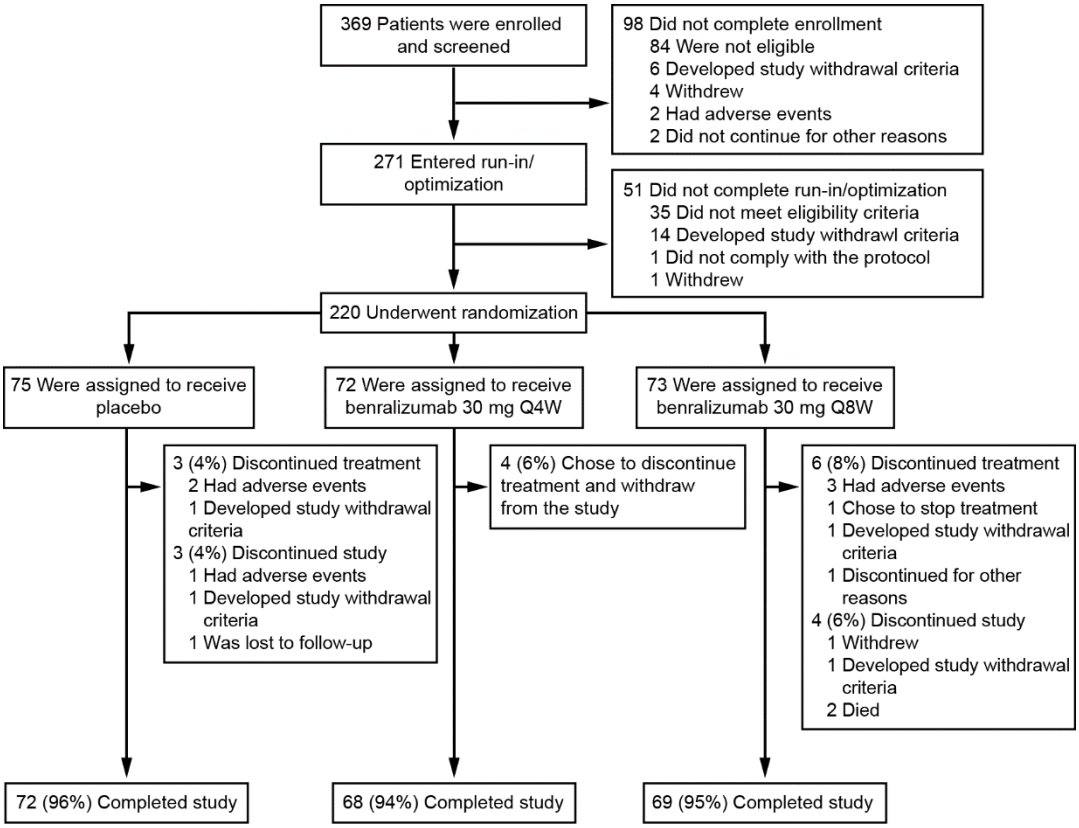
Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

*Five patients in the benralizumab Q4W group and seven patients in the benralizumab Q8W group had a positive anti-drug antibody response at any visit.

†One of five patients in the benralizumab Q4W group with a positive anti-drug antibody response had a post-baseline increase in blood eosinophils.

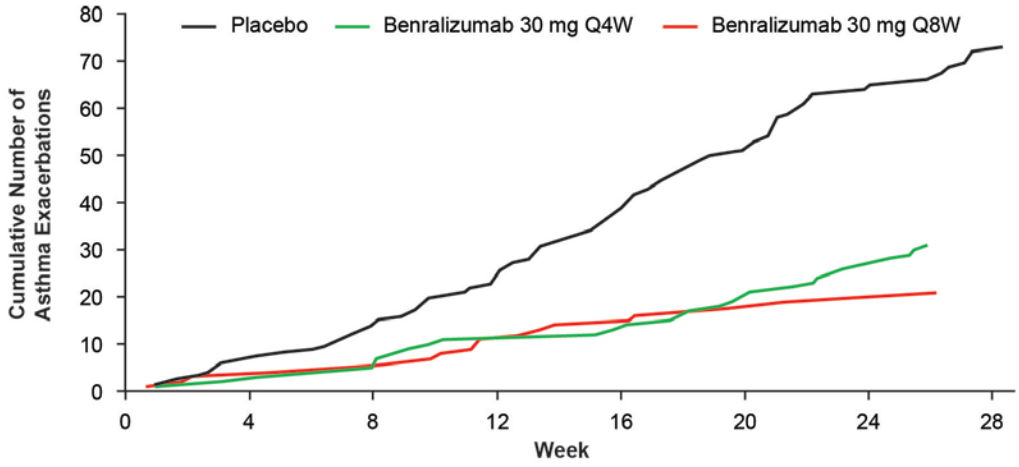
‡Three of seven patients in the benralizumab Q8W group with a positive anti-drug antibody response had a post-baseline increase in blood eosinophils.

Figure S1. Patient Enrollment and Disposition



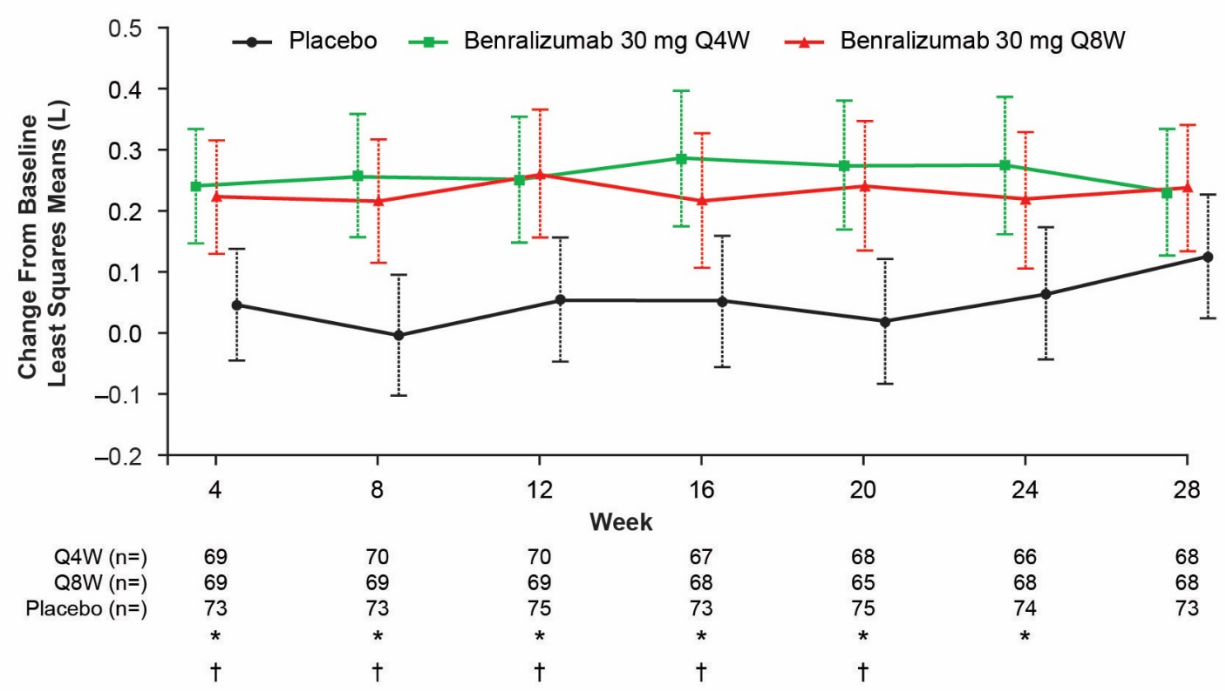
The diagram details patient enrollment and disposition in the ZONDA trial. Two patients in the benralizumab Q8W group discontinued treatment but attended all study visits and completed the study. Q4W denotes every 4 weeks regimen, Q8W every 8 weeks regimen, and SC subcutaneous injection.

Figure S2. Cumulative Number of Asthma Exacerbations



Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

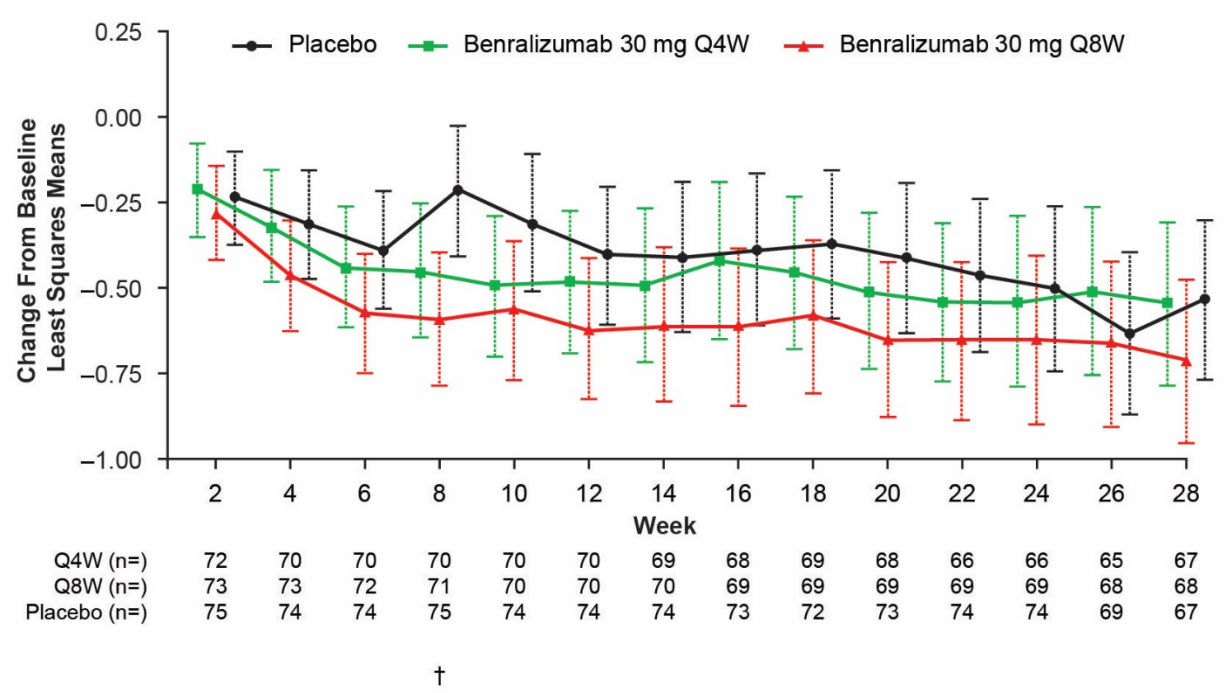
Figure S3. Change from Baseline to End of Therapy in FEV_1



Change from baseline in prebronchodilator FEV_1 was analyzed with a mixed-effect model for repeated measures, which included treatment group, region, and baseline prebronchodilator FEV_1 as covariates. Error bars represent 95% confidence intervals. Nominal P values were calculated using the repeated measures analysis. FEV_1 denotes forced expiratory volume in 1 s, Q4W every 4 weeks regimen, and Q8W every 8 weeks regimen. *P<0.05 for benralizumab Q4W versus placebo. †P<0.05 for benralizumab Q8W versus placebo.

The least squares mean changes from baseline to week 28 in prebronchodilator FEV_1 were 0.126 L, 0.232 L, and 0.239 L for patients who received placebo, benralizumab Q4W, or benralizumab Q8W, respectively. The least squares mean differences at week 28 for benralizumab Q4W and Q8W, versus placebo, were 0.105 L (95% CI, –0.040 to 0.251; P=0.153) and 0.112 L (95% CI, –0.033 to 0.258; P=0.129), respectively.

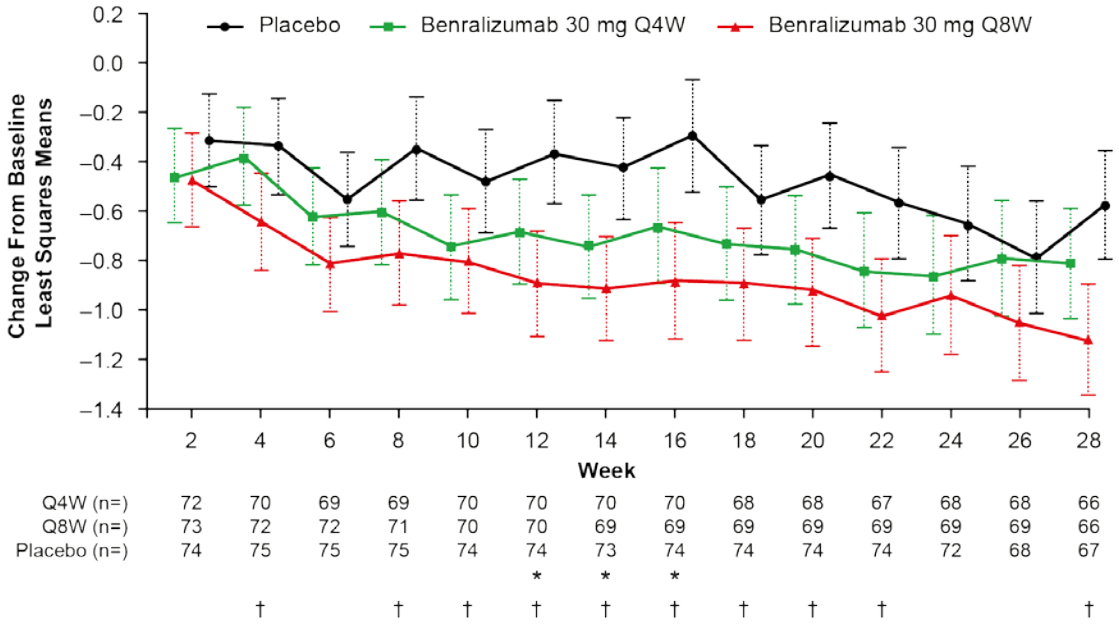
Figure S4. Change from Baseline to End of Therapy in Total Asthma Symptom Score



The total asthma symptom score is a composite of morning assessments of asthma symptoms, night-time awakenings, and rescue medication use, and an evening assessment of activity impairment, scored on a 0–6 scale. A greater score indicates a greater symptom burden. Change from baseline in score was analyzed with a mixed-effect model for repeated measures, which included treatment group, region, and baseline total asthma symptom score as covariates. For this analysis, it was assumed that missing data were random. Error bars represent 95% confidence intervals. Nominal P values were calculated using the repeated measures analysis. Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen. †P<0.05 for benralizumab Q8W vs. placebo.

The least squares mean changes from baseline to week 28 in total asthma symptom scores were –0.53, –0.54, and –0.71 for patients who received placebo, benralizumab Q4W, or benralizumab Q8W, respectively. The least squares mean differences at week 28 for benralizumab Q4W and Q8W, versus placebo, were –0.01 (95% CI, –0.35 to 0.32; P=0.947) and –0.18 (95% CI, –0.51 to 0.16; P=0.291), respectively.

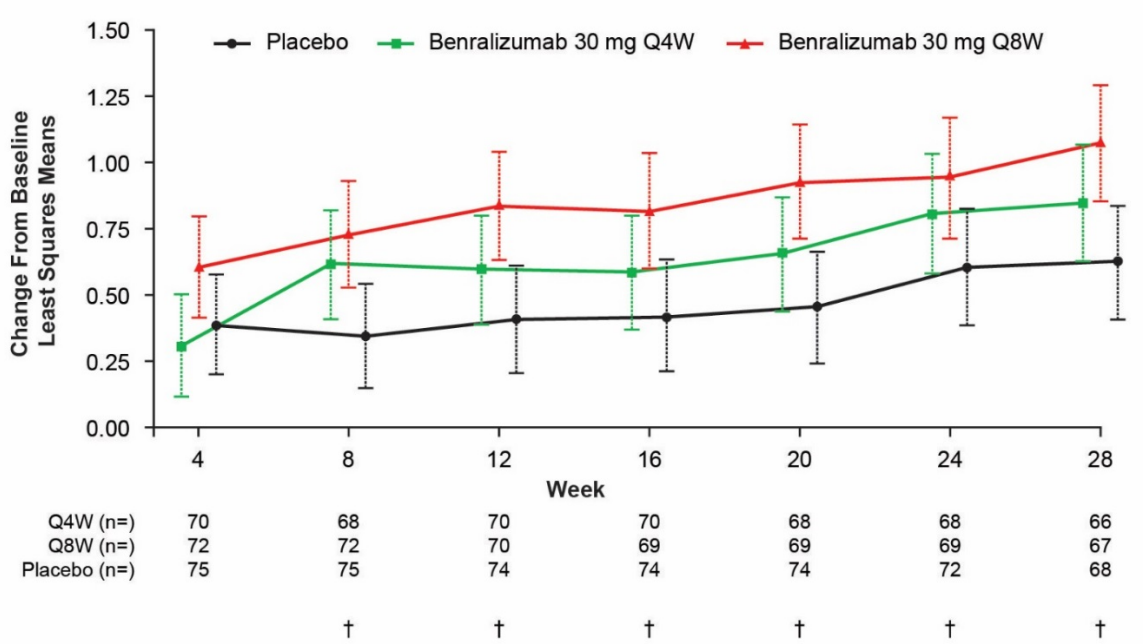
Figure S5. Change from Baseline to End of Therapy in Asthma Control Questionnaire 6 Score



The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale. Low numbers represent better control. Score changes of ≥0.5 were considered clinically meaningful. Change from baseline in Asthma Control Questionnaire 6 score was analyzed with a mixed-effect model for repeated measures, which included treatment group, region, and baseline questionnaire score as covariates. For this analysis, it was assumed that missing data were random. Error bars represent 95% confidence intervals. Nominal P values were calculated using the repeated measures analysis. Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen. *P<0.05 for benralizumab Q4W versus placebo. †P<0.05 for benralizumab Q8W versus placebo.

The least squares mean changes from baseline to week 28 in Asthma Control Questionnaire 6 scores were –0.57, –0.81, and –1.12 for patients who received placebo, benralizumab Q4W, or benralizumab Q8W, respectively. The least squares mean differences at week 28 for benralizumab Q4W and Q8W, versus placebo, were –0.24 (95% CI, –0.55 to 0.08; P=0.139) and –0.55 (95% CI, –0.86 to –0.23; P=0.001), respectively.

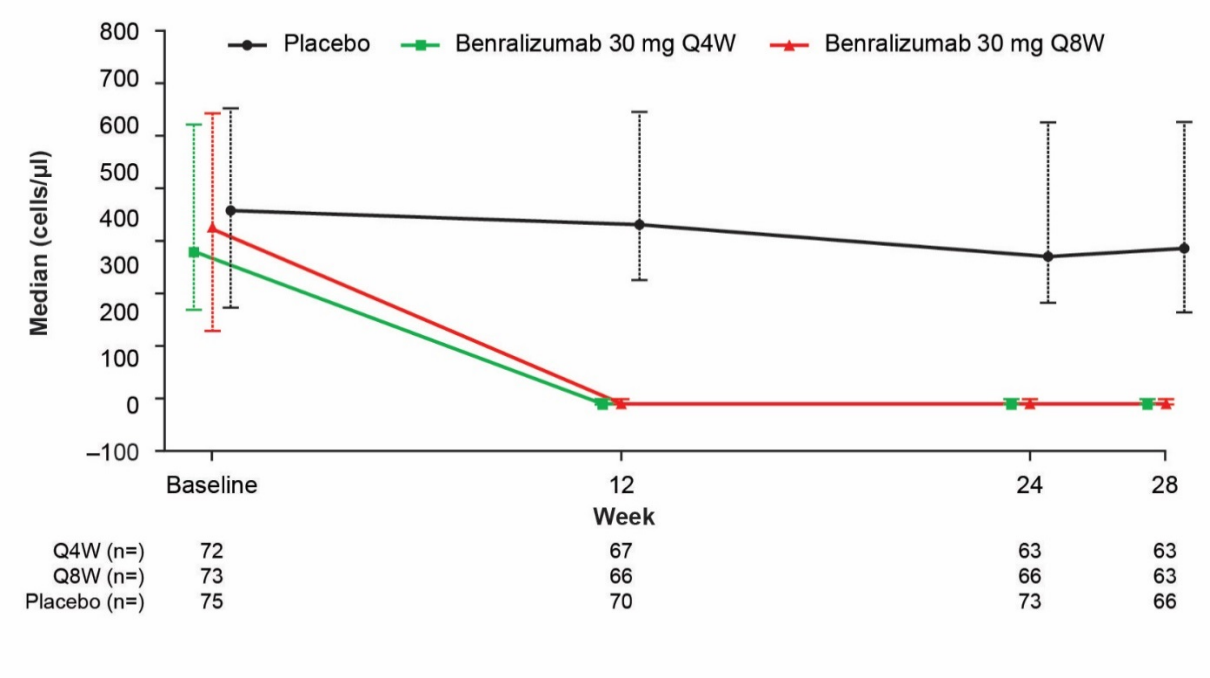
Figure S6. Change from Baseline to End of Therapy in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older



The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale. Greater scores indicate better asthma-related quality of life. Score changes of ≥0.5 were considered clinically meaningful. Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older score was analyzed with a mixed-effect model for repeated measures, which included treatment group, region, and baseline questionnaire score as covariates. For this analysis, it was assumed that missing data were random. Error bars represent 95% confidence intervals. Nominal P values were calculated using the repeated measures analysis. Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen. †P<0.05 for benralizumab Q8W versus placebo.

The least squares mean changes from baseline to week 28 in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older scores were 0.63, 0.85, and 1.08 for patients who received placebo, benralizumab Q4W, or benralizumab Q8W, respectively. The least squares mean differences at week 28 for benralizumab Q4W and Q8W, versus placebo, were 0.23 (95% CI, –0.08 to 0.53; P=0.151) and 0.45 (95% CI, 0.14 to 0.76; P=0.004), respectively.

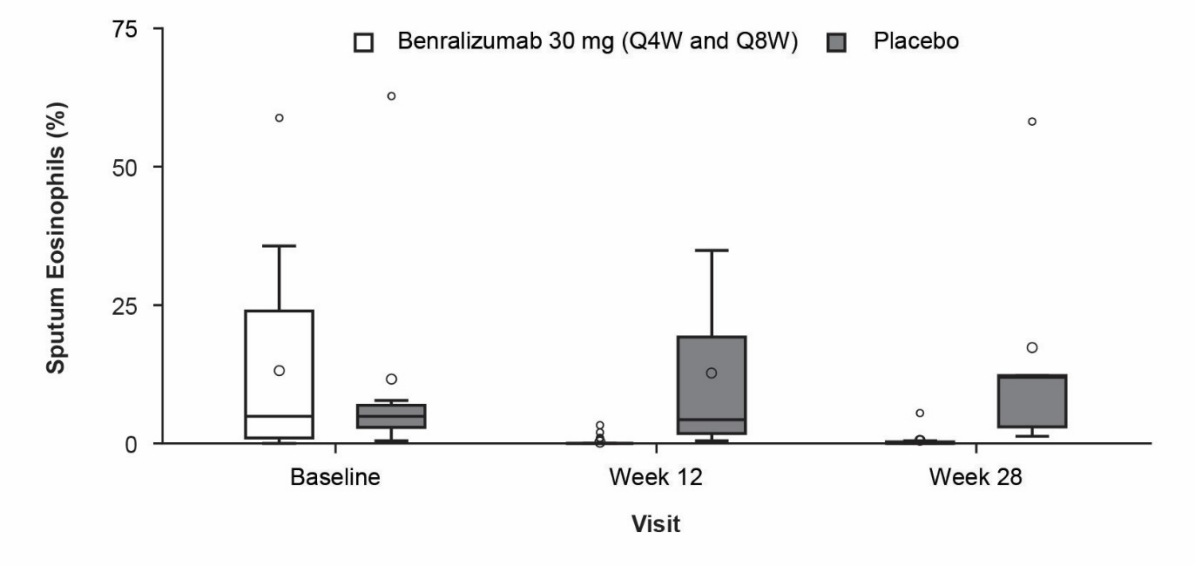
Figure S7. Blood Eosinophil Counts



Error bars represent upper and lower quartiles. Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

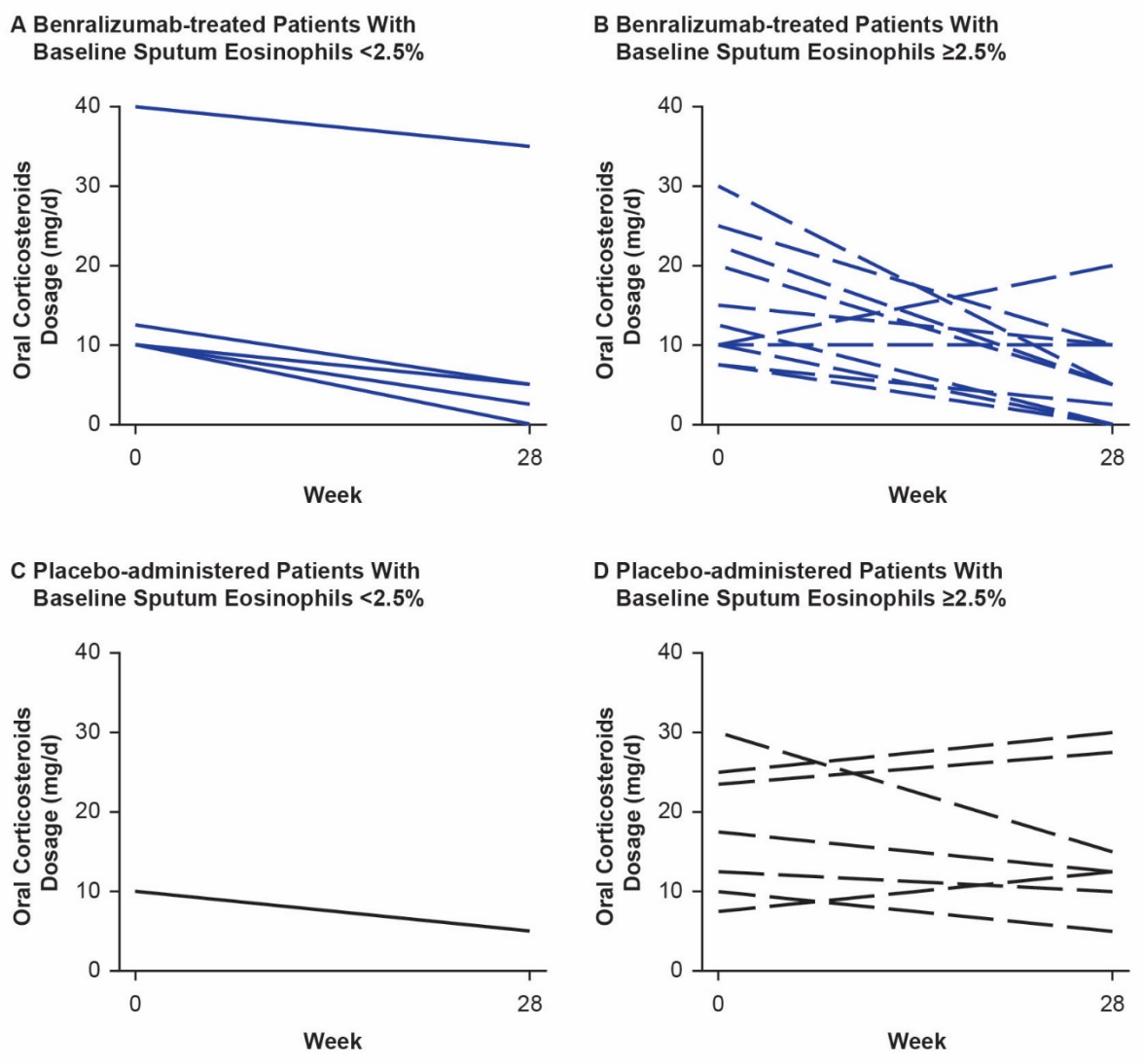
Median blood eosinophil counts at week 28 were 0 cells/µl (range 0–560) for patients treated with benralizumab Q4W, 0 cells/µl (range 0–440) for patients treated with benralizumab Q8W, and 340 cells/µl (range 0–2960) for patients who received placebo. The median percent changes from baseline in blood eosinophil counts at week 28 were –100% (range –100 to 2) for benralizumab Q4W and –100 % (range –100 to 0) for benralizumab Q8W, compared with –6% (range –100 to 1600) for placebo. The least squares mean differences at week 28 (repeated measures analysis) for benralizumab Q4W and Q8W, versus placebo, were –162% (95% CI, –220 to –104; P<0.001) and –159 (95% CI, –218 to –101; P<0.001), respectively.

Figure S8. Sputum Eosinophilia



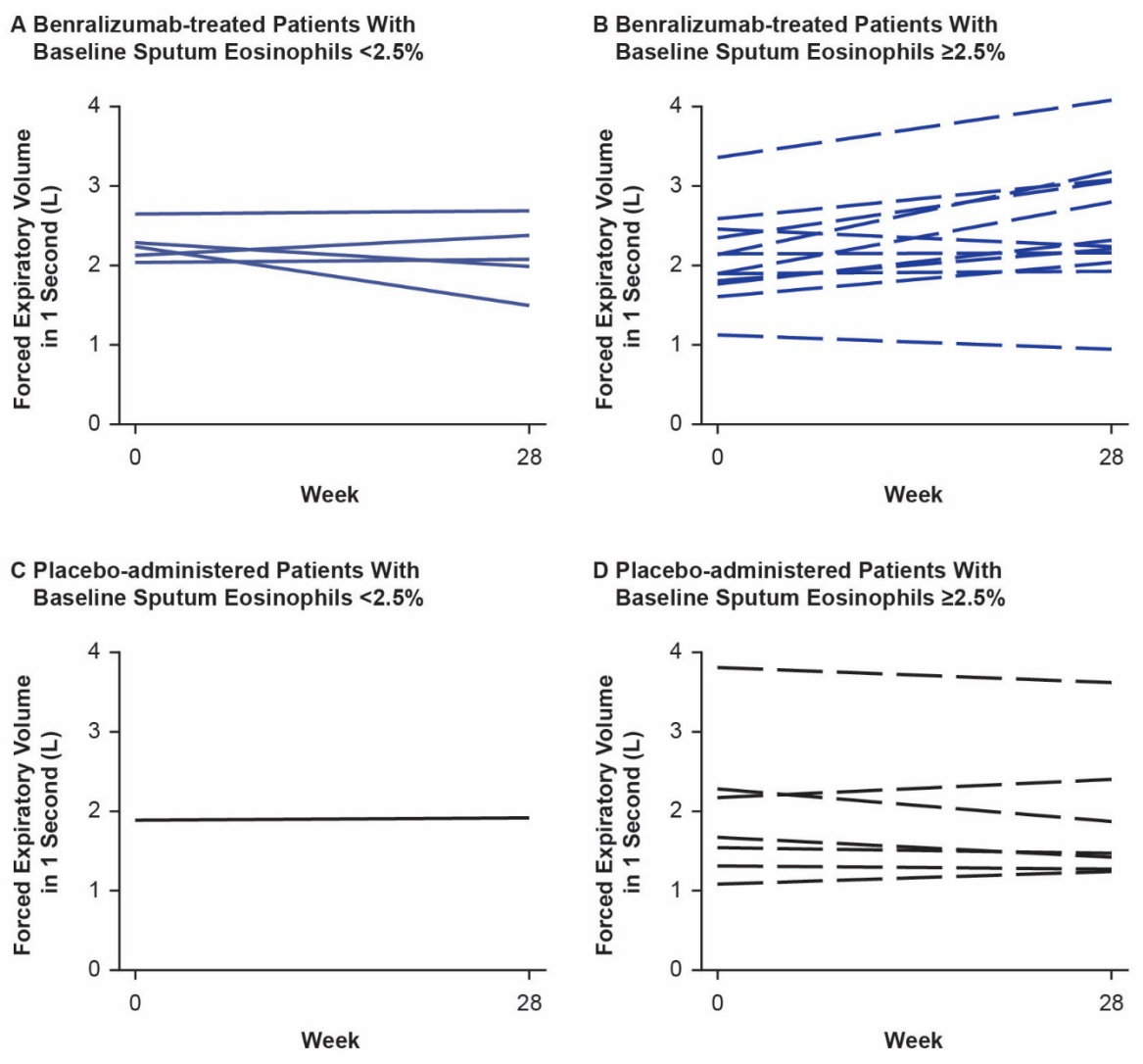
Median sputum eosinophils were depleted for patients treated with benralizumab from 4.90% (range, 0.0–59.0; n = 18) at baseline, to 0.0% (range, 0.0–3.3; n = 16) at week 12, and 0.15% (range, 0.0–0.8; n = 8) at week 28. For patients who received placebo, median sputum eosinophil counts increased from 4.90% (range, 0.5–63.0; n = 8) at baseline, to 17.55% (range, 0.5–35.0; n = 4) at week 12, and 12.15% (range, 1.3–58.3; n = 4) at week 28. The least squares mean changes from baseline at week 12 were –8.14% (95% CI, –13.80 to –2.48; n = 12) for patients treated with benralizumab and 9.50% (95% CI, –0.18 to 19.17; n = 4) for patients who received placebo. The least squares mean changes from baseline at week 28 (repeated measures analysis) were –7.95% (95% CI, –18.96 to 3.06; n = 7) for benralizumab and 11.34% (95% CI, –5.99 to 28.66; n = 3) for placebo. The least squares mean differences at week 12 and week 28 for benralizumab, versus placebo, were –17.64% (95% CI, –29.03 to –6.25) and –19.29% (95% CI, –39.84 to 1.26), respectively. Other biomarkers tested did not demonstrate clear treatment differences.

Figure S9. Oral Glucocorticoid Dose by Baseline Sputum Eosinophilia



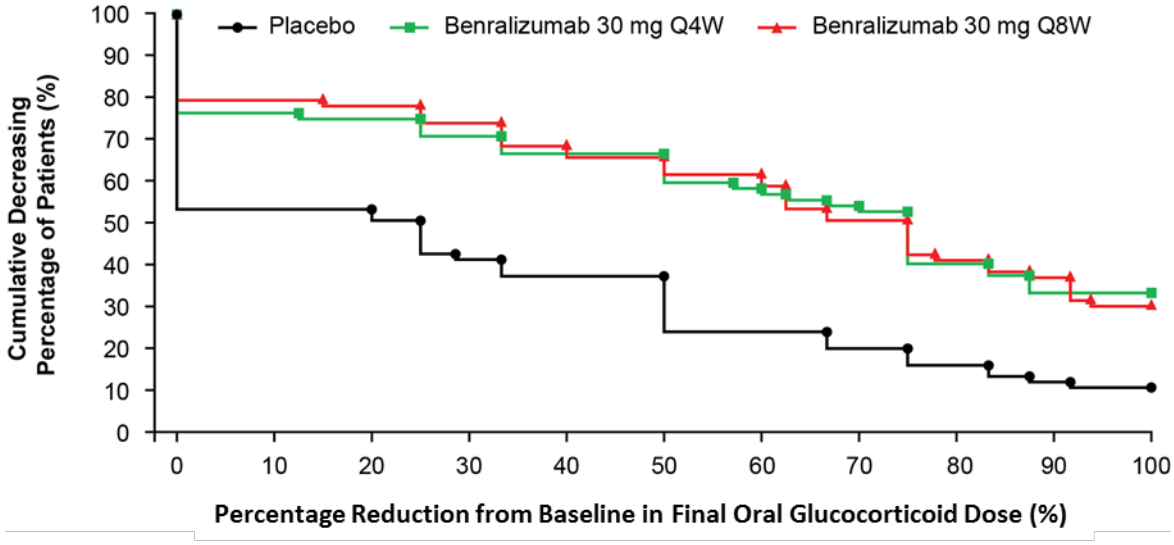
Panels A and B provide oral glucocorticoid doses for patients treated with benralizumab who had baseline sputum eosinophils <2.5% (n = 5) or ≥2.5% (n = 13), respectively. Panels C and D indicate oral glucocorticoid doses for patients who received placebo who had baseline sputum eosinophils <2.5% (n = 1) or ≥2.5% (n = 7), respectively.

Figure S10. Lung Function by Baseline Sputum Eosinophilia



Panels A and B provide forced expiratory volume in 1 second for patients treated with benralizumab who had baseline sputum eosinophils <2.5% (n = 5) or ≥2.5% (n = 13), respectively. Panels C and D indicate forced expiratory volume in 1 second for patients who received placebo who had baseline sputum eosinophils <2.5% (n = 1) or ≥2.5% (n = 7), respectively.

Figure S11. Cumulative Distribution of Percentage Reduction from Baseline in Final Oral Glucocorticoid Dose



Q4W denotes every 4 weeks regimen, and Q8W every 8 weeks regimen.

8. References

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