

Original Article

A Randomized Pragmatic Trial of Changing to and Stepping Down Fluticasone/Formoterol in Asthma

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What is already known about this topic? A few randomized trials have investigated step-down of inhaled corticosteroid therapy; however, very few have looked at predictors for response to step-down.

What does this article add to our knowledge? We identified exacerbation history in the last 12 months to be a significant predictor for exacerbations after inhaled corticosteroid/long-acting β_2 agonist therapy step-down.

How does this study impact current management guidelines? This study suggests that asthma stability for 3 months, as indicated in current guidelines and consensus documents, is likely to be insufficient to determine whether a patient is suitable for therapy step-down.

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Abbreviations used

ACQ7- 7-question Asthma Control Questionnaire
*F*_{ENO}- Fractional exhaled nitric oxide
 FP/FOR- Fluticasone propionate/formoterol fumarate
 FP/SAL- Fluticasone propionate/salmeterol xinafoate
*F*_{VC}- Forced vital capacity
 GINA- Global Initiative for Asthma
 ICS- Inhaled corticosteroid
 LABA- Long-acting β_2 agonist
 Mini-AQLQ- Mini Asthma Quality of Life Questionnaire
 pMDI- Pressurized metered-dose inhaler
 VAS- Visual analog scale

BACKGROUND: Guidelines recommend reducing treatment in patients with well-controlled asthma after 3 months of stability. However, there is inadequate real-life data to guide physicians on therapy change in daily practice.

OBJECTIVE: To assess asthma control after change to and step-down of fluticasone propionate/formoterol fumarate dihydrate (FP/FOR) in real-life patients.

METHODS: In a randomized controlled, pragmatic, open-label trial, 225 well-controlled patients with asthma were randomized (1:2) to maintain high-dose fluticasone propionate/salmeterol xinafoate (FP/SAL, 1000/100 μ g) or switch to FP/FOR (1000/40 μ g) daily for 12 weeks (phase 1). One hundred sixteen patients stable on FP/FOR at week 12 were subsequently randomized (1:1) to maintain this therapy, or stepped down to FP/FOR (500/20 μ g) daily for 12 weeks (phase 2). The primary end point was the 7-question Asthma Control Questionnaire (ACQ7) score.

RESULTS: In phase 1, FP/FOR (1000/40 μ g) ($n = 126$) was noninferior to FP/SAL (1000/100 μ g) ($n = 73$) for ACQ7 (difference in means, -0.12 ; 95% CI, -0.32 to 0.09). In phase 2, FP/FOR (500/20 μ g) ($n = 52$) was noninferior to FP/FOR (1000/40 μ g) ($n = 52$) for ACQ7 (difference in means, 0.01 ; 95% CI, -0.20 to 0.22). There was no significant difference in exacerbation rate between the groups in either phase. However, 1 to 2 exacerbations in 12 months before phase 1 were associated with the occurrence of an exacerbation after step-down ($P = .007$).

CONCLUSIONS: In patients with well-controlled asthma, a change from FP/SAL to FP/FOR did not compromise asthma control. Step-down of FP/FOR was well tolerated; however, in contrast to current guidelines, our data suggest caution in stepping down patients uncontrolled in the last 12 months. Larger step-down studies are required to confirm these findings. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: ACQ7; Biomarkers; Combination therapy; Fluticasone; Formoterol; Fractional exhaled nitric oxide; Inhaled corticosteroids; Pragmatic trials; Salmeterol; Step-down; Antiasthmatic agents

The Global Initiative for Asthma (GINA) document recommends a step-up in treatment for patients whose asthma is not controlled on low-dose inhaled corticosteroid (ICS) monotherapy to a combination of an ICS and a long-acting β_2 agonist (LABA).¹ Once asthma has been well controlled for at least 3 months, a stepwise reduction of treatment, by approximately 25% to 50% each time, is recommended such that patients

should be maintained at the lowest possible dose of ICS that effectively achieves disease stability.¹ Yet these recommendations are often not implemented, leading many patients with asthma to be overtreated with high doses of ICS and LABA, which increases treatment costs and unnecessarily exposes the patients to treatment side effects.² Although ICS reduces exacerbations, real-life data suggest that LABA is more effective in controlling asthma symptoms.³ It is therefore possible that even symptomatic patients who are not frequently exacerbating could be managed with lower doses of ICS without compromising asthma control.

A few randomized trials have investigated the step-down of ICS therapy⁴⁻¹⁰; however, very few have looked at predictors for response to step-down, and the findings from these studies have not provided conclusive answers as to who can be safely stepped down.¹⁰⁻¹³ Importantly, none of the studies undertook simultaneous step-down of both ICS and LABA, which is highly relevant in daily clinical practice. Therefore, there is clearly a need for pragmatic evidence-based data on the effectiveness and safety of the step-down of ICS/LABA combination therapy. This may help overcome the hesitancy that clinicians experience to change or reduce treatment, particularly in those patients they have spent time and effort in stabilizing in their day-to-day practice.

The primary objective of this randomized controlled, pragmatic trial was to assess asthma control after a change from fluticasone propionate/salmeterol xinafoate (FP/SAL) to fluticasone propionate/formoterol fumarate dihydrate (FP/FOR) and then step-down of FP/FOR, for which the treatments were all delivered by a pressurized metered-dose inhaler (pMDI) with the same ICS. In addition, we sought to identify factors that might predict worsening of asthma after step-down, because such factors may guide individualized treatment decisions in a clinical setting and improve clinical outcomes.

METHODS

Study design

This was a 24-week randomized controlled, pragmatic, open-label trial (clinicaltrials.gov: NCT02388373; EudraCT: 2013-005365-39) consisting of a 12-week change phase (phase 1) followed by a 12-week step-down phase (phase 2) (Figure 1). To obtain a representative sample of real-life well-controlled adult patients with asthma, study participants were recruited from 27 primary care practices across England (between July 2014 and September 2015).

In phase 1, the investigative treatment was fluticasone propionate/formoterol fumarate dihydrate 250 μ g/10 μ g taken 2 puffs twice a day (hereafter indicated as "FP/FOR(1000)") (Flutiform 250 pMDI, Napp Pharmaceuticals Ltd., Cambridge, UK), and the comparator treatment was fluticasone propionate/salmeterol xinafoate 250 μ g/25 μ g taken 2 puffs twice a day (hereafter indicated as "FP/SAL(1000)") (Seretide 250 Evohaler pMDI, GlaxoSmithKline, Brentford, UK). In phase 2, the investigative treatment was FP/FOR 125 μ g/5 μ g taken 2 puffs twice a day (hereafter indicated as "FP/FOR(500)") (Flutiform 125 pMDI, Napp Pharmaceuticals Ltd.). The comparator treatment in phase 2 was FP/FOR(1000).

In phase 1, participants meeting the eligibility criteria were randomized (2:1) to either change to FP/FOR(1000) or stay on FP/SAL(1000). After 12 weeks, participants in the FP/FOR(1000) arm who had remained stable on the therapy and provided consent to continue were randomized (1:1) to either stay on FP/FOR(1000) or step down to FP/FOR(500) for 12 weeks. There was also an interim visit at week 4 of phase 2. Randomization for both phases

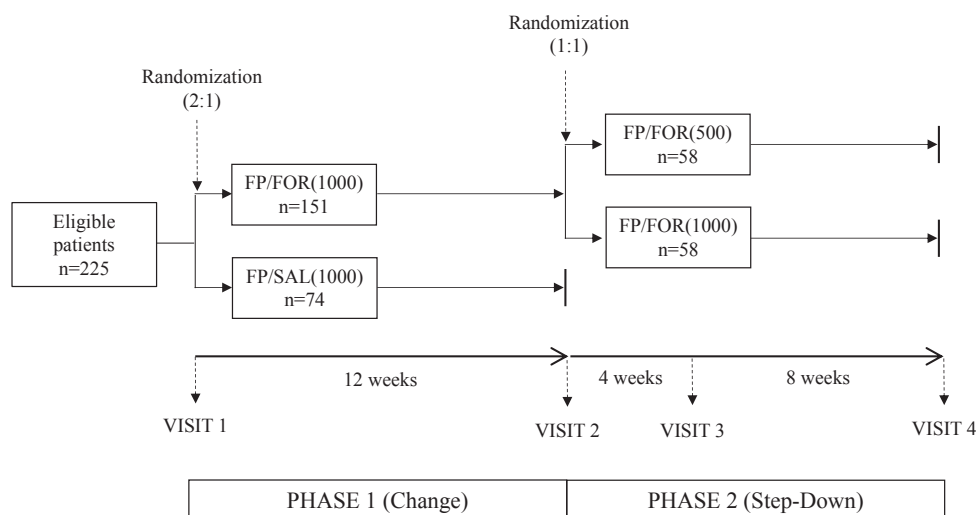


FIGURE 1. Study design and number of patients randomized to each phase. Scheme depicting the study design, timeline, and the number of patients randomized into the 2 study phases. *FP/FOR*, Fluticasone propionate/formoterol fumarate dihydrate; *FP/SAL*, fluticasone propionate/salmeterol xinafoate.

was performed using a centralized computer-based program, stratified in blocks of 3 for phase 1 and blocks of 4 for phase 2, on the basis of center code and occurrence of exacerbations in the 12 months before enrollment into phase 1 (no exacerbation or 1-2 exacerbations).

Study population

Participants eligible for phase 1 were aged between 18 and 75 years, had a diagnosis of asthma, had been prescribed FP/SAL(1000) (as Seretide 250 Evohaler pMDI 2 puffs twice a day) for at least 6 months before enrollment, and demonstrated a satisfactory inhaler technique without serious inhaler technique errors, after device training if required, at screening. Exclusion criteria were diagnosis of any chronic respiratory disease other than asthma, pregnancy, 1 or more severe asthma exacerbations in the 3 months before enrollment, 3 or more severe asthma exacerbations in the 12 months before enrollment, and uncontrolled asthma assessed in accordance with the 2012 GINA recommendations on the basis of symptoms in the last week.¹⁴ A *severe exacerbation* was defined as worsening of asthma requiring treatment with a course of oral corticosteroids, hospitalization, or accident and emergency department attendance. Participants eligible for phase 2 had been previously randomized to FP/FOR in phase 1, had not had any severe exacerbations during phase 1, and were considered suitable for step-down by the consenting physician.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and approved by the National Research Ethics Service Committee East of England (Cambridgeshire and Hertfordshire). Conduct of the trial at the study centers was approved by the local National Health Service research and development offices. All patients provided written informed consent at the beginning of each phase before any study-specific procedures were conducted.

Study outcomes

The primary outcome in both phases was asthma control measured with the 7-question Asthma Control Questionnaire (ACQ7) score.¹⁵ Secondary outcome measures included occurrence

of asthma exacerbations (as defined in the previous section), asthma control assessed by the research health care professional at each site in accordance with the 2012 GINA recommendations (ie, uncontrolled, partially controlled, and controlled asthma),¹⁴ Mini Asthma Quality of Life (Mini-AQLQ) score,¹⁶ visual analog scale (VAS) test score (to assess patients' perception of asthma symptoms on a scale from 0 [not at all bothersome] to 10 [extremely bothersome]; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org),^{17,18} and lung function (as assessed by forced vital capacity [FVC], FEV₁, FVC% predicted, FEV₁% predicted, and FEV₁/FVC ratio). An additional secondary outcome in phase 2 was fractional exhaled nitric oxide (FENO), measured using the NIOX MINO or VERO device (Aerocrine AB, Solna, Sweden) to assess airway inflammation.^{19,20} All outcomes were also assessed and analyzed for phase 2 at an interim visit (week 4), except for exacerbations for which the 4-week period was not considered sufficiently long. Blood eosinophil levels were measured at phase 2 baseline and other clinical and demographic characteristics were used to test for correlation with response to step-down. Adherence was calculated from dose counter values and analyzed in both phases. Finally, adverse events (AEs) were classified on the basis of System Organ Class of the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 (MedDRA MSSO, McLean, Va)²¹ and summarized by treatment group.

Sample size

The study was powered to reject the null hypothesis that the mean ACQ7 scores are not equivalent between 2 treatments when the expected difference in mean ACQ7 score is 0.0, with a common SD of 0.8, and the acceptable maximum difference is -0.3. In phase 1, a sample size of 201 (134 FP/FOR and 67 FP/SAL, 2:1 ratio) was estimated to have 80% power to reject the null hypothesis at .050 one-sided significance level. Assuming a 10% dropout rate, 224 patients were required for randomization for phase 1. It was estimated that 51 patients in each group would continue to complete phase 2 of the study, providing 59% power to reject the null hypothesis in phase 2.

Statistical analysis

An intention-to-treat analysis as initially presented in the study protocol (see [Figure E2](#) in this article's Online Repository at www.jaci-inpractice.org) was not considered appropriate because patients randomized to the experimental FP/FOR group were more likely to switch to the control FP/SAL treatment (ie, revert to usual treatment) during the study than vice versa and therefore noninferiority could have been erroneously concluded. Hence, an amendment to the analysis plan was made before initiating data analyses (see [Figure E3](#) in this article's Online Repository at www.jaci-inpractice.org). In each phase, for the analysis of the primary outcome, ACQ7, we defined a noninferiority analysis set, which included all patients who remained in the study for at least 8 weeks (ie, if terminating early, did not complete the final visit of that phase any earlier than 8 weeks after the baseline visit) and did not change treatment at any time during the follow-up period (ie, before the final visit of that phase). For secondary outcome analyses, we defined a full analysis set, which included all randomized patients. Secondary outcomes were tested for superiority.

Baseline characteristics were compared using Mann-Whitney *U* test and chi-square test for continuous and categorical variables, respectively. The ACQ7 score was analyzed using a linear mixed model and adjusted for baseline ACQ7 score and randomization variables (ie, occurrence of exacerbations in the 12 months before enrollment into phase 1 and center number [fitted as a random effect]). For both phases, noninferiority boundary for difference in adjusted mean ACQ7 scores between the groups was set at 0.3, with noninferiority declared if the upper limit of 95% CI was 0.3 or less. Lung function outcomes, VAS score, and Mini-AQLQ score were analyzed using a linear mixed model, adjusting for randomization variables; VAS score was also corrected for baseline VAS score. Significance was declared if the lower limit of 95% CI was more than 0. GINA asthma control and FENO were analyzed using an ordinal mixed model, and logistic mixed model was used to compare the occurrence of exacerbations. Significance was declared if the lower limit of 95% CI was more than 1. A chi-square test was used to compare adherence using data from inhaler dose counters.

To investigate potential predictive markers for response to step-down, only patients randomized to FP/FOR(500) in phase 2 were considered. Two definitions for worsening or maintenance of asthma control after step-down were used as outcomes in these analyses. First, patients were classified on the basis of a change in the ACQ7 score at week 12 from phase 2 baseline, with worsening defined as an increase in of 0.5 or more in the ACQ7 score. Second, patients were classified on the basis of an occurrence of an exacerbation, with worsening of asthma defined as an occurrence of 1 or more exacerbation in phase 2. Univariate logistic regression models were used to test whether age, sex, smoking status, selected comorbidities, number of exacerbations in the 12 months before phase 1, and baseline ACQ7 score, GINA, FENO, blood eosinophil count, and FEV₁% predicted were related to the 2 response outcomes.

For all analyses in which *P* value is provided, statistical significance was set at .05. All analyses were performed using Statistical Analysis Software version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient disposition and characteristics

Of the 259 participants enrolled in the study, 225 met all eligibility criteria and were randomized (2:1) into phase 1—151 to FP/FOR(1000) and 74 to FP/SAL(1000) ([Figure 2](#)). Of the

34 patients who failed at 1 or more eligibility criteria, 27 had uncontrolled asthma according to GINA criteria, 5 failed to achieve a satisfactory inhaler technique, 3 had an asthma exacerbation in the 3 months before screening visit, and 2 had 3 or more exacerbations in the 12 months before screening visit. A total of 134 (88.7%) participants in the FP/FOR(1000) group and 73 (98.6%) in the FP/SAL(1000) group completed the 12-week outcome visit. One hundred twenty-six participants in the FP/FOR(1000) group and 73 in the FP/SAL(1000) group met the criteria for the noninferiority analysis set for phase 1. Of the 134 participants in the FP/FOR(1000) group who completed phase 1, 116 were eligible and randomized into phase 2—58 to FP/FOR(1000) and 58 to FP/FOR(500) ([Figure 3](#)). Of the remaining 18 patients, 5 were not eligible for phase 2 because of an exacerbation in phase 1 and 13 patients did not provide consent to phase 2; 3 of the 13 patients were uncontrolled according to GINA criteria, 3 reported AEs on FP/FOR, 1 was uncontrolled and reported AEs, and 6 did not want to continue in the study for other reasons. Fifty-four participants in the FP/FOR(1000) group and 53 in the FP/FOR(500) group completed the 12-week outcome visit. Finally, 52 participants in each group met the criteria for the noninferiority analysis set for phase 2. The demographic and clinical characteristics of the participants did not differ significantly between the groups in either phase ([Table I](#)).

Change from FP/SAL to FP/FOR (phase 1)

At week 12 of phase 1, asthma was well controlled in both FP/FOR(1000) and FP/SAL(1000) groups (mean ACQ7 scores, 0.7 and 0.8, respectively), and FP/FOR(1000) was noninferior to FP/SAL(1000) in terms of ACQ7 score at 0.3 noninferiority boundary (difference in means, -0.12 ; 95% CI, -0.32 to 0.09) ([Table II](#)). Using the minimal clinically important difference of 0.5 in ACQ7 score, 18.0% of patients in the FP/FOR(1000) group and 15.3% in the FP/SAL(1000) group improved from baseline, whereas 12.8% and 19.4% deteriorated, respectively. There was no significant difference between the FP/FOR(1000) group and the FP/SAL(1000) group in Mini-AQLQ score, VAS score, lung function measures, and percentage of patients with an exacerbation during phase 1 ([Table II](#)). However, the odds of being more controlled according to GINA criteria were significantly higher for the FP/FOR(1000) group (odds ratio, 2.00; 95% CI, 1.14 to 3.52; $P = .016$) ([Table II](#)). Adherence was high in both groups and there was no significant difference in the distribution into adherence categories between the groups in patients with GINA asthma control outcome data ($P = .51$) (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Step-down of FP/FOR (phase 2)

At week 12 of phase 2, good control of asthma was maintained in both FP/FOR(1000) and FP/FOR(500) groups, although there was a small but clinically nonsignificant worsening in mean ACQ7 scores from phase 2 baseline in both groups ([Table III](#)). Adjusted difference in means at week 12 was 0.01 (95% CI, -0.20 to 0.22) within the 0.3 noninferiority boundary, indicating that FP/FOR(500) was noninferior to FP/FOR(1000). Using the minimal clinically important difference of 0.5 in ACQ7 score, 7.5% of participants in the FP/FOR(500) group and 7.4% in the FP/FOR(1000) group improved from baseline, whereas 22.6% and 18.5% deteriorated, respectively.

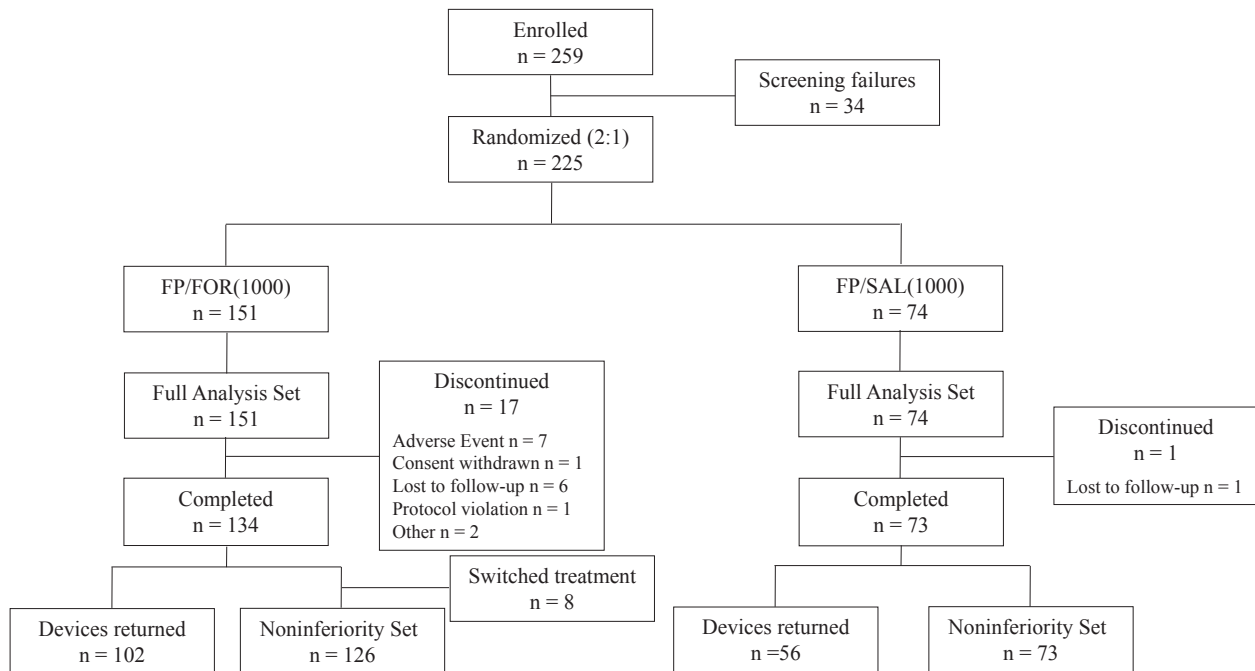


FIGURE 2. CONSORT diagram for phase 1. CONSORT diagram showing the number of patients at different stages of phase 1, including those initially enrolled in the study, those lost after screening for inclusion/exclusion criteria or for dropouts, and those who completed phase 1. The noninferiority set included all patients who used the randomized treatment for at least 8 weeks and did not change treatment at any time during the follow-up period. The full analysis set included all randomized patients. *FP/FOR*, Fluticasone propionate/formoterol fumarate dihydrate; *FP/SAL*, fluticasone propionate/salmeterol xinafoate.

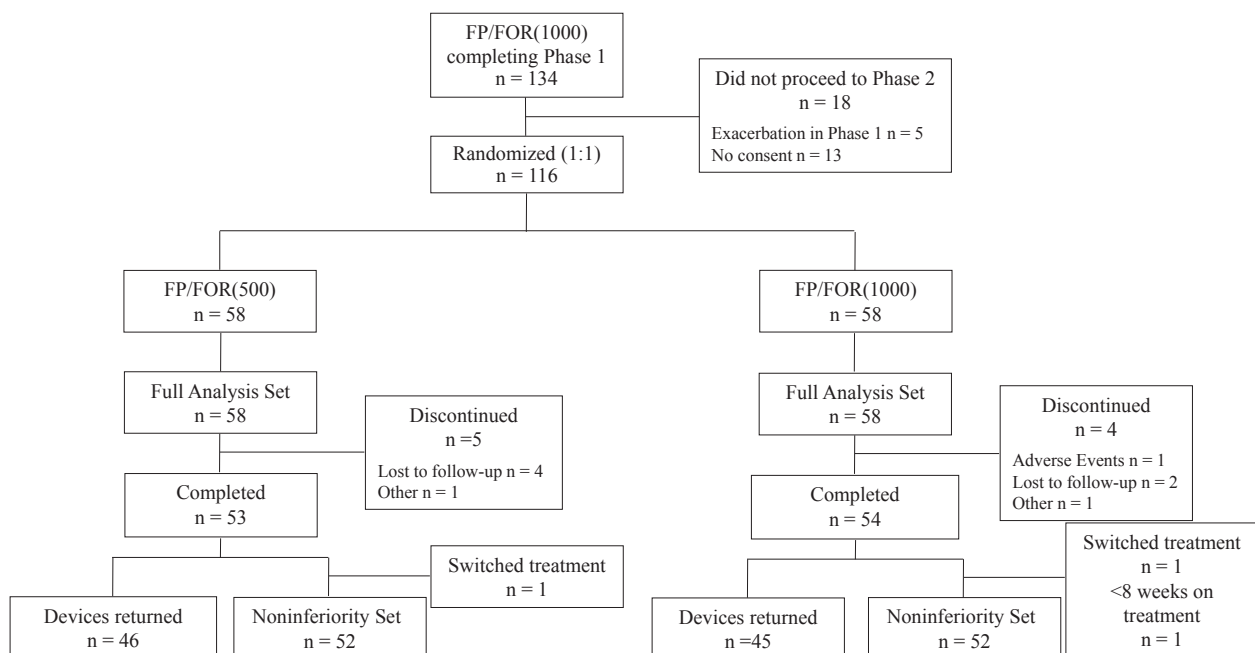


FIGURE 3. CONSORT diagram for phase 2. CONSORT diagram showing the number of patients at different stages of phase 2, including those lost after screening or for dropouts and those who completed phase 2. The noninferiority set included all patients who used the randomized treatment for at least 8 weeks and did not change treatment at any time during the follow-up period. The full analysis set included all randomized patients. *FP/FOR*, Fluticasone propionate/formoterol fumarate dihydrate.

TABLE I. Patients' baseline characteristics

Characteristic	Phase 1			Phase 2		
	FP/FOR(1000) (N = 151)	FP/SAL(1000) (N = 74)	P value	FP/FOR(500) (N = 58)	FP/FOR(1000) (N = 58)	P value
Age (y)						
Mean $\pm$ SD	53.0 $\pm$ 13.4	55.1 $\pm$ 13.7	.204*	52.3 $\pm$ 13.8	53.5 $\pm$ 13.1	.689*
Minimum, maximum	20.0, 74.0	20.0, 74.0		21.0, 72.0	20.0, 74.0	
Sex: male, n (%)	69 (45.7)	31 (41.9)	.59†	23 (39.7)	29 (50.0)	.263†
Ethnic group, n (%)						
Asian/Asian British	1 (0.7)	1 (1.4)	.685†	1 (1.7)	0 (0.0)	.315†
Black/African/Caribbean/black British	1 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
White	149 (98.7)	73 (98.6)		57 (98.3)	58 (100.0)	
Body mass index categorized, n (%)						
Normal	26 (17.2)	13 (17.6)	.803†	9 (15.5)	9 (15.5)	.432†
Obese	69 (45.7)	34 (45.9)		28 (48.3)	25 (43.1)	
Overweight	54 (35.8)	27 (36.5)		19 (32.8)	24 (41.4)	
Underweight	2 (1.3)	0 (0.0)		2 (3.4)	0 (0.0)	
Asthma exacerbations in the 12 mo before phase 1, n (%)						
0	113 (74.8)	56 (75.7)	0.984†	44 (75.9)	42 (72.4)	0.899†
1	29 (19.2)	14 (18.9)		11 (19.0)	13 (22.4)	
2	9 (6.0)	4 (5.4)		3 (5.2)	3 (5.2)	
Employment status, n (%)						
Employed	94 (62.3)	44 (59.5)	0.043†	34 (58.6)	40 (69.0)	0.397†
Retired	35 (23.2)	26 (35.1)		12 (20.7)	11 (19.0)	
Unemployed	22 (14.6)	4 (5.4)		12 (20.7)	7 (12.1)	
Smoking status, n (%)						
Never smoked	63 (41.7)	33 (44.6)	0.773†	23 (39.7)	24 (41.4)	0.291†
Ex-smoker	63 (41.7)	28 (37.8)		22 (37.9)	28 (48.3)	
Smoker	22 (14.6)	10 (13.5)		12 (20.7)	6 (10.3)	
Data missing	3 (2.0)	3 (4.1)		1 (1.7)	0 (0.0)	
Alcohol units/wk, n (%)						
0	54 (35.8)	30 (40.5)	0.938†	25 (43.1)	17 (29.3)	0.216†
1-10	61 (40.4)	26 (35.1)		23 (39.7)	22 (37.9)	
10-30	29 (19.2)	15 (20.3)		7 (12.1)	15 (25.9)	
30-50	4 (2.6)	2 (2.7)		1 (1.7)	3 (5.2)	
50-100	3 (2.0)	1 (1.4)		2 (3.4)	1 (1.7)	

*P value from Mann-Whitney U test.

†P value from chi-square test.

There was no significant difference between the FP/FOR(500) group and the FP/FOR(1000) group in Mini-AQLQ score, VAS score, lung function measures, FENO, or GINA asthma control at week 4 or week 12, and percentage of participants with an exacerbation during phase 2 (Table III). Finally, there was no significant difference in the distribution into adherence categories between the groups ($P = .69$) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Predictors for worsening of asthma after step-down

To identify factors that might predict worsening of asthma after step-down, selected demographic and clinical variables were tested for correlation with deterioration in the ACQ7 score by 0.5, or occurrence of an exacerbation in phase 2 in the FP/FOR(500) group. None of the tested variables showed a statistically significant relationship with worsening of the ACQ7 score (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). However, a significant relationship was

found with history of exacerbations in the last 12 months before the study when occurrence of an exacerbation after step-down was used as the outcome variable ($P = .007$) (Table IV; see also Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Adverse events

Four serious adverse events (SAEs) were reported during the study of which 2 were considered to be possible serious adverse reactions to study drug. Both these 2 serious adverse reactions were hospitalizations due to pneumonia: one occurred in the FP/SAL(1000) group and the other in the FP/FOR(500) group. The other 2 SAEs were a death due to causes unrelated to the study in the FP/FOR(500) group and a self-inflicted injury in a patient in the FP/SAL(1000) group. Occurrence of AEs recorded as treatment-related was overall low in both phases (see Tables E5 and E6 in this article's Online Repository at www.jaci-inpractice.org).

TABLE II. Phase 1 outcomes

Outcome	Phase 1 baseline		Phase 1 week 12		Estimate of treatment effect (95% CI)*	P value
	FP/FOR(1000)	FP/SAL(1000)	FP/FOR(1000)	FP/SAL(1000)		
ACQ7 score, n	126	73	125	72		
Mean $\pm$ SD	0.7 $\pm$ 0.6	0.7 $\pm$ 0.6	0.7 $\pm$ 0.8	0.8 $\pm$ 0.8	−0.12 (−0.32 to 0.09)	NA†
Minimum, maximum	0.0, 3.1	0.0, 2.4	0.0, 5.1	0.0, 4.3		
Mini-AQLQ score, n	150	74	133	73		
Mean $\pm$ SD	6.0 $\pm$ 1.0	5.9 $\pm$ 1.0	6.1 $\pm$ 1.1	5.8 $\pm$ 1.1	0.24 (−0.05 to 0.53)	.103
Minimum, maximum	2.0, 7.0	3.0, 7.0	1.1, 7.0	2.6, 7.0		
GINA, n (%)						
Controlled	68 (45.0)	32 (43.2)	71 (53.0)	28 (38.4)	2.00 (1.14 to 3.52)	.016
Partially controlled	83 (55.0)	42 (56.8)	53 (39.6)	33 (45.2)		
Uncontrolled	0 (0.0)	0 (0.0)	10 (7.5)	12 (16.4)		
VAS score, n	149	74	134	73		
Mean $\pm$ SD	16.6 $\pm$ 18.8	20.8 $\pm$ 24.0	14.1 $\pm$ 22.1	18.0 $\pm$ 23.5	−2.01 (−7.33 to 3.32)	.458
Minimum, maximum	0.0, 100.0	0.0, 95.0	0.0, 100.0	0.0, 83.0		
Exacerbations, n (%)						
None	NA	NA	144 (95.4)	67 (90.5)	2.36 (0.75 to 7.47)	.143
≥ 1			7 (4.6)	7 (9.5)		
Spirometry, n	151	74	133	72		
FEV ₁ (L), mean $\pm$ SD	2.6 (0.8)	2.5 (0.8)	2.6 (0.7)	2.5 (0.8)	0.09 (−0.13 to 0.31)	.426
FEV ₁ % predicted, mean $\pm$ SD	89.0 (17.7)	89.8 (18.9)	88.4 (16.8)	89.3 (18.1)	−0.76 (−5.69 to 4.17)	.762
FVC (L), mean $\pm$ SD	3.6 (1.0)	3.4 (1.0)	3.6 (1.0)	3.5 (0.9)	0.15 (−0.13 to 0.43)	.285
FVC% predicted, mean $\pm$ SD	97.9 (17.2)	99.7 (16.3)	100.8 (16.4)	101.0 (17.6)	−0.01 (−4.74 to 4.72)	.997

NA, Not applicable.

*ACQ7 score, Mini-AQLQ score, VAS score, and spirometry were analyzed with linear mixed model. GINA was analyzed with ordinal mixed model and exacerbations with logistic mixed model.

†FP/FOR(1000) was considered noninferior to FP/SAL(1000) if estimate of treatment effect was within a 0.3 boundary and upper limit of the 95% CI was ≤ 0.3 .

DISCUSSION

There is currently little real-life evidence to support pragmatic recommendations in existing asthma guidelines on how to effectively step down treatment for individual patients in day-to-day practice. To address this gap, we conducted a randomized controlled, pragmatic trial to assess asthma control in a real-life population of adult patients after ICS/LABA treatment change and step-down. We showed that patients previously stable on FP/SAL(1000) maintained good asthma control after changing to FP/FOR(1000) in phase 1, and asthma control was also maintained after stepping down from FP/FOR(1000) to FP/FOR(500) in phase 2 of our study. Our study is the first to simultaneously step down both the ICS and LABA components of a combination treatment in well-controlled patients with asthma and is supported by previous studies suggesting that reducing ICS therapy can maintain or even improve asthma control.^{4,6,8,22,23} However, we observed that those patients who had an exacerbation after a step-down of their ICS/LABA dose had significantly more exacerbations in the year before the study, whereas no such association was found in the group maintained on FP/FOR(1000) in phase 2 of our study (results not shown). To our knowledge, this is the first prospective study to suggest that disease stability for 3 months, as indicated in current guidelines and consensus documents, is likely to be insufficient to determine whether a patient is suitable for step-down.

We sought to identify factors that could predict worsening of asthma, but found no association between specific baseline characteristics (such as age, sex, smoking status, or asthma control) or biomarkers (eg, blood eosinophils and FENO) and response to step-down in terms of occurrence of exacerbations or

decrease in asthma control as assessed with ACQ7. Data on potential factors associated with response to step-down from previous studies are limited. Moreover, although many factors (including hyper-responsiveness to histamine and mannitol, percentage of sputum eosinophils, FENO, and FEV₁% predicted, among others) have shown a potential association with response to therapy reduction, in multiple studies none of these factors has been consistently confirmed.¹⁰⁻¹² It therefore remains unclear how patients suitable for step-down should be identified in routine daily clinical practice. Our findings suggest that the patient's exacerbation history can provide a very practical and simple predictor that can be easily and readily applied in day-to-day clinical practice. This is in line with data from a previous claims database study, which found that the length of asthma stability before stepping down asthma medication was strongly associated with the risk of an asthma exacerbation in the subsequent 24-month period.²⁴

Tools to assess asthma control are another factor that may influence not only interpretation of research results but also decisions in clinical settings. Our findings highlight the importance of using different tools to assess asthma control. Indeed, it has been suggested that an inappropriate assessment of asthma control might even contribute to overtreatment of patients in clinical practice.¹⁴ Although we found that asthma control in terms of ACQ7 was similar between the FP/FOR(1000) and FP/SAL(1000) groups, a significantly higher percentage of patients were controlled on FP/FOR(1000) when control was defined according to GINA criteria. This finding might be explained by various factors including the fundamental differences in the properties of the 2 assessment tools. ACQ7 is assessed with a

TABLE III. Phase 2 outcomes

Outcome	Phase 2 baseline		Phase 2 week 4		Phase 2 week 12		Estimate of treatment effect (95% CI)* week 4	P value	Estimate of treatment effect (95% CI)* week 12	P value
	FP/FOR(500)	FP/FOR(1000)	FP/FOR(500)	FP/FOR(1000)	FP/FOR(500)	FP/FOR(1000)				
ACQ7 score, n	52	52	51	52	52	52				
Mean $\pm$ SD	0.6 $\pm$ 0.8	0.6 $\pm$ 0.6	0.8 $\pm$ 0.9	0.6 $\pm$ 0.5	0.8 $\pm$ 0.8	0.7 $\pm$ 0.8	0.21 (−0.02 to 0.43)	NA†	0.01 (−0.20 to 0.22)	NA†
Minimum, maximum	0.0, 5.1	0.0, 2.7	0.0, 4.3	0.0, 2.6	0.0, 4.7	0.0, 3.7				
Mini-AQLQ score, n	58	58	53	57	53	54				
Mean $\pm$ SD	6.1 $\pm$ 1.3	6.2 $\pm$ 0.9	6.1 $\pm$ 1.0	6.3 $\pm$ 0.6	6.2 $\pm$ 1.1	6.3 $\pm$ 0.9	−0.12 (−0.35 to 0.11)	.320	−0.04 (−0.31 to 0.24)	.793
Minimum, maximum	1.0, 7.0	4.0, 7.0	3.1, 7.0	4.5, 7.0	2.1, 7.0	2.4, 7.0				
GINA, n (%)										
Controlled	33 (56.9)	31 (53.4)	25 (47.2)	33 (56.9)	26 (49.1)	30 (55.6)				
Partially controlled	17 (29.3)	22 (37.9)	21 (39.6)	23 (39.7)	19 (35.8)	15 (27.8)	0.59 (0.28 to 1.24)	.161	0.86 (0.40 to 1.85)	.697
Uncontrolled	3 (5.2)	1 (1.7)	7 (13.2)	2 (3.4)	8 (15.1)	9 (16.7)				
VAS, n (%)										
Score $\leq$ 15	40 (75.5)	38 (70.4)	42 (79.2)	42 (72.4)	37 (69.8)	38 (70.4)	1.35 (0.53 to 3.44)	.529	0.79 (0.30 to 2.09)	.636
Score >15	13 (24.5)	16 (29.6)	11 (20.8)	16 (27.6)	16 (30.2)	16 (29.6)				
Exacerbations, n (%)										
None	NA	NA	NA	NA	51 (87.9)	52 (89.7)	NA	NA	0.82 (0.25 to 2.77)	.753
$\geq$ 1					7 (12.1)	6 (10.3)				
Spirometry, n	58	58	53	58	53	58				
FEV ₁ (L), mean $\pm$ SD	2.5 $\pm$ 0.7	2.7 $\pm$ 0.8	2.5 $\pm$ 0.7	2.5 $\pm$ 0.8	2.5 $\pm$ 0.7	2.7 $\pm$ 0.8	−0.14 (−0.42 to 0.14)	.320	−0.14 (−0.42 to 0.14)	.320
FEV ₁ % predicted, mean $\pm$ SD	86.8 $\pm$ 14.3	91.2 $\pm$ 16.3	87.9 $\pm$ 14.4	89.6 $\pm$ 17.0	87.9 $\pm$ 14.4	89.6 $\pm$ 17.0	−1.76 (−7.75 to 4.23)	.561	−1.76 (−7.75 to 4.23)	.561
FVC (L), mean $\pm$ SD	3.5 $\pm$ 0.9	3.8 $\pm$ 1.1	3.5 $\pm$ 0.9	3.8 $\pm$ 1.1	3.5 $\pm$ 0.9	3.8 $\pm$ 1.1	−0.29 (−0.69 to 0.10)	.144	−0.29 (−0.69 to 0.10)	.144
FVC% predicted, mean $\pm$ SD	98.7 $\pm$ 13.4	103.1 $\pm$ 16.9	99.2 $\pm$ 12.8	101.4 $\pm$ 17.9	99.2 $\pm$ 12.8	101.4 $\pm$ 17.9	−2.15 (−8.09 to 3.80)	.475	−2.15 (−8.09 to 3.80)	.475
FENO, n (%)										
$\leq$ 25 ppb	42 (85.7)	47 (88.7)	41 (78.8)	45 (80.4)	39 (79.6)	42 (79.2)	1.13 (0.44 to 2.91)	.802	1.12 (0.41 to 3.05)	.830
25-50 ppb	7 (14.3)	5 (9.4)	10 (19.2)	11 (19.6)	7 (14.3)	10 (18.9)				
$\geq$ 50 ppb	0 (0.0)	1 (1.9)	1 (1.9)	0 (0.0)	3 (6.1)	1 (1.9)				

NA, Not applicable; ppb, parts per billion.

*ACQ7 score, Mini-AQLQ score, VAS score, and spirometry were analyzed with linear mixed model. GINA and FENO were analyzed with ordinal mixed model and exacerbations with logistic mixed model.

†FP/FOR(500) was considered noninferior to FP/FOR(1000) if estimate of treatment effect was within a 0.3 boundary and upper limit of the 95% CI was $\leq$ 0.3.

TABLE IV. Relationship between history of exacerbations and occurrence of an exacerbation following step-down

Exacerbations in 12 mo before phase 1, n (%)	No exacerbations in phase 2 (N = 51)	Exacerbation in phase 2 (N = 7)	Total (N = 58)	OR (95% CI)	P value
None	42 (95.5)	2 (4.5)	44 (100.0)		
1	8 (72.7)	3 (27.3)	11 (100.0)		
2	1 (33.3)	2 (66.7)	3 (100.0)	11.67 (2.16-91.20)*	.007*

OR, Odds ratio.

Data are presented as n (%).

*Because of the small number of patients in the individual groups, patients with no exacerbations in 12 mo before phase 1 were compared with the combined group of patients with 1 or 2 exacerbations.

validated questionnaire and gives a score between 0 and 6, whereas no standardized questionnaire exists for assessment of asthma control according to GINA criteria, which categorize patients into 3 groups using specified cutoffs. It is also possible that the sensitivity of these methods varies depending on the level of asthma control, although this hypothesis should be further explored. Finally, we acknowledge the potential risk of assessor bias associated with the assessment of GINA asthma control by unblinded health care professionals.

We acknowledge that the present study has its limitations. First, the 12-week follow-up period in each phase is likely to have been insufficient to capture seasonal variations in asthma control and exacerbation rates, and the power to detect significant predictors of response to step-down was limited because of the relatively small number of patients (especially in the group of patients with asthma worsening). Although patient retention rates were high in both groups in both phases, our study design might have contributed to the differential rate of noncompletion and missing outcome data between the groups in phase 1; the dropout rate in the FP/FOR(1000) group (11.3%) was significantly higher than in the FP/SAL(1000) group, in which only 1 patient (1.4%) discontinued. This might have been anticipated given that all randomized patients had used FP/SAL(1000) for at least 6 months and were well controlled when randomized to FP/FOR(1000). Although baseline demographic or clinical characteristics, including asthma control, were not significantly associated with noncompletion in phase 1 (results not shown), we were not able to investigate the potential impact of factors such as worsening of asthma or device preference on noncompletion. Only 2 serious treatment-related AEs were reported during the study, one of which occurred in the FP/SAL(1000) group and the other in the FP/FOR(500) group. Both SAEs were hospitalizations due to pneumonia, risk of which is increased in patients with chronic obstructive pulmonary disease treated with ICS.^{25,26} However, conclusive clinical evidence for intraclass differences in the magnitude of the risk among ICS products in chronic obstructive pulmonary disease is still lacking, and the role of long-term ICS use in increasing the risk of pneumonia and other side effects in patients with asthma also remains to be confirmed.²⁷⁻²⁹

In summary, our findings suggest that patients with well-controlled asthma can be switched from FP/SAL(1000) to FP/FOR(1000) and stepped down to FP/FOR(500) without compromising asthma control or increasing the risk of exacerbations. Importantly, our results suggest that caution should be exercised in stepping down ICS/LABA in patients with a history of 1 or more exacerbations in the last year, even if asthma has been stable and well controlled for the previous 3 months. The

patient's clinical history can provide a simple predictor of future exacerbation risk. Larger studies with longer follow-up periods and further reductions in therapy will be required to further investigate asthma outcomes after step-down and to confirm whether other factors including biomarkers could be useful for predicting response to step-down.

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TABLE E1. Adherence in phase 1

Adherence*	FP/FOR(1000)	FP/SAL(1000)	Total
Total	105 (69.5%)	55 (74.3%)	160 (71.1%)
≤50%	5 (4.8%)	3 (5.5%)	8 (5.0%)
51%-70%	12 (11.4%)	5 (9.1%)	17 (10.6%)
71%-99%	54 (51.4%)	34 (61.8%)	88 (55.0%)
≥100%	34 (32.4%)	13 (23.6%)	47 (29.4%)

*Adherence was calculated from dose counter values for those patients who returned their study devices taking into account the number of days in phase 1. For example, 100% adherence means that the patients used on average 4 doses a day over the number of days between their baseline visit and week 12 visit.

TABLE E2. Adherence in phase 2

Adherence*	FP/FOR(500)	FP/FOR(1000)	Total
Total	47 (81.0%)	45 (77.6%)	92 (79.3%)
≤50%	1 (2.1%)	3 (6.7%)	4 (4.3%)
51%-70%	1 (2.1%)	2 (4.4%)	3 (3.3%)
71%-99%	23 (48.9%)	22 (48.9%)	45 (48.9%)
≥100%	21 (44.7%)	18 (40.0%)	39 (42.4%)

*Adherence was calculated from dose counter values for those patients who returned their study devices taking into account the number of days in phase 2. For example, 100% adherence means that patients used on average 4 doses a day over the number of days between their baseline visit and week 12 visit.

TABLE E3. Predictor analyses based on change in ACQ7 score

Description	Maintenance of asthma control* (N = 41)	Worsening of asthma control (N = 12)	OR (95% CI) [†]	P value [‡]
Age (y)				
N	41	12	1.03 (0.98-1.09)	.256
Mean ± SD	52.0 ± 13.6	57.0 ± 12.6		
Sex, n (%)				
Female	23 (71.9)	9 (28.1)	2.35 (0.60-11.75)	.247
Male	18 (85.7)	3 (14.3)		
Smoking status, n (%)				
Never smoked	14 (70.0)	6 (30.0)	1.71 (0.31-13.64)	.562
Ex-smoker	18 (81.8)	4 (18.2)	0.89 (0.14-7.36)	.903
Current smoker	8 (80.0)	2 (20.0)		
Anxiety/depression, n (%)				
Yes	10 (76.9)	3 (23.1)	1.03 (0.20-4.30)	.966
No	31 (77.5)	9 (22.5)		
Diabetes, n (%)				
Yes	2 (100.0)	0 (0.0)	NA	NA
No	39 (76.5)	12 (23.5)		
Eczema, n (%)				
Yes	3 (75.0)	1 (25.0)	1.15 (0.05-10.06)	.907
No	38 (77.6)	11 (22.4)		
Gastroesophageal reflux disease, n (%)				
Yes	6 (75.0)	2 (25.0)	1.17 (0.15-6.04)	.863
No	35 (77.8)	10 (22.2)		
Rhinitis, n (%)				
Yes	6 (66.7)	3 (33.3)	1.94 (0.36-9.03)	.406
No	35 (79.5)	9 (20.5)		
Baseline ACQ7 score, n (%)				
≤0.75	32 (80.0)	8 (20.0)	0.56 (0.14-2.49)	.424
>0.75	9 (69.2)	4 (30.8)		
Baseline GINA, n (%)				
Controlled	27 (81.8)	6 (18.2)	0.52 (0.14-1.94) [‡]	.323
Partially controlled	11 (64.7)	6 (35.3)		
Uncontrolled	3 (100.0)	0 (0.0)		
Exacerbations in 12 mo before phase 1, n (%)				
None	31 (79.5)	8 (20.5)	1.55 (0.35-6.12) [§]	.538
1	8 (72.7)	3 (27.3)		
2	2 (66.7)	1 (33.3)		
FENO, n (%)				
≤25 ppb	35 (79.5)	9 (20.5)	0.64 (0.12- 5.00)	.63
>25 ppb	5 (71.4)	2 (28.6)		
Blood eosinophils, n (%)				
≥400/μL	5 (83.3)	1 (16.7)	0.63 (0.03-5.08)	.701
<400/μL	19 (76.0)	6 (24.0)		
FEV ₁ % predicted, n (%)				
<70%	1 (25.0)	3 (75.0)	11.40 (1.18-260.7)	.053
≥70% and <80%	6 (75.0)	2 (25.0)	1.27 (0.15-7.80)	.805
≥80% and <90%	15 (88.2)	2 (11.8)	0.51 (0.07-2.72)	.453
≥90%	19 (79.2)	5 (20.8)		

NA, Not applicable; OR, odds ratio; ppb, parts per billion.

*Maintenance of asthma control was defined as change of less than 0.5 in ACQ7 score from baseline to week 12.

†OR and P value were obtained from univariate logistic regression model. OR > 1 indicates increased odds of asthma control. Reference category is category without estimate attached unless grouping is indicated.

‡Controlled were compared with partially controlled/uncontrolled because there were no uncontrolled in the “Worsening of asthma control” group.

§“One” and “Two” exacerbation groups were combined for calculation of OR and P value.

TABLE E4. Predictor analyses based on occurrence of exacerbations

Description	Maintenance of asthma control (N = 51)*	Worsening of asthma control (N = 7)	OR (95% CI)†	P value‡
Age (y)				
N	51	7	1.01 (0.96-1.08)	.656
Mean ± SD	52.0 ± 14.1	54.4 ± 12.7		
Sex, n (%)				
Female	30 (85.7)	5 (14.3)	1.75 (0.34-13.03)	.527
Male	21 (91.3)	2 (8.7)		
Smoking status, n (%)				
Never smoked	19 (82.6)	4 (17.4)	0.75 (0.75-0.75)	.729
Ex-smoker	19 (86.4)	3 (13.6)	NA	NA
Current smoker	12 (100.0)	0 (0.0)		
Anxiety/depression, n (%)				
Yes	12 (85.7)	2 (14.3)	1.30 (0.17-6.94)	.771
No	39 (88.6)	5 (11.4)		
Diabetes, n (%)				
Yes	2 (100.0)	0 (0.0)	NA	NA
No	49 (87.5)	7 (12.5)		
Eczema, n (%)				
Yes	5 (100.0)	0 (0.0)	NA	NA
No	46 (86.8)	7 (13.2)		
Gastroesophageal reflux disease, n (%)				
Yes	7 (87.5)	1 (12.5)	1.05 (0.05-7.56)	.968
No	44 (88.0)	6 (12.0)		
Rhinitis, n (%)				
Yes	9 (100.0)	0 (0.0)	NA	NA
No	42 (85.7)	7 (14.3)		
Baseline ACQ7 score, n (%)				
≤0.75	38 (88.4)	5 (11.6)	0.86 (0.16-6.47)	.862
>0.75	13 (86.7)	2 (13.3)		
Baseline GINA, n (%)				
Controlled	29 (87.9)	4 (12.1)	1.01 (0.20-5.57)‡	.989
Partially controlled	18 (85.7)	3 (14.3)		
Uncontrolled	4 (100.0)	0 (0.0)		
Exacerbations in 12 mo before phase 1, n (%)				
None	42 (95.5)	2 (4.5)		
1	8 (72.7)	3 (27.3)	11.67 (2.16-91.20)§	
2	1 (33.3)	2 (66.7)		.007
FENO, n (%)				
≤25 ppb	43 (87.8)	6 (12.2)	0.84 (0.11-17.22)	.879
>25 ppb	6 (85.7)	1 (14.3)		
Blood eosinophils, n (%)				
≥400/μL	4 (66.7)	2 (33.3)	12.00 (0.94-298.30)	.063
<400/μL	24 (96.0)	1 (4.0)		
FEV ₁ % predicted, n (%)				
<70%	5 (71.4)	2 (28.6)	0.85 (0.11-4.99)	.858
≥70% and <80%	8 (100.0)	0 (0.0)	0.34 (0.02-2.60)	
≥80% and <90%	16 (94.1)	1 (5.9)		.359
≥90%	22 (84.6)	4 (15.4)		

NA, Not applicable; OR, odds ratio; ppb, parts per billion.

*Maintenance of asthma control was defined as no exacerbations in phase 2.

†OR and P value were obtained from univariate logistic regression model. OR > 1 indicates increased odds of asthma control. Reference category is category without estimate attached unless grouping is indicated.

‡Controlled were compared with partially controlled/uncontrolled because there were no uncontrolled in the “Worsening of asthma control” group.

§“One” and “Two” exacerbation groups were combined for calculation of OR and P value.

||The <70% and the ≥70 and <80% groups were combined for analysis and compared with the ≥90% group.

TABLE E5. AEs recorded as treatment-related in phase 1

System Organ Class (MedDRA version 17.0)	FP/FOR(1000) (N = 151)	FP/SAL(1000) (N = 74)	Total (N = 225)
Cardiac disorders, n patients (%)	3 (2.0)	0 (0.0)	3 (1.3)
Gastrointestinal disorders, n patients (%)	5 (3.3)	0 (0.0)	5 (2.2)
General disorders and administration site conditions, n patients (%)	3 (2.0)	0 (0.0)	3 (1.3)
Infections and infestations, n patients (%)	4 (2.6)	1 (1.4)*	5 (2.2)
Metabolism and nutrition disorders, n patients (%)	2 (1.3)	0 (0.0)	2 (0.9)
Nervous system disorders, n patients (%)	2 (1.3)	0 (0.0)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders, n patients (%)	8 (5.3)	1 (1.4)	9 (4.0)
Skin and subcutaneous tissue disorders, n patients (%)	1 (0.7)	0 (0.0)	1 (0.4)
Total, n patients (%)†	18 (11.9)	2 (2.7)	20 (8.9)

*One of these was hospitalization due to pneumonia classified as a serious adverse event.

†Patients who had treatment-related AEs in more than 1 System Organ Class category are counted once in the total.

TABLE E6. AEs recorded as treatment-related in phase 2

System Organ Class (MedDRA version 17.0)	FP/FOR(125) (N = 58)	FP/FOR(250) (N = 58)	Total (N = 116)
Cardiac disorders, n patients (%)	1 (1.7)	1 (1.7)	2 (1.7)
Gastrointestinal disorders, n patients (%)	1 (1.7)	1 (1.7)	2 (1.7)
Infections and infestations, n patients (%)	2 (3.4)*	1 (1.7)	3 (2.6)
Metabolism and nutrition disorders, n patients (%)	0 (0.0)	1 (1.7)	1 (0.9)
Respiratory, thoracic, and mediastinal disorders, n patients (%)	6 (10.3)	2 (3.4)	8 (6.9)
Total, n patients (%)†	8 (13.8)	3 (5.2)	11 (9.5)

*One of these was hospitalization due to pneumonia classified as a suspected unexpected serious adverse event.

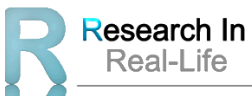
†Patients who had treatment-related AEs in more than 1 System Organ Class category are counted once in the total.

TABLE E7. Primary care sites and principal investigators

Study site	Principal investigator
Atherstone Surgery, 1 Ratcliffe Road, Atherstone CV9 1EU	Dr John Winward
Beacon Medical Group, Plympton Health Centre, Mudge Way, Plymouth PL7 1AD	Dr Timothy Bray
Bridgnorth Medical Practice, Northgate Health Centre/Northgate, Old Smithfield, Bridgnorth WV16 4EN	Dr Aaron Tindall
Claremont Medical Practice, Exmouth Health Centre, Claremont Grove, Exmouth EX8 2JF	Dr Kevin Douglas
Coleridge Medical Centre, Canaan Way, Ottery St Mary, Devon EX11 1EQ	Dr Nigel De Sousa
Creffield Medical Centre, 15 Cavalry Road, Colchester CO2 7GH	Dr Vivien St Joseph
Framfield House Surgery, Framfield Medical Centre, Ipswich Road, Woodbridge IP12	Dr Phil Weeks, Dr Lucy Williams
Great Sutton Medical Centre, Old Chester Road, Ellesmere Port, Cheshire CH66 3SP	Dr John Wearne
Guildowns Group Practice, 91 Wodeland Avenue, Guildford GU2 4YP	Dr Rani Shenoy
Haven Surgery, The Haven Surgery, The Haven, Burnhope, Durham DH7 0BD	Dr Rina Miah
Haxby Group Practice, Haxby & Wigginton Health Centre, The Village, Wigginton, York YO32 2LL	Dr William Laughey
Honiton Surgery, Marl pits Ln, Honiton EX14 2NY	Dr David Seamark
Hoveton & Wroxham Medical Centre, Stalham Road, Hoveton, Norwich NR12 8DU	Dr Carsten Dervedde
Jorvik Gillygate Practice, Woolpack House, The Stonebow, York YO1 7NP	Dr David Hartley
Manor Surgery, Forth Noweth, Redruth TR15 1AU	Dr Andrew Craze
Mirfield Health Centre, Doctor Ln, Mirfield WF14 8DU	Dr Paul Jones
Old Bridge Surgery, The Looe Health Centre, Station Road, Looe PL13 1HA	Dr Pascual Daza-Ramirez, Dr Kate Gummow
Peaseway Medical Centre, 2 Pease Way, Newton Aycliffe DL5 5NH	Dr Andrew Clarke
Pound Hill Medical Group, 1 Crawley Lane, Pound Hill, Crawley, West Sussex RH10 7DX	Dr Neil Jackson
Priory Medical Centre, Cape Road, Warwick, CV34 4UN	Dr Nicholas Yeats
Priory Medical Group, Priory Medical Centre, Cornlands Road, Acomb, York YO24 3WX	Dr Peter Anderson
Robert Darbishire Practice, Rusholme Health Centre, Walmer Street, Manchester M14 5NP	Dr Aneez Esmail
Stockingate Surgery, 69 Stockingate, South Kirkby, Pontefract WF9 3PE	Dr Antonia Schlesinger
Swadlincote Surgery, Darklands Road, Swadlincote DE11 0PP	Dr Daniel Hendriksen
Todmorden Group Practice, Todmorden Group Practice, Lower George Street, Todmorden OL14 5RN	Dr Dinesh Kumar
The Village Practice, Thornton Medical Centre, Church Road, Thornton-Cleveleys FY5 2TZ	Dr Preeti Pandya
White Rose Surgery, Exchange Street, South Elmsall, Pontefract WF9 2RD	Dr Rachel Buckley
Whitstable Medical Practice, Estuary View Medical Centre, Boorman Way, Whitstable CT5 3SE	Dr Hilary Pinnock
Wymondham Medical Centre, Postmill Close, Wymondham, Norfolk NR18 0RF	Dr Stephen Thurston
York Medical Group, 199 Acomb Road, York YO24 4HD	Dr Mark Roman

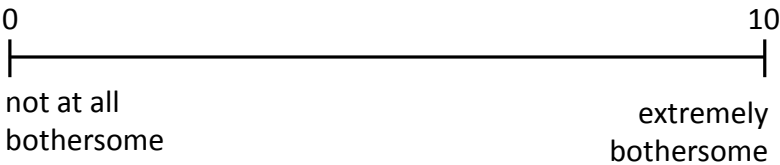
Patient ID: _____

Date: _____



VISUAL ANALOG SCALE TEST

Put a mark on the line below to indicate how much your asthma symptoms bother you



SCORE (to be filled by research team): _____mm

Full Clinical Study Protocol
A guideline approach to therapy step-down utilising Flutiform® change and step-down
Protocol Version 2.3

Study number: OR00213

EudraCT number: 2013-005365-39

Protocol v.1.0 Approval Date: 20th January 2014

Protocol v.2.0 Approval Date: 10th April 2014

Protocol v.2.1 Approval Date: 13th May 2014

Protocol v.2.2 Approval Date: 24th June 2014

Protocol v.2.3 Approval Date: 17th November 2014

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Supplier and part study funding	Chief Investigator Organisation	Medical Expert
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This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); European Union (EU) Directives; Directive 2001/20/EC ('The Clinical Trials Directive'); local country regulations; the sponsor's Standard Operating Procedures (SOPs); and the Clinical Research Organisation's Standard Operating Procedures (SOPs).

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INVESTIGATOR AGREEMENT**Clinical Study Protocol****A guideline approach to therapy step-down utilising Flutiform[®] change and step-down v.2.3****Investigator:** _____**Title:** _____**Address of Investigational Center:** _____

Tel: _____

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to conduct this clinical research study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience, which were furnished to me by the sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study.

I agree to keep records on all patient information (i.e. case report forms and informed consent statements), study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

Investigator's Signature**Date**

Sponsor's Authorised Representative



17th November 2014

Catherine Hutton**Sponsor's Representative's Signature****Date**

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Seretide[®] Evohaler[®] is a registered trademark of the GlaxoSmithKline group of companies.

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

Professor David Price, Dr Omar Usmani

A contact number with 24-hour access will be given to the patients at the beginning of the study

For serious adverse events:

Sites will submit serious adverse event reports to RiRL (email: fflux@rirl.org)

For medical issues telephone the physician responsible (above)

For operational issues, contact

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CLINICAL STUDY PROTOCOL SUMMARY

Title of Study: A guideline approach to therapy step-down utilising Flutiform® change and step-down

Protocol version: 2.3

Study Number: OR00213

EudraCT Number: 2013-005365-39

Chief Investigator: Professor David Price

Clinical Research Organisation: Research in Real Life Research Network

Part study funder: Napp Pharmaceuticals Limited

Name of Active Ingredients: fluticasone and formoterol

Name of Investigational Product: Inhaled Fluticasone/Formoterol as combination therapy via Flutiform®

Phase of Clinical Development: 4

Number of Investigational Centres Planned: approximately 40 Centres

Country of the study: UK

General Design and Methodology:

This is a two-phase, intention-to-treat study, comprising a change phase followed by a step-down phase.

Phase 1: Change from high dose Fluticasone/Salmeterol to high dose Flutiform®

At the baseline visit, patients will be randomly assigned to one of the treatment groups (below) with 2:1 randomisation for the 12 weeks Phase 1 study.

- Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform®)
- Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® Evohaler®)

Phase 2: Step-down from high dose Flutiform® to medium dose Flutiform®

Once Phase 1 is completed the remaining patients in the Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform®) arm will be randomly assigned to one of the treatment groups (below) with 1:1 randomisation for the 12 weeks Phase 2 study if they haven't had any exacerbations in Phase 1.

- Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform®)
- Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform®)

Phase 1 Objective:

Establish whether comparable asthma control can be maintained when patients previously controlled with Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® Evohaler®) change to high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform) compared with maintaining on high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® Evohaler®).

Phase 2 Objective:

Establish whether patients controlled on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform® 250) can be successfully stepped down to medium dose Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform® 125) and achieve comparable asthma control.

Number of Patients Planned:

Phase 1: When the sample size is 201 (67 Seretide®: 134 Flutiform®), a two group t-test of equivalence in means, with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis that the mean ACQ7 scores are not equivalent (based on an acceptable maximum difference of -0.3 in mean ACQ7 score, i.e. lower confidence limit of -0.3 and a common standard deviation of 0.8) when the expected difference in mean ACQ7 score is 0.000. Assuming a drop-out rate of about 10%, approximately 224 patients (75 Seretide®: 149 Flutiform®) will be randomised in this study to ensure that a minimum of 201 patients complete all visits and critical assessments.

Phase 2: The number of patients available in Phase 2 is based on those who successfully complete Phase 1 and are willing to take part in Phase 2. Therefore an estimation of power has been performed based on worst and best case scenario, using a two-group t-test of equivalence in means, with a 0.050 one-sided significance level, a maximum difference of -0.4 in mean ACQ7 score (i.e. lower confidence limit of -0.4) and common standard deviation of 0.8.

Minimum Phase 2: Assuming a combined 10% drop-out rate prior to randomisation and during study (approximately 14 patients) from Phase 1 and a further 14% lost due to lack of asthma control (approximately 18 patients), a sample size of 102 (51 Flutiform® 250: 51 Flutiform® 125) would provide 80% power to detect a maximum difference of -0.4 mean difference in ACQ7.

Maximum Phase 2: Assuming a maximum expected sample size of 140 (70 Flutiform® 250: 70 Flutiform® 125) from Phase 1 would provide 90% power to detect a maximum difference of -0.4 mean difference in ACQ7.

Study Population: It is planned to enrol approximately 224 patients aged 18 to 75 who have a current diagnosis of asthma. The diagnosis of asthma must be in accordance with the Global Initiative for Asthma (GINA). 149 of the 224 patients will be invited to participate in Phase 2 of the study.

Length of the Study: Length of the study will be approximately 11 months from screening the first patient to the completion of the last patient visit.

End of the Study:

Last patient's last visit.

Inclusion Criteria: Patients may be included in the study if they meet all of the following criteria:

- Age 18-75
- Able and willing to provide written informed consent and to comply with the study protocol
- Current diagnosis of asthma (as evidenced by appropriate diagnostic code)
- Received Seretide® 250 Evohaler® 2 puffs twice daily for the last 6 months
- No asthma exacerbation* in last 3 months
- ≤2 exacerbations* in last 12 months
- No critical errors in device use after training (during baseline visit)

- Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after discontinuation of study drug. Acceptable methods of contraception include intrauterine device (IUD) known to have a failure rate of less than 1% per year, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, and partner vasectomy.
- * Exacerbation defined as acute course of oral steroids, emergency room attendance and/or hospitalisation for asthma

There is no need for a run-in period, as patients will already be receiving the control device.

As patients have had controlled asthma for at least 3 months (demonstrated by absence of exacerbations), there are no considered ethical issues to step-down.

Exclusion Criteria:

Patients will be excluded from participating in this study if they meet any of the following criteria:

- Chronic respiratory disease other than asthma
- Uncontrolled asthma (GINA criteria)
- The patient has used a clinical trial investigational drug within the last year before the screening visit
- Hypersensitivity to Flutiform[®], its component Formoterol or its excipients
- Pregnant subjects

Investigational Product:

- Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®])
- Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform[®])

Placebo: Yes. Seretide[®] Evohaler[®] placebo and Flutiform[®] placebo will be used for inhaler technique training only.

Reference Therapy: Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide[®] Evohaler[®])

Rescue Medication: Patients will be able to use their regular rescue medication during the study as prescribed to them by their primary care physician.

Blinding: No.

Method of Randomisation: A centralised randomisation programme will be used to randomise patients.

TABLE OF CONTENTS

INVESTIGATOR AGREEMENT.....	3
CLINICAL STUDY PERSONNEL CONTACT INFORMATION	4
CLINICAL STUDY PROTOCOL SUMMARY.....	5
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	11
1. BACKGROUND	12
1.1. Introduction.....	12
1.2. Compliance statement.....	13
1.3. Population to be studied.....	14
2. STUDY OBJECTIVES AND RATIONALE	15
3. STUDY DESIGN	18
3.1. General design and study scheme	18
3.2. Phase 1 (Change) - Study design and methodology	19
3.2.1 Phase 1: Objectives.....	19
3.2.2 Phase 1: Outcomes.....	20
3.2.3 Phase 1: Eligibility criteria	21
3.2.4 Phase 1: Study procedures	22
3.2.5 Phase 1: Sample size calculation	29
3.2.6 Phase 1: Study medication.....	30
3.2.7 Phase 1: Study device resource required	30
3.3. Phase 2 (Step-down) - Study design and methodology	31
3.3.1 Phase 2: Objectives.....	31
3.3.2 Phase 2: Outcomes.....	32
3.3.3 Phase 2: Eligibility criteria	33
3.3.4 Phase 2: Study procedures	33
3.3.5 Phase 2: Power calculation	36
3.3.6 Phase 2: Study medication.....	36
3.3.7 Phase 2: Study device resources required.....	36
4. STUDY PRODUCT AND ITS DOSAGE	38
4.1. Flutiform® 250 and Flutiform® 125.....	38
4.2. Seretide® 250 Evohaler®	39
5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN SUBJECTS	40
5.1. Flutiform® and its known and potential risks and benefits.....	40

5.1.1.	Interaction with other medicinal products	40
5.2.	Seretide [®] Evohaler [®] and its known and potential risks and benefits.....	41
6.	STUDY DRUG SUPPLY AND ACCOUNTABILITY	42
6.1.	Study drug storage and security.....	42
6.1.1.	Storage at the study centre	42
6.1.2	Storage after dispensing.....	42
6.2.	Study drug accountability	42
7.	PATIENT MANAGEMENT DURING THE CONDUCT OF THE STUDY	44
8.	STUDY TERMINATION AND PATIENT WITHDRAWAL	45
8.1.	Study termination.....	45
8.2.	Patient withdrawal	45
9.	PATIENT PAYMENTS	46
10.	ADVERSE EVENT REPORTING	47
10.1.	Definition of Adverse Events	47
10.2.	Recording and reporting adverse events.....	49
11.	STATISTICAL ANALYSIS	51
11.1.	General.....	51
11.2.	Summary statistics for Phase 1 and Phase 2.....	51
11.3.	Statistical analysis for Phase 1 and Phase 2.....	52
11.4.	Missing data.....	53
12.	ELECTRONIC CASE REPORT FORM AND STUDY DATASET	55
12.1.	Data collection	55
12.1.1.	Electronic case report form (eCRF).....	55
12.1.2.	Questionnaires	56
12.2.	Data quality control	56
12.3.	Data queries	56
13.	QUALITY CONTROL AND QUALITY ASSURANCE	57
13.1.	Protocol amendments and protocol deviations	57
13.1.1.	Protocol amendments.....	57
13.1.1.	Protocol deviations	57
13.2.	Information to study personnel	58
13.3.	Study monitoring	58
13.4.	Audit and inspection	59
14.	ETHICS	60

14.1.	COMPLIANCE WITH LAWS AND REGULATIONS	60
14.2.	Registration of the clinical study	60
14.3.	Research Ethics Committees	60
14.4.	NHS R&D.....	61
14.5.	Informed consent	61
14.6.	Confidentiality regarding study patients.....	61
14.7.	Declaration of the end of the clinical study	62
15.	TIME SCHEDULE AND DELIVERY	63
16.	FINANCING AND INSURANCE.....	64
17.	REPORTING AND PUBLICATION OF RESULTS	65
18.	REFERENCES	66
APPENDIX A. ASTHMA CONTROL QUESTIONNAIRE		68
APPENDIX B. ASTHMA REVIEW QUESTIONNAIRE.....		69
APPENDIX C. CRITICAL ERRORS ASSOCIATED WITH INHALATION DEVICES		71

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACQ	Asthma Control Questionnaire
ACQ7	Asthma Control Questionnaire score calculated based on seven questions
BTS	British Thoracic Society
CDMS	Clinical Data Management System
COPD	Chronic Obstructive Pulmonary Disease
eCRF	electronic case report form
FeNO	Fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IPCRG	International Primary Care Respiratory Group
ITT	Intent-to-Treat
LABA	long-acting beta-agonist
MDI	metered dose inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
Mini-AQLQ	Mini Asthma Quality of Life Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PEF	peak expiratory flow rate
RCT	Randomised Controlled Trial
RiRL	Research in Real Life Ltd
SABA	short-acting beta-agonist
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
SOP	standard operating procedure
SPC	Summary of Product Characteristics
TA	Technology Appraisal
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
VAS	Visual Analog Scale

1. BACKGROUND

1.1. Introduction

Asthma is a chronic inflammatory condition of the airways. Poorly controlled asthma has a substantial impact on quality of life and healthcare resources. Inhaled corticosteroids (ICS) are the primary anti-inflammatory therapy for treatment of asthma. Where asthma control is inadequately maintained on ICS therapy alone, second line therapies can be added, for example a long acting bronchodilator such as a long-acting beta₂ agonist (LABA). Compared to using single therapy devices (i.e. an ICS inhaler plus a LABA inhaler), combination therapy devices (containing both an ICS and a LABA) have been associated with significant improvements in patient outcomes in patients not adequately controlled on ICS alone.

National Institute for Health and Care Excellence (NICE) guidance on the use of inhaled corticosteroids in adults and children over 12 (TA138), recommends use of a combination inhaler device as an option in patients in whom treatment with an ICS and LABA is considered appropriate (1).

Flutiform[®] is a low cost combination therapy inhaler for use in asthma at Step 3/4 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines. Flutiform[®], which is the first asthma therapy to combine the potent ICS fluticasone with the fast-acting inhaled LABA formoterol, has been shown to be a safe and effective therapy for the management of asthma (2-9). In a comparison against the current market leader, Seretide[®] Evohaler[®] metered dose inhaler (MDI) which contains fluticasone propionate and salmeterol, Flutiform[®] was shown to be as effective and have a faster onset of action (3,8,9).

According to NICE guidance (TA138), if a combination device is chosen, then the least costly device that is suitable for the individual is recommended (1). At current prices, the Flutiform[®] 250 formulations are cheaper than the Seretide[®] 250 Evohaler[®].

One fully-published Phase 3, open-label, 12-week trial involving 202 adults compared Flutiform[®] 125 (fluticasone/formoterol 125µg/ 5µg) with a fluticasone/salmeterol 125µg/ 25µg combination inhaler, as well as Flutiform[®] 50 (fluticasone/formoterol 50µg/5µg) with a fluticasone/salmeterol 50µg/25µg combination inhaler (8). The results of this study indicate that fluticasone/formoterol is as effective as fluticasone/salmeterol. However Flutiform[®] 250

(fluticasone/formoterol 250µg/10µg) and fluticasone/salmeterol 250µg /25µg have not been compared before, and pragmatic studies are required to demonstrate that patients can be safely and effectively changed from fluticasone/salmeterol 250µg/25µg as Seretide® 250 Evohaler® to fluticasone/formoterol 250µg/10µg as Flutiform® 250.

According to the (BTS/SIGN guidelines for asthma (10), ICS dose should be stepped up during periods of poor asthma control and stepped down once asthma is controlled. Reductions in ICS dose should be considered every three months, with ICS dose reduced by approximately 25% - 50% each time, and the patient being maintained at the lowest possible dose of inhaled steroid. However, BTS/SIGN guidelines acknowledge that many patients are over-treated with ICS in daily clinical practice. It is important that the therapy offers optimum clinical benefit and cost-effectiveness and is prescribed at the most appropriate dose to maintain asthma control. Key goals are necessary for ensuring optimum outcomes for the patient and the National Health Service (NHS). The NHS has identified over-treatment with ICS in daily clinical practice as a priority area. Studies which demonstrate that patients can be safely and effectively changed from Seretide® Evohaler® to Flutiform® and that patients receiving Flutiform® can be safely stepped-down in terms of ICS dose are necessary to achieve these goals.

1.2. Compliance statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g. European Union [EU] Directive 2001/20/EC and 2005/28/EC). Any episodes of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the applicable GCP guidelines for collecting, recording, and reporting the data accurately and properly. Investigator Agreements to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background and requirements of the study and with the properties of the study

drug(s) as described in the Summary of Product Characteristics (SPC) or prescribing information.

The Chief Investigator has overall responsibility for the conduct and administration of the study at different study centres and the Principal Investigators in each local study centre have the overall responsibility for the conduct and administration in each individual local study centre.

1.3. Population to be studied

It is planned that this study will enrol approximately 224 adult patients (18-75 years) with asthma. Eligible patients will have controlled asthma (absence of exacerbations in the last 3 months and ≤ 2 exacerbations in the 12 months prior to Phase 1 baseline) and have been using Seretide® 250 Evohaler® (2 puffs twice a day) for the 6 months prior to enrolment.

2. STUDY OBJECTIVES AND RATIONALE

This is a two-phase, intention-to-treat study, comprising a change phase followed by a step-down phase:

Phase 1 (primary objective): Change from high dose Seretide® 250 Evohaler® to high dose Flutiform® 250

Establish whether comparable asthma control can be maintained when patients previously controlled with Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® 250 Evohaler®) are changed to high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform® 250) compared to maintenance on high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® 250 Evohaler®).

Phase 2 (primary objective): Step-down from high dose Flutiform® 250 to medium dose Flutiform® 125

Establish whether patients controlled on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform® 250) can be successfully stepped down to medium dose Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform® 125) for a 3 month period, where successful step-down is defined as the maintenance of asthma control (as assessed by Asthma Control Questionnaire).

Eligible patients will be patients with controlled asthma (absence of exacerbations in the 3 months and ≤ 2 exacerbations in the 12 months prior to Phase 1 baseline) and have been using Seretide® 250 Evohaler® (2 puffs twice a day) for the 6 months prior to enrolment. Selection of this patient population will ensure:

- There will be no run-in period as patients will already be receiving the control device.
- As patients have had controlled asthma for at least 3 months (demonstrated by absence of exacerbations), there are no considered ethical reasons when stepping down patients.

Flutiform[®] is for use in asthma at Step 3/4 of the BTS/SIGN guidelines. The requirement that patients are on high dose treatment was to ensure patients are not looking to increase their ICS dose.

The primary outcomes of the study are as follows:

Phase 1: Mean change in Asthma Control Questionnaire (ACQ) (Appendix A) score from Phase 1 baseline to Phase 1 week 12.

Phase 2: Mean change in Asthma Control Questionnaire (ACQ) score from Phase 2 baseline to Phase 2 week 12.

The secondary outcomes of the study are as follows:

Phase 1:

- The following will be compared between both cohorts at week 12, adjusting for baseline:
 - Lung function as measured by Forced Expiratory Volume in 1 second (FEV₁) and Forced Vital Capacity (FVC)
 - GINA asthma control
 - Visual Analog Scale (VAS) Score
 - Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) Score
- Proportion of patients with asthma control, defined as:
 - No exacerbations
 - No change in therapy
 - GINA asthma control achieved
- Adverse events

Phase 2:

- The following will be compared between both cohorts at week 12, adjusting for baseline:
 - Lung function (FEV₁ and FVC)
 - Fractional Exhaled Nitric oxide (FeNO) to assess airway inflammation
 - GINA asthma control
 - Visual Analog Scale (VAS) Score

- Mini-AQLQ score
- Proportion of patients with asthma control, defined as:
 - No exacerbations
 - No change in therapy
 - GINA asthma control achieved
- Adverse events

In addition, there is a visit at Phase 2 week 4 to measure FeNO levels, lung function and asthma control and quality of life. These will be reported as secondary outcomes. We will also measure blood eosinophil counts at Phase 2 baseline visit. This will be used as a second, independent measure of inflammation in addition to FeNO.

3. STUDY DESIGN

3.1. General design and study scheme

This will be a two-phase, pragmatic, open-label, randomised controlled trial (RCT), composed of a change phase (Phase 1) followed by a step-down phase (Phase 2) (Figure 1). Each phase is 12 weeks in length. Clinical assessments will be carried out either by Research in Real Life Research Network (RiRL-RN) approved healthcare professional (HCP), or the participating practices' own HCP if preferred by the practice.

Phase 1 (Change):

In patients with stable controlled asthma receiving high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide[®] 250 Evohaler[®]) compare asthma control outcomes following randomisation to either:

- Change to high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250) for 12 weeks.

OR

- Maintain on high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide[®] 250 Evohaler[®]) for 12 weeks.

Phase 2 (Step-down):

In patients controlled on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250), compare asthma control outcomes following 12 weeks of:

- Maintaining on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250) for 12 weeks.

OR

- Stepping down to medium dose Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform[®] 125) for 12 weeks.

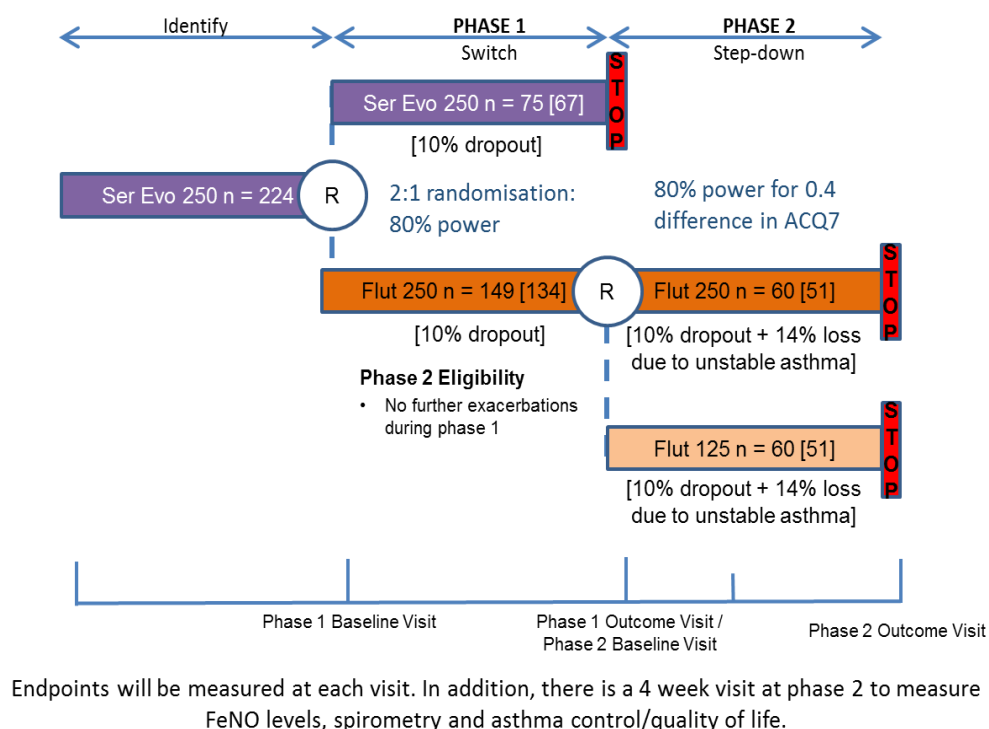


Figure 1. Schematic overview of the study design.

3.2. Phase 1 (Change) - Study design and methodology

224 Patients receiving high dose ICS/LABA as Seretide® 250 Evohaler® will be enrolled into Phase 1.

3.2.1 Phase 1: Objectives

The design of Phase 1 is illustrated in Figure 2.

Phase 1 will establish whether comparable asthma control can be maintained when patients previously controlled with Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® 250 Evohaler®) are changed to high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform® 250) compared to maintenance on high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide® 250 Evohaler®).

Asthma control will be evaluated using measures of asthma control that are routinely used in primary care.

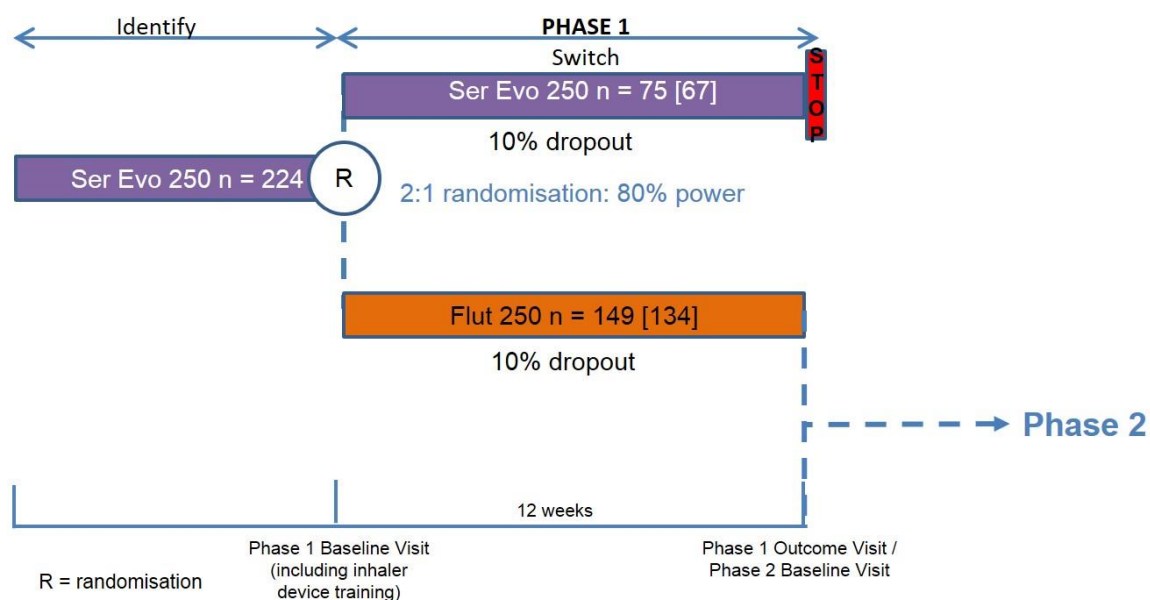


Figure 2: Design of Phase 1 of the study (Change) – a comparison of Flutiform[®] 250 with Seretide[®] 250 Evohaler[®] in maintaining asthma control.

3.2.2 Phase 1: Outcomes

Primary Outcome:

- ACQ7 score at week 12 adjusting for baseline*

Secondary Outcomes:

- The following will be compared between cohorts at week 12, adjusting for baseline:
 - Lung function as measured by Forced Expiratory Volume in 1 second (FEV₁) and Forced Vital Capacity (FVC)
 - GINA asthma control
 - Visual Analog Scale (VAS) Score
 - Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) Score
- Proportion of patients with asthma control, defined as:
 - No exacerbations
 - No change in therapy
 - GINA asthma control achieved

- Adverse events in both cohorts
- * Outcome previously utilised in published pragmatic trials (11).

3.2.3 Phase 1: Eligibility criteria

As a pragmatic study, the eligibility criteria for this study is limited to those criteria essential to maintain safety, while ensuring maximum applicability to the primary care population.

Patients will be required to meet the following eligibility criteria:

Inclusion criteria:

- Age 18-75
 - Able and willing to provide written informed consent and to comply with the study protocol.
 - Current diagnosis of asthma (as evidenced by appropriate diagnostic code)
 - Received Seretide® 250 Evohaler® 2 puffs twice daily for the last 6 months
 - No asthma exacerbation* in last 3 months
 - ≤2 exacerbations* in last 12 months
 - No errors in device use after training (during baseline visit)
 - Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after discontinuation of study drug. Acceptable methods of contraception include intrauterine device (IUD) known to have a failure rate of less than 1% per year, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, and partner vasectomy.
- * Exacerbation defined as acute course of oral steroids, emergency room attendance and/or hospitalisation for asthma

The inclusion criteria requiring patients to be receiving Seretide® 250 Evohaler® and to have controlled asthma was set for the following reasons:

- No run-in period will be required as patients will already be receiving the control device.
- It is good practice to review current medication and potentially change to a different medication, as patients have had controlled asthma for at least 3 months (demonstrated

by absence of exacerbations and controlled asthma using GINA asthma control definitions).

Exclusion criteria

- Other chronic respiratory disease than asthma (e.g. Chronic Obstructive Pulmonary Disease (COPD))
- Uncontrolled asthma (GINA criteria)
- The patient has used a clinical trial investigational drug within the last year before the screening visit
- Hypersensitivity to Flutiform[®], its component Formoterol or its excipients
- Pregnant subjects

3.2.4 Phase 1: Study procedures

Phase 1 consists of two visits over a 12 week period. A signed and dated informed consent will be obtained during visit 1, before any procedures commence. After giving informed consent, patients will proceed through the study visit as depicted in Figure 3.

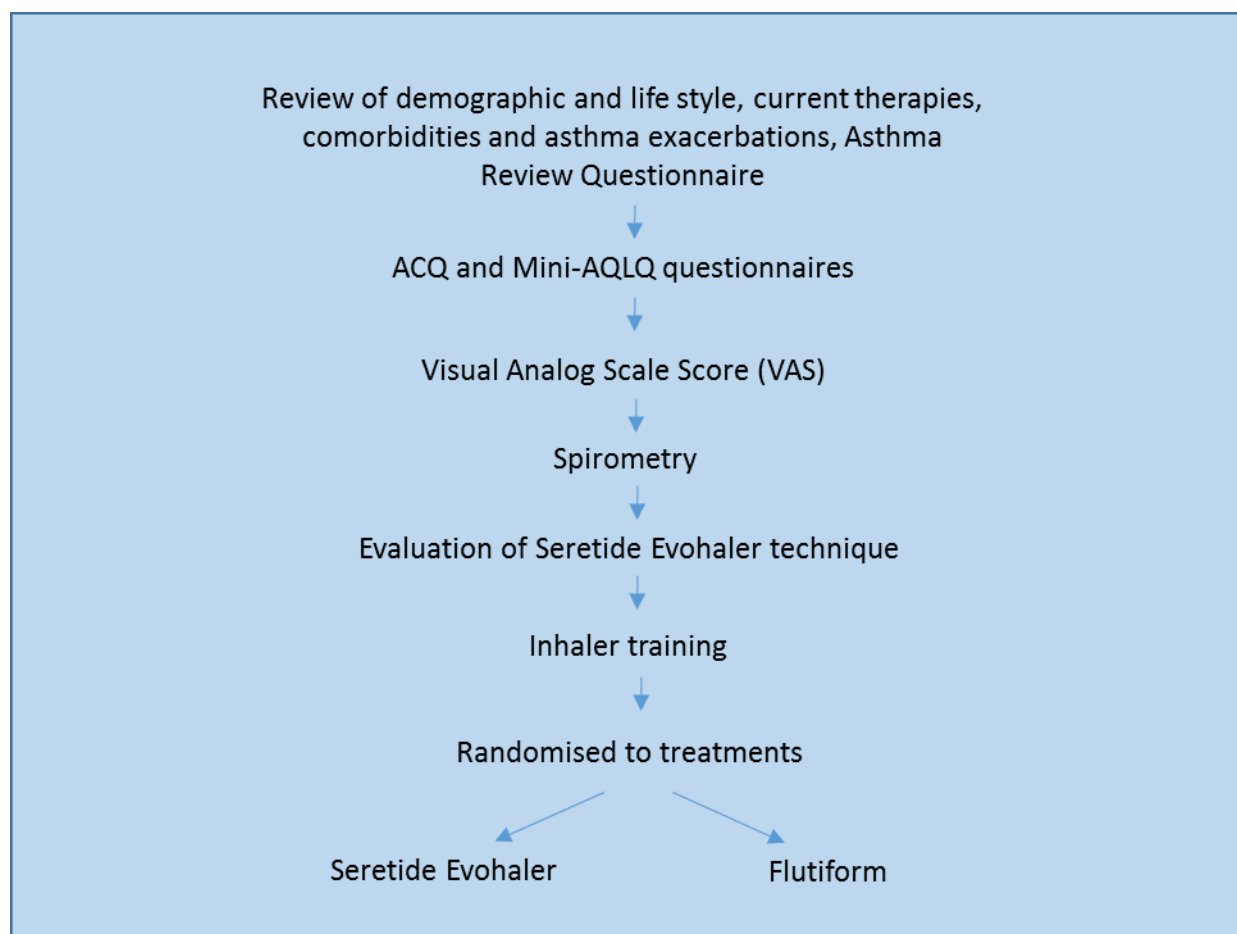


Figure 3: Flow diagram of the conduct of Phase 1 visit 1. All procedures will be undertaken within a single study visit.

As shown in Figure 3, Phase 1 visit 1 includes review of demographics and life style, current therapies, comorbidities and asthma exacerbations. Asthma control will be evaluated based on GINA criteria. After screening, patients who are eligible to continue in the study will have their current device (i.e. Seretide[®] 250 Evohaler[®]) technique evaluated. Patients will only be trained to use their current inhaler (control device) when critical errors are detected. All patients will be trained to use Flutiform[®] (investigative device). Patients who can demonstrate no errors in using both control and investigative device will be invited and randomised to participate in the full 12 weeks Phase 1 of the study.

Phase 1 is an intention-to-treat, pragmatic, open-label, randomised controlled trial (RCT) of Flutiform[®] 250 versus Seretide[®] 250 Evohaler[®] in patients with controlled asthma.

A full list of procedures for the study visits is shown in Table 1 below, the explanation of each step is provided in more detail.

Table 1: Procedures during Phase 1 baseline and outcome visits.

Phase 1 Procedures	Phase 1 Baseline Visit	Phase 1 Outcome Visit
Informed consent	✓	
Pregnancy test (for woman of childbearing potential)	✓	
Asthma review:	✓	
Demographics and life style	✓	
Co-morbidities and asthma and other medication	✓	✓
Asthma exacerbations in last 3 months	✓	✓
Asthma exacerbations in last 12 months	✓	
Asthma control status according to Global Initiative for Asthma criteria	✓	✓
Asthma Review Questionnaire	✓	
Asthma Control Questionnaire (ACQ)	✓	✓
Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)	✓	✓
Visual Analog Scale (VAS) Score	✓	✓
Lung function (FEV ₁ , FEV ₁ % pred., FVC, FEV ₁ /FVC)	✓	✓
Evaluation of current device inhaler technique	✓	
Investigational and control device training (HCP training followed by test for critical errors)	✓	
Phase 1 Randomisation	✓	
Dispensing of Phase 1 randomised treatment (either Flutiform [®] 250 or Seretide [®] 250 Evohaler [®])	✓	

Adverse events		✓
Device compliance		✓

Informed Consent

All patients will be asked to give written informed consent having had sufficient time to review and consider the patient information sheet. A signed and dated informed consent form will be obtained before screening procedures commence.

After informed consent is obtained, patients who are screened will be assigned a permanent identification number such that all patients from each investigational centre are given consecutive identification numbers following their inclusion.

A patient who is screened but not enrolled, e.g. because entry criteria were not met or enrolment did not occur within the specified time, may not be considered for screening again.

Pregnancy test

Women of childbearing potential (not surgically sterile or at least 2 years postmenopausal) will undertake a urine pregnancy test and will only be eligible to participate in the study if the test is negative.

Asthma review

Demographics and life-style

Demographic information including age, height, weight, date of diagnosis of asthma and occupation, and life-style information including current and past smoking history and alcohol consumption will be recorded.

Asthma exacerbations in the last 3 and 12 months (routine data and patient reported)

A review of the routine data will also be performed to establish the number of asthma exacerbations (defined as acute course of oral steroids, emergency room attendance and/or

hospitalisation for asthma) recorded in the 3 and 12 month periods prior to Phase 1 baseline visit.

Patients will also be asked the number of times they have had an asthma exacerbation in the 3 and 12 months prior to Phase 1 baseline visit to confirm events recorded in the routine data.

Co-morbidities

Current co-morbidities will be identified by diagnostic codes (and or therapy) and will be confirmed by the patient.

Asthma and other medications

A review of asthma and concomitant therapies currently prescribed and used by the patient will be performed to confirm patient eligibility.

Asthma Review Questionnaire

We will perform an asthma review using a questionnaire by Optimum Patient Care (Appendix B). While this questionnaire will not provide analyses outcomes, we will use this questionnaire to collect information about the patients and their asthma. In addition, a subset of questions in this questionnaire will be used for determining level of asthma control according to GINA guidelines (see below).

Asthma control and quality of life

Mini asthma quality of life questionnaire

The Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) is a 15-question, validated tool for evaluating quality of life in patients with asthma. Comprised of 4 domains (symptoms, activity limitation, emotional function and environmental stimuli), each question is scored using a 7 point scale (0-6, 0= no impairment and 6 = maximum impairment). The overall score is the average of the scores for the 15 questions (12).

Asthma control questionnaire (ACQ)

The Asthma control questionnaire (ACQ) is a seven question (i.e. the top scoring 5 symptoms, daily rescue bronchodilator use and FEV1% pred.), validated tool for assessing asthma control (Appendix A). In this protocol, 'ACQ7' will be used instead of ACQ to indicate the measurement of all seven questions, rather than five questions sometimes used by other studies.

Patients are asked to recall how their asthma has been during the last 7 days and to evaluate their asthma against 5 symptom questions and a rescue bronchodilator use question on a 7-point scale (0 = no impairment, 6 = maximum impairment). In addition, the HCP will grade the FEV₁ % predicted on a 7 point scale (0 to 6). The questions are equally weighted and ACQ7 score is the mean of the 7 questions, generating a value between 0 (totally controlled) and 6 (severely uncontrolled) (www.qoltech.co.uk/acq.html; Appendix A) (13).

Global Initiative for Asthma

Assessment of asthma control will be made using the Global Initiative for Asthma (GINA) Control criteria (Table 2).

Table 2: Global Initiative for Asthma Criteria for Asthma (GINA) Control

Characteristic	Controlled	Partly Controlled	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice per week	Three or more features of “partly controlled” asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less per week)	More than twice per week	
Lung function (PEF or FEV ₁)	Normal	<80% predicted or personal best (if known)	

FEV₁=forced expiratory flow in 1 second; PEF=peak expiratory flow.

Visual Analog Scale (VAS) score

The Visual Analog Scale (VAS) score has become a standard measurement for rhinitis studies and correlates well with the Total nasal symptom score. A recent study suggests that it could also be a useful and simple tool for assessing asthma control and we will therefore include it as an exploratory outcome in this study (14). The test involves asking patients to place a mark on a line to indicate how much their symptoms bother them. Scores range from not at all bothersome (0mm) to extremely bothersome (100mm).

Lung function

Post-bronchodilator forced expiratory volume in one second (FEV₁), percentage of predicted forced expiratory volume in one second (FEV₁ % predicted), forced vital capacity (FVC) and percentage of predicted forced vital capacity (FVC % predicted) will be measured.

Evaluation of current device inhaler (Seretide® Evohaler®) technique

Inhalers will be used in the patient's usual manner: either with or without a spacer. Errors will be evaluated by a HCP from a list collated from best evidence (peer-reviewed articles and steering committee; see Appendix C).

Investigational and control device training

Patients will be trained to use the investigative (Flutiform®) and control (Seretide® 250 Evohaler®) devices using placebo inhalers, following a 3-step training procedure. Patients will only be trained on the Seretide® 250 Evohaler® if critical errors are found during the evaluation of current device inhaler technique.

In the first training step the patient will be requested by the HCP to read the Patient Information Leaflet with instructions on how to use the inhaler (step 1). After reading the instructions the patient will be asked to demonstrate how they would use the inhaler. If one or more critical errors are observed, the patient will be shown by the HCP how to use the inhaler (step 2). Finally, if critical errors are still observed after this step, tuition by HCP will be repeated (step 3). If the patient is not able to use the inhaler without critical errors after the three training steps, he/she will not be eligible to take part in the study. If the patient is able to use the inhaler without errors, he/she will be randomised to treatment and will not need to proceed through any remaining training steps.

Phase 1 Randomisation

This is an open-label study and there is no blinding. A centralised randomisation programme will be used to randomise patients to receive either Flutiform® 250 treatment or Seretide® 250 Evohaler® treatment. The HCP will be asked to enter:

- Number of asthma exacerbations in the last 12 months (prior to Phase 1 baseline visit)
- Practice ID

The programme will allocate the patient to a device. This stratified randomisation will minimise the likelihood for significant baseline differences between arms in terms of number of asthma exacerbations in the 12 months prior to baseline.

Dispensing of Phase 1 randomised treatment

The HCP will dispense the randomised study treatment. Patients will receive 3 study devices. As each study device will provide 30 days of therapy, the 3 devices will provide sufficient therapy for the 12-week treatment period.

The study devices will be numbered 1, 2 and 3. The dates for 30 and 60 days after the baseline visit will be written on devices 2 and 3, respectively. Patients will be asked to start using device number 1 from that evening, stop using device 1 and start using device 2 from the date 30 days after the baseline visit, and stop using device 2 and start using device 3 from the date 60 days after the baseline visit.

Device compliance

Device compliance will be assessed for both the investigational and control devices.

Flutiform[®] 250

The Flutiform device has an inbuilt dose counter. Therefore compliance will be assessed by recording the number of doses used at the start and end of the study.

Seretide[®] 250 Evohaler[®]

The Evohaler device has an inbuilt dose counter. Therefore compliance will be assessed by recording the number of doses used at the start and end of the study.

3.2.5 Phase 1: Sample size calculation**Flutiform[®] 250 vs. Seretide[®] 250 Evohaler[®]**

When the sample size is 201 (67 Seretide[®] 250 Evohaler[®]: 134 Flutiform[®] 250), a two group t-test of equivalence in means, with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis that the mean ACQ7 scores are not equivalent (based on an acceptable maximum difference of -0.3 in mean ACQ7 score, i.e. lower confidence limit of -0.3 and a common standard deviation of 0.8) when the expected difference in mean ACQ7 score is 0.000.

Assuming a drop-out rate of about 10%, approximately 224 patients (75 Seretide[®]: 149 Flutiform[®]) will be randomised into this study to ensure that a minimum of 201 patients

complete all visits and critical assessments. Any patient who withdraws after randomisation will not be replaced.

3.2.6 Phase 1: Study medication

Investigational Product



Inhaled fluticasone/formoterol (250µg/10µg) as combination therapy via Flutiform® (Napp Pharmaceuticals Limited, Cambridge, UK).

Comparator Control Product



Inhaled fluticasone/salmeterol (250µg/25µg) as combination therapy via Seretide® 250 Evohaler® (Allen & Hanburys Ltd, Uxbridge, UK).

3.2.7 Phase 1: Study device resource required

The number of placebo inhaler devices required for training purposes only, will be 80 for each device. The number of active inhaler devices, based on the power calculations and drop-out rate, is shown in Table 3. To ensure sufficient supply of inhalers at each site we estimate that 670 Flutiform and 337 Seretide inhalers will be required in Phase 1.

Table 3: Number of active inhaler devices required for Phase 1

Active Device	Dose per actuation	Daily Dose	Actuations/device	Number of Devices	Patients per arm	Minimum number of devices	Estimated number of devices
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				per patient		used per arm	required (+50%)
Flutiform®	250	1000	120	3	149	447	670
Evoaler®	250	1000	120	3	75	225	337

3.3. Phase 2 (Step-down) - Study design and methodology

In Phase 2, following a 12 week period on Flutiform® 250 (Phase 1), a step-down of ICS/LABA dose from Flutiform® 250 to Flutiform® 125 will be evaluated to establish whether asthma control following a reduction in ICS/LABA is comparable to that of patients continuing to receive Flutiform® 250.

The number of patients available for Phase 2 of the study is based on those who successfully completed the Flutiform® 250 arm of the Phase 1 study, maintained their asthma control, and are willing to take part in Phase 2. The expected number of patients to enter into the Flutiform® 250 arm of the Phase 1 is 149.

Assuming a combined 10% drop-out rate prior to randomisation and during study (approximately 14 patients) from Phase 1 and a further 14% lost due to lack of asthma control (approximately 18 patients), a sample size of 102 (51 Flutiform® 250; 51 Flutiform® 125) would provide 80% power to detect a maximum difference of -0.4 mean difference in ACQ7.

In order to achieve 90% power, 140 patients would be required (70 randomised to Flutiform® 250; 70 randomised to Flutiform® 125).

3.3.1 Phase 2: Objectives

The design of Phase 2 is illustrated in Figure 5.

Phase 2 will establish whether comparable asthma control can be maintained when patients previously controlled with high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform® 250) are stepped down to medium dose Fluticasone/Formoterol (250/10 2 puffs

twice daily as Flutiform[®] 125) compared to maintenance on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250).

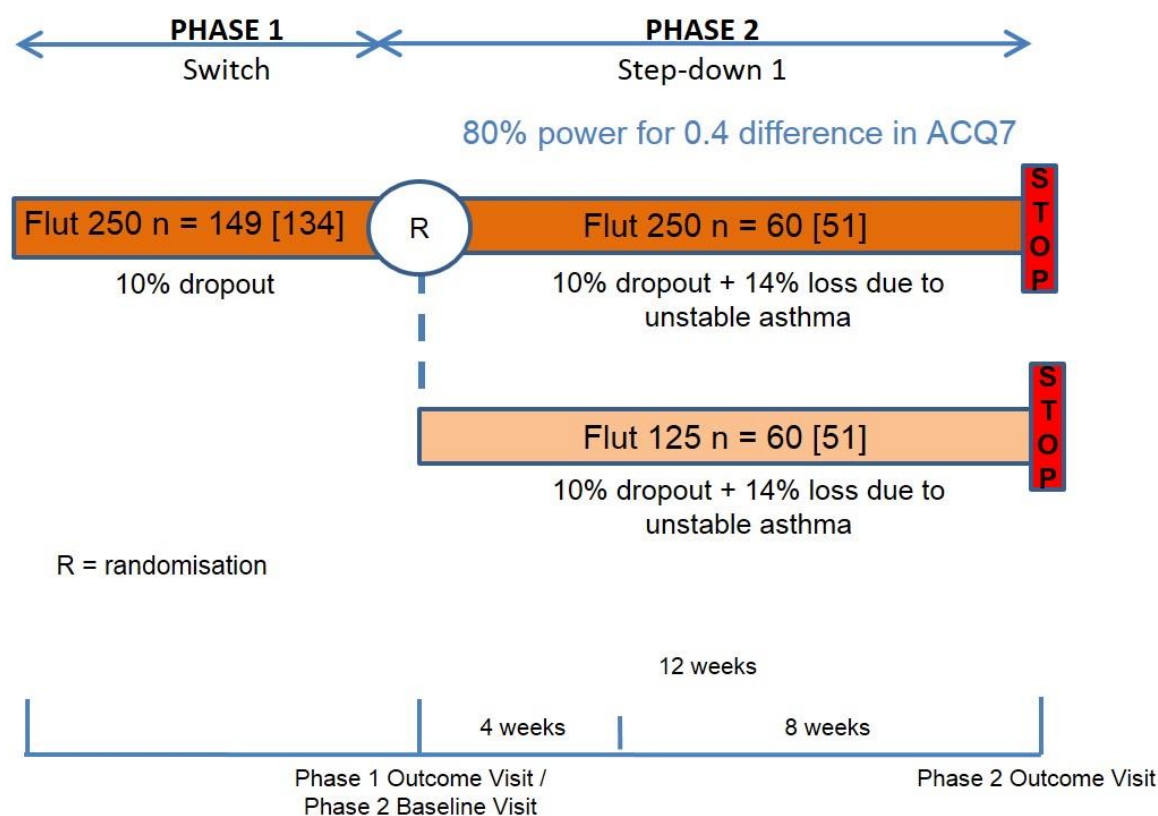


Figure 4: Design of the Phase 2 (Step-Down) – a comparison of clinical non-inferiority of Flutiform[®] 250 with Flutiform[®] 125. Minimum expected number of patients at the end of Phase 2 is 102.

3.3.2 Phase 2: Outcomes

Primary Outcome:

- ACQ7 score at week 12 adjusting for baseline

Secondary Outcomes:

- The following compared between cohorts at week 12, adjusting for baseline:
 - Lung function (FEV₁ and FVC)
 - Nitric oxide (FeNO) - to assess airway inflammation
 - GINA asthma control
 - Vital Analog Scale (VAS) score

- Mini-AQLQ score
- Proportion of patients with asthma control, defined as:
 - No exacerbations
 - No change in therapy
 - GINA asthma control achieved
- Adverse events in both cohorts
- In addition, there is a visit during Phase 2 at week 4 to measure FeNO levels, lung function and asthma control and quality of life. These will also be reported as secondary outcomes.
- We will also measure blood eosinophil counts at Phase 2 baseline visit. These will be used as a second, independent measure of inflammation in addition to FeNO.

3.3.3 Phase 2: Eligibility criteria

Patients completing Phase 1 will be evaluated for eligibility to enter Phase 2 according to the following eligibility criteria.

Inclusion criteria:

- Randomised to Flutiform[®] 250 in Phase 1
- At completion of Phase 1 had stable asthma with no exacerbations in the 12 weeks of the Phase 1 study (exacerbation defined as acute course of oral steroids, emergency room attendance and/or hospitalisation for asthma)

3.3.4 Phase 2: Study procedures

Procedures listed in Table 4 will be performed in Phase 2.

In addition to the outcomes measured in Phase 1, in Phase 2 we will measure fractional exhaled nitric oxide (FeNO), which is a non-invasive and effective way of monitoring asthma severity and managing real-life asthma (15). More importantly, it may be useful for identifying and for excluding ICS-responsive airway inflammation. In this study we will evaluate whether FeNO could be used as a marker for how patients respond to step-down of treatment.

To complement FeNO as an inflammatory marker we will also determine peripheral blood eosinophil counts at Phase 2 baseline visit. This will involve taking approximately 8ml of blood. If a patient does not wish to give blood, they can still participate in all other aspects of the study.

Table 4: Study procedures for Phase 2

Phase 2 Procedures	Phase 2 Baseline Visit*	Phase 2 Interim visit	Phase 2 Outcome Visit
Asthma exacerbations since phase 1 (eligibility)	✓		
Asthma exacerbations during phase 2 (outcomes)		✓	✓
Co-morbidities and asthma and other medication	✓	✓	✓
Asthma control status according to Global Initiative for Asthma criteria	✓	✓	✓
Adverse events		✓	✓
Asthma Control Questionnaire (ACQ)	✓	✓	✓
Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)	✓	✓	✓
Visual Analog Scale (VAS) Score	✓	✓	✓
Exhaled NO (FeNO)	✓	✓	✓
Blood eosinophil count	✓		
Lung function (FEV ₁ ; FEV ₁ % pred., FVC; FEV ₁ /FVC)	✓	✓	✓
Phase 2 Randomisation	✓		
Dispensing of Phase 2 randomised treatment	✓		

Device compliance		✓	✓
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*Performed on the same day as Phase 1 outcome visit.

Phase 2 Randomisation

A centralised randomisation programme will be used to randomise patients to receive either Flutiform® 250 treatment or Flutiform® 125 treatment. The HCP will be asked to enter:

- Number of asthma exacerbations in last 12 months (prior to Phase 1 baseline visit)
- Practice ID

The programme will automatically allocate the patient to a device.

This stratified randomisation will minimise the likelihood for significant baseline differences between arms in terms of number of asthma exacerbations in the 12 months prior to Phase 1 baseline visit.

Dispensing of Phase 2 randomised treatment

The HCP will dispense the randomised study treatment. Patients will receive 3 study devices. As each study device will provide 30 days of therapy, the three devices will provide sufficient therapy for the 12-week treatment period.

The study devices will be numbered 1, 2 and 3. The dates for 30 and 60 days after the baseline visit will be written on devices 2 and 3, respectively. Patients will be asked to start using device number 1 from that evening, stop using device 1 and start using device 2 from the date 30 days after the baseline visit, and stop using device 2 and start using device 3 from the date 60 days after the baseline visit.

Device compliance

Device compliance will be assessed for both the investigational and control devices.

Flutiform® 125

The Flutiform device has an inbuilt dose counter. Therefore compliance will be assessed by recording the number of doses used at the start and end of the study.

Flutiform® 250

The Flutiform device has an inbuilt dose counter. Therefore compliance will be assessed by recording the number of doses used at the start and end of the study.

3.3.5 Phase 2: Power calculation

Step-down from Flutiform[®] 250 to Flutiform[®] 125

Based on the expected sample size available following Phase 1, a sample size of 102 (51 Flutiform[®] 250: 51 Flutiform[®] 125), using a two group t-test of equivalence in means, with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis that the mean ACQ7 scores are not equivalent (based on an acceptable maximum difference of -0.4 in mean ACQ7 score, i.e. lower confidence limit of -0.4 and a common standard deviation of 0.8) when the expected difference in mean ACQ7 score is 0.000.

3.3.6 Phase 2: Study medication

Investigational Product



Inhaled fluticasone/formoterol (125µg/10µg) as combination therapy via Flutiform[®] 125 (Napp Pharmaceuticals Limited, Cambridge, UK).

Comparator / Control Product



Inhaled fluticasone/formoterol (250µg/10µg) as combination therapy via Flutiform[®] 250 (Napp Pharmaceuticals Limited, Cambridge, UK).

3.3.7 Phase 2: Study device resources required

The number of inhalers required for the Phase 2 of the study, based on the power calculations and drop-out rate, is shown in Table 5. To ensure sufficient supply of inhalers at each site we estimate that 270 inhalers will be required per arm in Phase 2.

Table 5: Number of inhaler devices required for Phase 2

Active Device	Dose per actuation	Daily Dose	Actuations/ device	Number of Devices per patient	Patients per arm	Minimum number of Devices used per arm	Estimated number of devices required (+50%)
Flutiform [®] 125	125	500	120	3	60	180	270
Flutiform [®] 250	250	1000	120	3	60	180	270

4. STUDY PRODUCT AND ITS DOSAGE

4.1. Flutiform[®] 250 and Flutiform[®] 125

Flutiform[®] is a pressurised metered dose inhaler containing two active substances: an inhaled corticosteroid (ICS: fluticasone propionate) and a long-acting β 2-agonist (LABA: formoterol fumarate). Fluticasone propionate is a corticosteroid which has potent anti-inflammatory action and reduces swelling and irritation in the lungs. Its chemical name is S-(fluoromethyl) 6 α , 9-difluoro - 11 β , 17 – dihydroxy - 16 α - methyl - 3oxoandrosta - 1, 4 - diene - 17 β -carbothioate, 17-propionate. It is a white powder with a molecular weight of 500.6 and an empirical formula of C₂₅H₃₁F₃O₅S. Formoterol fumarate dehydrate is a long-acting bronchodilator, which helps the airways in the lungs to stay open. Its chemical name is (R*,R*)-N-[2-Hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl] amino] ethyl] phenyl]. It has a molecular weight of 840.92 and an empirical formula of 2(C₁₉H₂₄N₂O₄)·C₄H₄O₄·2(H₂O). It has a faster onset of bronchodilation than salmeterol, and the rapid onset of formoterol (1-3 minutes) is similar to that of the short-acting beta-2 agonist (SABA) salbutamol (3,8,9).

Flutiform[®] is licensed for regular treatment of asthma where the use of a combination product (ICS/LABA) is appropriate:

- For patients not adequately controlled with ICS and ‘as required’ inhaled short-acting β 2-agonist or,
- For patients already adequately controlled on both an ICS and a LABA.

Flutiform[®] is available in three fixed-dose combinations of fluticasone/formoterol:

- Flutiform[®] 250 (fluticasone/formoterol: 250 μ g/10 μ g dose)
- Flutiform[®] 125 (fluticasone/formoterol: 125 μ g/5 μ g dose)
- Flutiform[®] 50 (fluticasone/formoterol: 50 μ g/5 μ g dose)

In this study, only Flutiform[®] 250 and the Flutiform[®] 125 will be investigated. The recommended frequency of dosing is two inhalations, twice daily:

- The Flutiform[®] 250 inhaler is indicated in adults, 18 years and over, only.
- The Flutiform[®] 125 inhaler is indicated in adults and adolescents over 12 years.

4.2. Seretide[®] 250 Evohaler[®]

Seretide[®] Evohaler[®] is a pressurised metered dose inhaler containing two active substances: an inhaled corticosteroid (ICS: fluticasone propionate) and a long-acting β 2-agonist (LABA: salmeterol xinafoate). Fluticasone propionate, as mentioned above, is a corticosteroid which has potent anti-inflammatory action and reduces swelling and irritation in the lungs. Salmeterol is a long-acting bronchodilator, which helps the airways in the lungs to stay open. The effects last for at least 12 hours.

Seretide[®] Evohaler[®] is licensed for the regular treatment of asthma where the use of a combination product (ICS/LABA) is appropriate:

- For patients not adequately controlled with ICS and ‘as required’ inhaled short-acting β 2-agonist or,
- For patients already adequately controlled on both an ICS and a LABA.

Seretide[®] Evohaler[®] is available in three fixed-dose combinations of fluticasone/ salmeterol:

- Seretide[®] Evohaler[®] 250 (fluticasone/ salmeterol: 250 μ g/25 μ g dose)
- Seretide[®] Evohaler[®] 125 (fluticasone/ salmeterol: 125 μ g/25 μ g dose)
- Seretide[®] Evohaler[®] 50 (fluticasone/ salmeterol: 50 μ g/25 μ g dose)

In the current study, only Seretide[®] Evohaler[®] 250 will be studied. The recommended frequency of dosing is two inhalations, twice daily:

- Seretide[®] 250 Evohaler[®] inhaler is indicated in adults and adolescents over 12 years.

5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN SUBJECTS

5.1. Flutiform® and its known and potential risks and benefits

Possible risks with the use of Flutiform® products may be anticipated from class labelling for the two components of the formulation, namely, ICS and inhaled LABAs. Many of the adverse events associated with ICS result from chronic-dose administration. Use of corticosteroids, even acutely, is contraindicated in patients with chronic infections (e.g. existing tuberculosis or ocular herpes simplex). In contrast, β 2-adrenoceptor agonists can have acute effects of clinical significance, such as cardiovascular effects, on single-dose administration. As such, the use of these drugs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension and in patients who are unusually hyper-responsive to sympathomimetic amines.

Clinical data shows that the use of a fluticasone propionate/formoterol fumarate dihydrate combination in both adults and children with persistent asthma provides greater improvement in pulmonary function and overall asthma control than either individual component alone (16, 17). Based on previous studies comparing Flutiform® and Seretide® Evohaler® it is expected that the safety and efficacy profile of the Flutiform® 250 will be comparable to Seretide® Evohaler® 250 for the long-term, twice daily, maintenance treatment of asthma. However, a previous study suggests that the LABA formoterol fumarate in Flutiform® has a faster onset of bronchodilation than salmeterol, and the rapid onset of formoterol (1-3 minutes) is similar to that of the short-acting beta-2 agonist (SABA) salbutamol (3,8,9).

5.1.1. Interaction with other medicinal products

Flutiform® contains sodium cromoglicate at non-pharmacological levels. Patients should not discontinue any cromoglicate containing medication while on Flutiform.

Fluticasone propionate, an individual component of Flutiform®, is a substrate of CYP3A4. The effects of short-term co-administration of strong CYP3A4 inhibitors together with Flutiform® inhaler are of minor clinical relevance, but caution needs to be taken in long-term treatment and co-administration. Particularly co-medication of ritonavir should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects. Information about

this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. As all patients enrolled into the study have been treated with Seretide® Evohaler® (contains fluticasone propionate), they would have been screened for potential adverse interactions of fluticasone propionate and other medicinal products.

Formoterol fumarate, as other β_2 agonists, should be administered with extreme caution to patients being treated with tricyclic antidepressants or monoamine oxidase inhibitors, and during the immediate two week period following their discontinuation, or other drugs known to prolong corrected QT interval.

The possible risks and adverse events that might be expected for this product are based on information derived from the Flutiform® Summary of Product Characteristics (SPC) (2).

5.2. Seretide® Evohaler® and its known and potential risks and benefits

A patient eligible for the study would have been prescribed and treated with Seretide® 250 Evohaler® (2 puffs twice a day) for at least six months. The potential risks and benefits would have been carefully considered by the prescribing doctors already. Additional information regarding risks and benefits to human patients may be found in the Seretide® Evohaler® SPC (18).

6. STUDY DRUG SUPPLY AND ACCOUNTABILITY

6.1. Study drug storage and security

6.1.1. Storage at the study centre

The study drugs (Flutiform[®], Seretide[®] Evohaler[®]) must be stored at controlled room temperature with no direct exposure to heat, cold, or high humidity and in a securely locked, substantially constructed cabinet or enclosure at the study centre. A log with daily temperature measurements will be kept and will be available for review by the monitor for the duration of the study. Complete instructions on receipt, storage and handling of study drugs will be detailed in the Operations Manual.

6.1.2 Storage after dispensing

Study drug that has been dispensed to randomised patients should be stored at room temperature in a dry place (e.g. not a bathroom) away from direct exposure to heat, cold, or high humidity. Storage of study drug in a non-controlled environment, such as a car is prohibited. These storage requirements will be carefully explained to patients when handing out drugs to the patients at the clinic. The use-by date on each device will be checked and the drug storage will be reviewed at each treatment visit to confirm that the device has not expired and the drug has been stored properly.

6.2. Study drug accountability

Each study drug shipment should include a packing slip, listing the contents of the shipment, drug return instructions and any other applicable forms.

RiRL is responsible for ensuring that deliveries of study drugs and other study materials from the supplier are correctly received and recorded, handled and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

A record of study drug accountability (i.e. study drugs and other materials received, used, retained and returned) must be prepared and signed by the Principal Investigator or designee, with an account given for any discrepancies. Study drug accountability will also include dose

counter readings, where applicable, at the beginning (at time of dispensing the inhaler) and end (at time of inhaler return) of the device cycle.

Used and unused study drug will be returned to the supplier.

7. PATIENT MANAGEMENT DURING THE CONDUCT OF THE STUDY

In accordance with a pragmatic study design, patients will receive usual care by their own GP during the conduct of the study.

Other than attending the required number of clinical visits (baseline, Phase 1 outcome visit/Phase 2 baseline visit, Phase 2 interim visit and Phase 2 outcome visit), patients will not be contacted by the research team.

8. STUDY TERMINATION AND PATIENT WITHDRAWAL

8.1. Study termination

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed as they are reported from the investigational centre to identify safety concerns. The study may be terminated by the sponsor at any time.

8.2. Patient withdrawal

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time for any reason. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, or other reasons concerning the health or well-being of the patient, or in case of a protocol deviations.

Should a patient decide to withdraw after the administration of the study product, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, and any explanation given by the patient as to why they are withdrawing from the study should be recorded.

The reason for and date of withdrawal from the study must be recorded in the eCRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event, monitoring will be continued at the discretion of the investigator (e.g. until the event has resolved or stabilised, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event must be recorded in the eCRF.

9. PATIENT PAYMENTS

Patients will be reimbursed £25 per visit for their travel and time .

10. ADVERSE EVENT REPORTING

All adverse events (AE's) occurring in patients during the course of their involvement in this clinical research study, related or unrelated to the study medication, will be reported according to the Clinical Trials Directive 2001/20/EC, Medicines for Human Use (Clinical Trials) Regulations 2004, ICH E2D guideline (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), and the UK Department of Health's Research Governance Framework for Health and Social Care requirements for managing AE's and in line with RiRL's requirements. We will ensure that these reporting procedures are also in line with the requirements of Napp.

10.1. Definition of Adverse Events

All types of Adverse Events are defined in Table 6.

Worsening of the disease during the study will be recorded as an Adverse Event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

An exacerbation of asthma is defined as worsening asthma requiring any treatment other than the study medication, rescue albuterol/salbutamol, and/or regular ICS use. This includes requiring the use of systemic corticosteroids and/or emergency room visit or hospitalisation, a change in patient's regular ICS dose, or the addition of other asthma medications.

An asthma exacerbation will not be considered an Adverse Event unless it meets the criteria for a serious adverse event. Asthma exacerbations that do not meet the criteria for reporting as a serious adverse event will be documented separately from Adverse Events.

Patients with an asthma exacerbation will not be discontinued from the study unless hospitalisation is required, the patient meets any of the stopping criteria in Section 8, or the Principal Investigator believes it is in the patient's best interest to be withdrawn from the study. However, patients who develop an asthma exacerbation in the Flutiform® 250 arm of the Phase 1 study will not be eligible to participate in the Phase 2 of the study.

Table 6: Definition of Adverse Events

Adverse Event	Definition
Adverse Event (AE)	An untoward medical occurrence which does not necessarily have a causal relationship to the IMP or comparator, such as: • intercurrent illnesses • physical injuries • events possibly related to concomitant medication • significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an adverse event.)
Adverse Drug Reaction (ADR)	An untoward and unintended response to an IMP which has a reasonable causal relationship to the IMP
Unexpected ADR	An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics) should be considered unexpected.
Serious Adverse Event (SAE)	An untoward medical occurrence which does not necessarily have a causal relationship to the IMP or comparator but which: • results in death • is life threatening • requires inpatient hospitalisation, or results in prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect. • is a medically important event or reaction
Serious Adverse Reaction (SAR)	An SAE that has a causal relationship to the IMP
Suspected Serious Adverse Reaction (SSAR)	A SAR is consistent with the information about the IMP listed in the Summary of Product Characteristics (SPC).

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is suspected to be caused by the IMP but which is not consistent with the information about the IMP in the SPC.
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10.2. Recording and reporting adverse events

The study period is defined for each patient as the time period from signature of the informed consent form through to the end of the treatment period. All adverse events (as defined in Table 6) that occur during the defined study period will be identified, recorded in the eCRF and reported in line with the sponsor's and regulatory requirements. If there is a serious adverse event, additional reporting on the Serious Adverse Event Form is required. Pregnancy is not considered a serious adverse event, however the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form.

All serious adverse events that occur during the study period, regardless of judged relationship to treatment with the study drug, must be reported to RiRL by the investigator within 24 hours of when the Investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day. Completing the Serious Adverse Event Form and reporting the event must not be delayed, even if not all information is available. The minimum data elements that should be provided are: an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect product. Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational centre to the same address as the initial report within 24 hours of when it becomes known.

The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to RiRL if the investigator becomes aware of them.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilised or returned to baseline, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the Investigator, must be recorded.

Each report of a serious adverse event will be reviewed and evaluated by the Investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease. On the basis of this assessment, a decision will be made concerning the need for further medical intervention. The Investigator and sponsor (or their designee) must ensure the event is reported to the appropriate authority and ethics committee in accordance with local regulations. Individual Case Safety Reports (ICSRs) for adverse drug reactions that are serious will be subject to expedited reporting in the UK. Non-serious adverse reactions, whether expected or not, would normally not be subject to expedited reporting.

11. STATISTICAL ANALYSIS

Intention-to-treat and per-protocol analyses will be undertaken. For the Intention-to-treat analysis, for each Phase, all patients entered into the study will be included in the analysis. For the per-protocol analysis, for each Phase, all patients entered who complete the Phase as per protocol (defined as attending both baseline and outcome visits irrespective of whether asthma control was maintained) will be included.

11.1. General

Statistically significant results will be defined as $p\text{-value} < 0.05$ and trends as $0.05 \leq p\text{-value} < 0.10$. All analyses will be carried out using SPSS version 20, SAS version 9.3 and Microsoft Office EXCEL 2007.

11.2. Summary statistics for Phase 1 and Phase 2

Summary statistics will be produced for both Phase 1 and Phase 2 of the study and for all baseline and outcome variables as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution).

11.3. Statistical analysis for Phase 1 and Phase 2

Baseline and outcome variables will be analysed as a complete dataset and by treatment groups.

Baseline variables will include:

- Demographics and Life style
- Data collected with the Asthma Review Questionnaire
- Asthma exacerbations in last 3 and 12 months
- Co-morbidities
- Asthma medications
- Other concomitant medications
- Lung function (FEV₁ and FVC)
- Nitric oxide (FeNO) levels (only Phase 2)
- Visual Analog Scale (VAS) Score
- ACQ7 Score
- Mini-AQLQ score
- Blood eosinophil count (only Phase 2 baseline)
- Number of Seretide 250 Evohaler refills in the past 6 months or 1 year, if available, as a measure of adherence to treatment prior to study

Outcome variables will include:

Primary Outcome:

- ACQ7 score at week 12 adjusting for baseline

Secondary Outcomes:

- The following compared between both cohorts at week 12, adjusting for baseline:
 - Lung function (FEV₁ and FVC)
 - Nitric oxide (FeNO) - to assess airway inflammation (Phase 2)
 - GINA asthma control
 - Mini-AQLQ
 - Visual Analog Scale (VAS) Score
- Proportion of patients with asthma control, defined as:
 - No exacerbations

- No change in therapy
- GINA asthma control achieved
- Adverse events in both cohorts

In addition, there is visit at Phase 2 week 4 to capture FeNO levels, lung function and asthma control and quality of life questionnaire score results. These will also be reported as secondary outcomes. Finally, as an independent measure of inflammation we will determine blood eosinophil counts at Phase 2 baseline visit in addition to FeNO.

Analysis of covariance (ANCOVA) (with control device as the reference treatment) will be used to compare outcome variables (ACQ7, Mini-AQLQ, lung function, nitric oxide (FeNO), VAS score, blood eosinophil count) between treatment groups. Unadjusted and adjusted results (with baseline variable and potential confounding factors as explanatory variables) will be presented.

Differences in the proportion of patients achieving asthma control/recording no exacerbations / no change in therapy during the treatment period, will be evaluated using Chi-squared test (unadjusted) and a generalised linear model using a binary distribution (adjusted for baseline variables).

All tests will be one-sided to show non-inferiority.

11.4. Missing data

The per-protocol will not account for missing data as missing data will be seen as a protocol violation and therefore a patient with missing data will be excluded from this population.

The Intent-to-Treat population (ITT) will have missing values imputed as follows:

Any missing data will be assessed and attempts made to ensure that there are no underlying reasons for the data not being collected. i.e. that the data are missing at random.

Phase 1:

Any missing data will be replaced by adopting a policy of Baseline Observation Carried Forward (BOCF). This is felt to be the most conservative approach as it would be expected

for patients to remain the same between baseline and week 12 as this phase looks at maintenance of asthma control.

Phase 2:

Any continuous missing data in phase 2 will be replaced by using a marginal mean imputation method using the known values in each treatment group. Categorical variables will be replaced by using a missing indicator variable to show the number (%) with missing values. This is seen as the most conservative approach as those dropping dose level will be likely to worsen in their asthma control.

As a sensitivity check, the ITT will also be analysed with no imputation for missing data to confirm the validity of the approach.

12. ELECTRONIC CASE REPORT FORM AND STUDY DATASET

12.1. Data collection

A clinical data management system (CDMS) will be used to hold data collected during the study. Data will be incorporated into the system from the eCRF. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture study data. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational centres by appropriately designated and trained personnel and CRFs must be completed for each patient screened who provided informed consent/assent according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by each investigator at each investigational centre. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

12.1.1. Electronic case report form (eCRF)

An eCRF will be designed for the purposes of recording study information provided by the patient during study visits. Features of the eCRF will include:

- password protected, with access limited to staff essential for entering or verifying data.
- identification of patients by unique patient and practice identifiers to maintain patient confidentiality.
- ensure that each time the patient record is accessed by a Researcher, Investigator or Monitor, the access will be logged.
- data management strategies to minimise missing data and incorrect data entry.

Data captured into the eCRF will be directly incorporated into the database system.

12.1.2. Questionnaires

All questionnaire results will be recorded into the eCRF.

12.2. Data quality control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a Data Management plan.

Data captured will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed.

12.3. Data queries

Data queries will be raised by the data management team and the trial monitor to be resolved by the Investigator team.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Protocol amendments and protocol deviations

13.1.1. Protocol amendments

No changes from the final protocol will be initiated without prior written approval and favourable opinion of a written amendment by the REC and R&D, and an approval by a regulatory authority (e.g. MHRA), except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration. Each Principal Investigator and the sponsor will sign the protocol amendment.

13.1.1. Protocol deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient(s) affected by the violation from the study or permit the patient(s) to continue in the study, with documented approval from the medical representative. The decision will be based on ensuring patient safety and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational centre personnel learn that a patient who did not meet protocol eligibility criteria was entered into the study, they must immediately inform the sponsor of the protocol violation. If such a patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

13.2. Information to study personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

13.3. Study monitoring

To ensure compliance with GCP guidelines, the study monitor or a representative is responsible for ensuring that patients have signed the informed consent form and that the study is conducted according to applicable SOPs, the study protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary link between the sponsor and the investigator. The study monitor will visit each investigator during and after the study to ensure adherence to the protocol. In addition, it is the responsibility of the study monitor to ensure that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and whenever changes to the consent form are warranted.

Study monitor will contact each investigator and visit the investigational centre at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (eCRFs and other pertinent source data records, to include specific electronic source documentation) relating to the study to verify adherence to the protocol and to ensure completeness, consistency, and accuracy of the data being recorded. The study monitor will

indicate verification and ensure that all required electronic signatures are being implemented accordingly in the eCRF.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational centre. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

13.4. Audit and inspection

The sponsor may audit the investigational centre to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements.

Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

14. ETHICS

14.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2D guideline (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), as well as with the EU Clinical Trials Directive (2001/20/EC).

The investigator is responsible for conducting the study in accordance with the procedures described in this protocol. All the personnel involved in the study will be fully informed about the nature of the study and will be subject to protocol procedures concerning their duties in the study. The investigator and the sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance to the highest standards of ICH E6 GCP guidelines and other relevant UK regulations.

14.2. Registration of the clinical study

This clinical study will be registered on clinical trials registry websites.

14.3. Research Ethics Committees

The study protocol and related forms will be submitted to an independent Research Ethics Committee (REC) before study is initiated. Notification of approval must be obtained from the REC in writing by the investigator before study initiation. The investigator is required to maintain accurate and complete records of all written correspondence sent to and received from the REC.

The study will be conducted on behalf of Professor David Price. RiRL will be responsible for conducting the study including submissions to the REC.

14.4. NHS R&D

Management approval for this study will be obtained from the NHS Trust R&D Office. No patient recruitment to a practice/hospital will take place until the study manager has received R&D approval for the practice.

14.5. Informed consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and dated by the patient. The investigator will keep the original consent form and provide a copy to the patient. It will also be explained to the patients that they are free to refuse entry into the study and are free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study given to patients will be in simple terms, however, as specified in the study inclusion criteria, only patients who are able and willing to read and comprehend written and verbal instructions will be enrolled into the study.

14.6. Confidentiality regarding study patients

The investigator will assure that the privacy of the patients, including their identity and all personal medical information, is maintained at all times. In this study, patients will be identified not by their names or initials, but only by an identification code.

Patient invitation letters will be sent directly from the practice or by using a secure mail provider, in which case a secure, encrypted data table of the eligible patients' names and addresses will be sent from the practice to the remote secure mail provider to maintain confidentiality. The mail provider holds a security management system and is compliant with APACS standard 55. In a process certified by NHS Information Governance, this document is held in a secure temporary file and destroyed once the mail has been sent.

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the eCRF. This review may be conducted by the study monitor, properly

authorised persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

All data will be handled as covered by the UK Data Protection Act 1998 and in accordance with patient confidentiality and the Caldicott principles.

14.7. Declaration of the end of the clinical study

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) will be notified of the end of trial within 90 days of the end of trial using the standard EudraCT declaration of end of trial form provided by the National Research Ethics Service.

15. TIME SCHEDULE AND DELIVERY

The total length of the study will be approximately 11 months from screening the first patient to completion of the last patient visit. The patient will be in the study for 3-6 months attending 2-4 visits.

16. FINANCING AND INSURANCE

This study is sponsored by Research in Real Life Ltd with partial funding from Napp Pharmaceuticals according to IMP Drug Supply Agreement signed by both parties on 20th December 2013.

A separate financial agreement will be made between the Principal Investigator and the RiRL before the study drug is delivered.

Research in Real Life Ltd has insurance which covers any harm, including non-negligent harm, for this study.

17. REPORTING AND PUBLICATION OF RESULTS

The clinical study report and a final review of the safety data should be provided to the supplier not later than 3 months after study database lock. Submission of a paper for publication in the scientific literature should be completed within 6 months of study database lock.

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APPENDIX A. ASTHMA CONTROL QUESTIONNAIRE

ASTHMA CONTROL QUESTIONNAIRE - The ACQ is copyright and is used with the permission of Professor Elizabeth Juniper

study ID

date

initials

visit

*Please complete all questions. Tick the box under the response that best describes how you have been **during the past week***

On average, during the past week, how often were you woken by your asthma during the night?	Never ☐	Hardly ever ☐	a few minutes ☐	several times ☐	many times ☐	a great many times ☐	unable to sleep because of asthma ☐
On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?	No symptoms ☐	Very mild symptoms ☐	mild symptoms ☐	moderate symptoms ☐	quite severe symptoms ☐	severe symptoms ☐	very severe symptoms ☐
In general, during the past week, how limited were you in your activities because of your asthma?	Not limited at all ☐	Very slightly limited ☐	slightly limited ☐	moderately limited ☐	very limited ☐	extremely limited ☐	totally limited ☐
In general, during the past week, how much shortness of breath did you experience because of your asthma?	None ☐	a very little ☐	a little ☐	a moderate amount ☐	quite a lot ☐	a great deal ☐	a very great deal ☐
In general, during the past week, how much of the time did you whoze ?	Not at all ☐	hardly any of the time ☐	a little of the time ☐	A moderate amount of the time ☐	A lot of the time ☐	Most of the time ☐	All of the time ☐
On Average, during the past week, how many puffs of short-acting bronchodilator (eg Ventolin) have you used each day?	None ☐	1-2 puffs most days ☐	3-4 puffs most days ☐	5-8 puffs most days ☐	9-12 puffs most days ☐	13-16 puffs most days ☐	more than 16 puffs most days ☐
<i>to be completed by the Researcher:</i> FEV % predicted	>95% predicted ☐	95-90% predicted ☐	89-80% predicted ☐	79-70% predicted ☐	69-60% predicted ☐	59-50% predicted ☐	<50% predicted ☐

APPENDIX B. ASTHMA REVIEW QUESTIONNAIRE

Asthma Questionnaire V9.0 10052011

Please take a few minutes to complete the whole questionnaire, following the instructions at the head of each section.

In the last week:

	0	1	2	3	4	5	6	7	8	9	10+
How many times have you used your reliever inhaler?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thinking about the last 7 days
(please tick one box for each question):

	0	1	2	3	4	5	6	7
How many days has asthma interfered with your normal activities (eg sport, school, work/housework)?	☒	☐	☐	☐	☐	☐	☐	☐
How many nights have you been affected/woken by asthma symptoms (including cough)?	☒	☐	☐	☐	☐	☐	☐	☐
How many days have you experienced asthma symptoms?	☒	☒	☒	☐	☐	☐	☐	☐

In the past 4 weeks, did you:

	Yes	No	Unsure
Miss any work, school, or normal daily activity because of your asthma?	☐	☐	☐
Wake up at night because of asthma?	☐	☐	☐
Believe that your asthma was well controlled?	☐	☐	☐
In general, do you use an inhaler for quick relief from asthma symptoms?	☐	☐	☐

If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?

0	1 to 4 puffs	5 to 8 puffs	9 to 12 puffs	More than 12 puffs
☐	☐	☐	☐	☐

In the last 12 months:

	0	1	2	3	4	5	6	7	8	9	10+
How many times have you needed a course of steroid tablets for worsening asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you had off work/education because of asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

How many times have you been admitted to hospital with breathing or chest problems?

0	1	2	3	4	5+
☐	☐	☐	☐	☐	☐

How many times have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?

0	1	2	3	4	5+
☐	☐	☐	☐	☐	☐

About smoking:

Which best describes you? ☐ Never smoked ☐ Used to smoke, but don't now ☐ Still smoking

If you smoke or used to smoke, how many do you/did you smoke per day?

1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
☐	☐	☐	☐	☐	☐	☐	☐

If you smoke, or used to smoke, how many years have you smoked/did you smoke?

1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
☐	☐	☐	☐	☐	☐	☐	☐

Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?

Yes	No
☐	☐

About your nose:

Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?

No	Occasionally & little bother	Occasionally & quite a bother	Most days but little bother	Most days & a lot of bother
☐	☐	☐	☐	☐

Do any of the following upset your asthma? Tick all that apply.

Colds	Strenuous activity or exercise	Allergies eg cats, dogs, pollen	Cigarette smoke
☐	☐	☐	☐

Please complete other side

Do you have a preventer inhaler (usually brown, orange, red or purple)? ☐ Yes ☐ No, skip to Section B	
Which statement best describes how you take your regular Asthma treatment. Please tick only one box	
☐ I take it every day ☐ I take it some days but others I do not ☐ I used to take it, but now I do not ☐ I take it only when I have symptoms ☐ I never take it	
Please tell us how well you use your preventer inhaler:	
"I think my inhaler technique is very poor" ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 "I think my inhaler technique is excellent"	
About your preventer inhaler:	
Strongly disagree Strongly agree	
I need to take my inhaler(s) regularly for my asthma to be well controlled	☐ ☐ ☐ ☐ ☐
I find my inhaler(s) difficult to use	☐ ☐ ☐ ☐ ☐
Having to take regular asthma medication worries me	☐ ☐ ☐ ☐ ☐
I would prefer to take my asthma medications in a once a day dose	☐ ☐ ☐ ☐ ☐
Still about your preventer inhaler:	
Never Always	
I use it only when I feel breathless	☐ ☐ ☐ ☐ ☐
I avoid using it if I can	☐ ☐ ☐ ☐ ☐
I forget to take it	☐ ☐ ☐ ☐ ☐
I decide to miss a dose	☐ ☐ ☐ ☐ ☐
I choose to take it once a day	☐ ☐ ☐ ☐ ☐
When you use your preventer inhaler:	
Yes No	
Do you feel a sensation at the back of the throat?	☐ ☐
Do you sometimes feel a need to cough	☐ ☐
Do you feel your medication is deposited at the back of your throat?	☐ ☐
Do you experience any of these side effects from your preventer inhaler? Please tick yes or no for each one	
Yes No Continual sore mouth/throat ☐ ☐	Yes No Hoarse voice ☐ ☐
Oral Thrush ☐ ☐	Abnormal Weight Gain ☐ ☐
Bruising ☐ ☐	Cough ☐ ☐
Section B: Have you had the way you take your inhaler(s) checked in the past 12 months? ☐ Yes ☐ No	
Have you seen a specialist respiratory doctor or nurse outside the practice? ☐ In the last year ☐ More than a year ago ☐ Never	
If you have a peak flow meter, please tell us your reading today:	
for example: 4 2 0 ☐ I don't have a peak flow meter	
In the future, would you be willing to participate in further research? If yes, please return your cover letter with this questionnaire ☐ Yes ☐ No	
Practice Ref:	Survey Ref:

APPENDIX C. CRITICAL ERRORS ASSOCIATED WITH INHALATION DEVICES

Error	Without spacer	With spacer
Does not remove cap	x	x
Does not breathe out slowly to empty the lungs – should be at least 2 seconds	x	-
Does not shake before actuation	x	-
Failure to actuate/ Failure to actuate a dose into the spacer	x	x
Does not know how to correctly assemble the spacer	na	x
Does not shake before placing into spacer	na	x
Does not insert mouthpiece into spacer. Ensure a tight seal - there should be a click heard with the volumatic and with the aerochamber it should be inserted with tight seal and the inhaler should be vertical at 90 degrees	na	x
Device not held upright	x	x
Failure to inhale	x	x
Actuation not corresponding with inhalation; actuation before inhalation or too late after inhalation (more than 2 seconds)	x	
Once actuated, inhalation is not slow and deep – defined as lasting at least 3 seconds	x	x
Patient coughed during the inhalation	x	x

Statistical Analysis Plan

**A guideline approach to therapy step-down utilising Flutiform[®] change and
step-down**

Version 1.2

Study number: OR00213

EudraCT number: 2013-005365-39

Date: 21st January 2016

Version: 1.2

Prepared by: Liz Gardener, Lead Statistician, CRS-Ltd

TABLE OF CONTENTS

1.	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	4
2.	INTRODUCTION	6
2.1.	Preface.....	6
2.2.	Purpose of the analyses.....	6
3.	STUDY OBJECTIVES AND ENDPOINTS.....	7
3.1.	Study Objectives	7
3.2.	Endpoints	7
3.3.	Derived Variables	9
4.	STUDY METHODS.....	11
4.1.	General Study Design and Plan.....	11
4.2.	Non-inferiority criteria	12
4.3.	Inclusion-Exclusion Criteria and General Study Population	12
4.4.	Randomisation and Blinding	13
4.5.	Study Variables	14
4.5.1.	Description of efficacy variables	15
4.5.2.	Study days and study windows	15
5.	SAMPLE SIZE	16
6.	GENERAL CONSIDERATIONS	17
6.1.	Timing of Analyses	17
6.2.	Analysis Populations	17
6.2.1.	Non-inferiority Analysis Population.....	17
6.2.2.	Full Analysis Population	17
6.2.3.	Per Protocol Population.....	17
6.2.4.	Safety Population	17
6.3.	Covariate and Subgroups	18
6.4.	Missing Data	18
6.5.	Interim Analyses and Data Monitoring	18
6.6.	Multi-centre Studies	18
6.7.	Multiple Testing.....	18

7.	SUMMARY OF STUDY DATA	19
7.1.	Patient Disposition	19
7.2.	Protocol violations	19
7.3.	Demographic and Baseline Variables	20
7.4.	Concurrent Illnesses and Medical Conditions.....	20
7.5.	Concurrent Medications.....	20
7.6.	Treatment Compliance (no change in treatment)	20
7.7.	Visit Dates	20
8.	EFFICACY ANALYSES	21
8.1.	Primary Efficacy Analysis.....	21
8.2.	Secondary Efficacy Analyses	22
8.3.	Exploratory.....	23
9.	SAFETY ANALYSES	24
9.1.	Extent of exposure	24
9.2.	Adverse events.....	24
9.3.	Deaths and Severe Asthma Exacerbations	24
9.4.	Pregnancies	25
9.5.	Clinical Laboratory Evaluations	25
9.6.	Other Safety Measures	25
10.	REPORTING CONVENTIONS	26
11.	TECHNICAL DETAILS	27
12.	SUMMARY OF CHANGES TO PROTOCOL	28
13.	REFERENCES	29
14.	LISTING OF TABLES, FIGURES AND LISTINGS	30
14.1.	Summary Tables	30
14.2.	Individual Patient Listings.....	43

1. List of Abbreviations and Definitions of Terms

<i>Abbreviation</i>	<i>Term</i>
<i>ACA</i>	<i>Asthma Control Assessment</i>
<i>ACQ</i>	<i>Asthma Control Questionnaire</i>
<i>ACQ7</i>	<i>Asthma Control Questionnaire score calculated based on seven questions</i>
<i>BTS</i>	<i>British Thoracic Society</i>
<i>CDMS</i>	<i>Clinical Data Management System</i>
<i>COPD</i>	<i>Chronic Obstructive Pulmonary Disease</i>
<i>CSR</i>	<i>Clinical Study Report</i>
<i>eCRF</i>	<i>electronic case report form</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>FeNO</i>	<i>Fractional exhaled nitric oxide</i>
<i>FEV1</i>	<i>forced expiratory volume in 1 second</i>
<i>FEV%P</i>	<i>Forced expiratory volume in 1 second as a percentage of predicted</i>
<i>FVC</i>	<i>forced vital capacity</i>
<i>FVC%P</i>	<i>Forced vital capacity as a percentage of predicted</i>
<i>GCP</i>	<i>Good Clinical Practice</i>
<i>GINA</i>	<i>Global Initiative for Asthma</i>
<i>HCP</i>	<i>Healthcare Professional</i>
<i>ICH</i>	<i>International Conference on Harmonisation</i>
<i>ICS</i>	<i>inhaled corticosteroid</i>
<i>IPCRG</i>	<i>International Primary Care Respiratory Group</i>
<i>ITT</i>	<i>Intent-to-Treat</i>
<i>LABA</i>	<i>long-acting beta-agonist</i>
<i>MAR</i>	<i>Missing at random</i>
<i>MCAR</i>	<i>Missing completely at random</i>
<i>MDI</i>	<i>metered dose inhaler</i>
<i>MeDRA</i>	<i>Medical Dictionary for Regulatory Activities</i>
<i>MHRA</i>	<i>Medicines and Healthcare products Regulatory Agency</i>

<i>Mini-AQLQ</i>	<i>Mini Asthma Quality of Life Questionnaire</i>
<i>MNAR</i>	<i>Missing not at random</i>
<i>NHS</i>	<i>National Health Service</i>
<i>NICE</i>	<i>National Institute for Health and Care Excellence</i>
<i>PEF</i>	<i>peak expiratory flow rate</i>
<i>RCT</i>	<i>Randomised Controlled Trial</i>
<i>RiRL</i>	<i>Research in Real Life Ltd</i>
<i>SAP</i>	<i>Statistical Analysis Plan</i>
<i>SABA</i>	<i>short-acting beta-agonist</i>
<i>SIGN</i>	<i>Scottish Intercollegiate Guidelines Network</i>
<i>SOP</i>	<i>standard operating procedure</i>
<i>SPC</i>	<i>Summary of Product Characteristics</i>
<i>TA</i>	<i>Technology Appraisal</i>
<i>SUSAR</i>	<i>suspected unexpected serious adverse reaction</i>
<i>UK</i>	<i>United Kingdom</i>
<i>VAS</i>	<i>Visual Analog Scale</i>

2. Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for study OR00213, A guideline approach to therapy step-down utilising Flutiform® change and step-down.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials (ICH, February 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol OR00213 v2.3.
- Case report forms (CRFs) for Study OR00213.
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports

The reader of this SAP is encouraged to also read the clinical study protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the clinical study report (CSR).

2.1. Preface

Flutiform® is a combination inhaler launched for treatment of asthma in the UK in 2012. More studies are still needed to evaluate its effectiveness compared to alternative treatments in a real life setting. This is also the first study to compare the effectiveness of high dosage Flutiform® 250 to the efficacy of high dosage Seretide® 250 Evohaler®. Prescribing patients with Flutiform® instead of Seretide® Evohaler® would reduce the overall burden on NHS.

The British Guidelines on the Management of Asthma recommends that patients should be maintained at the lowest possible dosage of treatment and that reductions should be considered every three months. However, in daily clinical practice this does not always happen and more scientific data are needed to help establish optimal ways of reducing asthma therapy. Currently there are no published studies looking at safety of reducing Flutiform® dosage in patients with controlled asthma.

2.2. Purpose of the analyses

These analyses will assess the non-inferiority and safety of changing to high dose Flutiform® 250 from high dose Seretide® 250 Evohaler® and the non-inferiority and safety of stepping down to medium dose Flutiform® 125 from high dose Flutiform® 250 and will be included in the clinical study report.

3. Study Objectives and Endpoints

3.1. Study Objectives

This is a pragmatic, two-phase, non-inferiority study, comprising a change phase followed by a step-down phase:

Phase 1 (primary objective): Change from high dose Seretide[®] 250 Evohaler[®] to high dose Flutiform[®] 250

Establish whether comparable asthma control can be maintained when patients previously controlled with Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide[®] 250 Evohaler[®]) are changed to and remain on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250) compared to maintenance on high dose Fluticasone/Salmeterol (250/25 2 puffs twice daily as Seretide[®] 250 Evohaler[®]).

Phase 2 (primary objective): Step-down from high dose Flutiform[®] 250 to medium dose Flutiform[®] 125

Establish whether patients controlled on high dose Fluticasone/Formoterol (250/10 2 puffs twice daily as Flutiform[®] 250) can be successfully stepped down to medium dose Fluticasone/Formoterol (125/5 2 puffs twice daily as Flutiform[®] 125) for a 3 month period, where successful step-down is defined as remaining on the step-down dose and maintenance of asthma control (as assessed by Asthma Control Questionnaire).

3.2. Endpoints

Phase 1: Change from high dose Seretide[®] 250 Evohaler[®] to high dose Flutiform[®] 250

Primary Endpoint:

- Asthma Control Questionnaire (ACQ7) score (based on seven questions) at week 12

Secondary Endpoints measured at 12 weeks

Endpoints to be formally analysed:

- Lung function as measured by Forced Expiratory Volume in 1 second (FEV₁), FEV₁ as a percentage of predicted (FEV₁%P), Forced Vital Capacity (FVC) and FVC as percentage of predicted (FVC%P).
- GINA asthma control
- Visual Analog Scale (VAS) Score
- Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) Score (by domain and overall)
- Asthma control 'no exacerbations'
- Asthma control 'no change in therapy'
- Asthma control achieved (using GINA)

Other endpoints:

- Net proportion deteriorating by 0.5 on the ACQ7 score (Guyatt GH, 1998;)
- Adverse events in both cohorts

Phase 2: Step-down from high dose Flutiform® 250 to medium dose Flutiform® 125

Primary Endpoint:

- ACQ7 score at week 12

Secondary Endpoints at week 12 and week 4:

Endpoints to be formally analysed:

- Lung function (FEV₁, FEV₁% P, FVC, FVC %P)
- Nitric oxide (FeNO) - to assess airway inflammation
- GINA asthma control
- Vital Analog Scale (VAS) score
- Mini-AQLQ score (overall and by domain)
- Asthma control 'no exacerbations'
- Asthma control 'no change in therapy'
- Asthma control achieved (using GINA)

Other endpoints:

- Net proportion deteriorating by 0.5 on the ACQ7 score (Guyatt GH, 1998;)
- Adverse events in both cohorts

Exploratory Endpoints

- Blood eosinophil counts at Phase 2 baseline visit will be correlated with FeNO at Phase 2 baseline and will be tested as a predictive marker for response to step-down of treatment.
- 4-week Asthma Control Assessment, measured at week 4 in Phase 2 will be used to investigate the relationship between responses to GINA questions and the 4-Week Asthma Control Assessment.

3.3. Derived Variables

Visits will be referred to in this section using the following numbering system:

- 1 – Phase 1 Screening Visit
- 2 – Phase 1 Post-randomisation
- 3 – Phase 1 Visit 2 (week 12) / Early Termination
- 4 – Phase 2 Screening
- 5 – Phase 2 Visit 2 (week 4)
- 6 – Phase 2 Visit 3 (week 12)/Early Termination

Asthma Control Questionnaire: ACQ7

The primary endpoint ACQ7 score will be derived from the responses to the six ACQ questions (ACQ1-ACQ6, scored from 0 to 6, no impairment to maximum impairment) recorded on the eCRF and the FEV₁% predicted graded on a 7 point scale. The questions are equally weighted and ACQ7 score is the mean of the 7 questions, generating a value between 0 (totally controlled) and 6 (severely uncontrolled)

$$ACQ7_i : 0 = ' >95\%', 1 = '95\%-90\%', 2 = '89\%-80\%', 3 = '79\%-70\%', 4 = '69\%-60\%', 5 = '59\%-50\%', \\ 6 = '<50\%' \quad \text{for visit } i=2, 3, 5, 6$$

$$ACQscore_i = mean(ACQ1_i, ACQ7_i) \quad \text{for visit } i=2, 3, 5, 6$$

Mini-AQLQ

The secondary endpoint, Mini-AQLQ score, will be derived from responses to 15 Mini-AQLQ questions (MAQLQ1-MAQLQ15) recorded on the eCRF. There are 15-questions in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli). The overall score is the mean of the scores for the 15 questions generating a value between 0 'no impairment' and 6 'maximum impairment'. The Symptoms domain score is the mean of questions 1, 4, 6, 8 and 10. The Activities domain score is the mean of questions 12, 13, 14 and 15. The Emotions domain score is the mean of questions 3, 5 and 9. The Environment domain score is the mean of questions 2, 7 and 11.

$$MAQLQ_i = 7 - mean((MAQLQ1_i, MAQLQ15_i))$$

$$MAQLQ_symptom_i = 7 - mean(MAQLQ1_i, MAQLQ4_i, MAQLQ6_i, MAQLQ8_i, MAQLQ10_i)$$

$$MAQLQ_activities_i = 7 - mean(MAQLQ12_i, MAQLQ13_i, MAQLQ14_i, MAQLQ15_i)$$

$$MAQLQ_emotion_i = 7 - mean(MAQLQ3_i, MAQLQ5_i, MAQLQ9_i)$$

$$MAQLQ_environ_i = 7 - mean(MAQLQ2_i, MAQLQ7_i, MAQLQ11_i)$$

for visit $i=2, 3, 5, 6$

4-week Asthma Control Assessment (ACA)

The 4-week ACA is derived from responses to four questions and spirometry output and categorises Asthma Control within the last four weeks into 0='Controlled', 1='Partly Controlled' or 2='Uncontrolled'.

ACA_i : 0 IF $ACA1_i$ ='Twice or less per week' AND $ACA2_i$ ='None' AND $ACA3_i$ ='None' AND $ACA4_i$ ='Twice or less per week' AND $FEV\%P_i \geq 80\%$
 1 IF ONE OR TWO OF ($ACA1_i$ ='More than twice per week' OR ' $ACA2_i$ ='Any' OR $ACA3_i$ ='Any' OR $ACA4_i$ ='More than twice per week' OR $FEV\%P_i < 80\%$)
 2 IF THREE OR MORE OF ($ACA1_i$ ='More than twice per week' OR ' $ACA2_i$ ='Any' OR $ACA3_i$ ='Any' OR $ACA4_i$ ='More than twice per week' OR $FEV\%P_i < 80\%$)
for visit $i=4, 5, 6$

Body Mass Index (BMI)

$$BMI = \frac{\text{weight}}{\text{height}^2} \text{ (kg/m}^2\text{)}$$

Adherence

$$\text{adhere}_3 = \frac{\sum_{j=1}^3 \text{device_j}_2 - \text{device_j}_3}{4(\text{date}_3 - \text{date}_1)} \times 100 \text{ (\%)} \\
\text{adhere}_5 = \frac{\sum_{j=1}^3 \text{device_j}_4 - \text{device_j}_5}{4(\text{date}_5 - \text{date}_4)} \times 100 \text{ (\%)} \\
\text{adhere}_6 = \frac{\sum_{j=1}^3 \text{device_j}_5 - \text{device_j}_6}{4(\text{date}_6 - \text{date}_5)} \times 100 \text{ (\%)}$$

*where adhere_i is adherence at visit i
 device_j_i is dose counter value from device j at visit i
 and date_i is date of visit i*

Change in ACQ

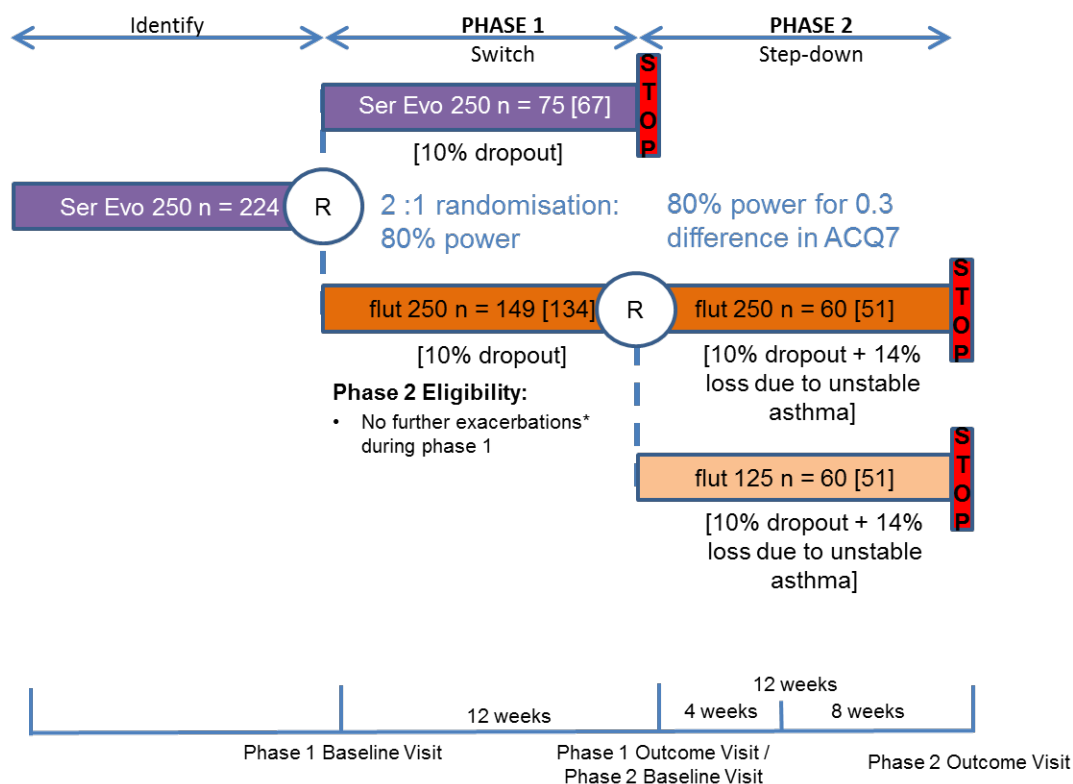
$ACQ7_chg_i$: 'Improvement' if $(ACQscore_i - ACQscore_{i-1}) \leq -0.5$
 'Maintenance' if $-0.5 < (ACQscore_i - ACQscore_{i-1}) < 0.5$
 'Deterioration' if $(ACQscore_i - ACQscore_{i-1}) \geq 0.5$

for visit $i=3, 6$

4. Study Methods

4.1. General Study Design and Plan

This will be a two-phase, multi-centre, pragmatic, open-label, randomised controlled trial (RCT) set in the UK. It will be composed of a change phase (Phase 1) followed by a step-down phase (Phase 2) (Figure 1). Each phase is 12 weeks in length. Phase 1 will be a parallel group non-inferiority study comparing real-life effectiveness of Flutiform[®] 250 versus Seretide[®] 250 Evohaler[®] in patients with asthma. Phase 2 will be a parallel group, non-inferiority study comparing effectiveness of Flutiform[®] 250 to Flutiform[®] 125 in patients whose asthma as stable in Phase 1.



Endpoints will be measured at each visit. In addition, there is a 4 week visit at phase 2 to measure FeNO levels, spirometry and asthma control/quality of life.

Figure 1. Schematic overview of the study design.

4.2. Non-inferiority criteria

Both phases are designed to test for non-inferiority with the non inferiority bound being set at 0.3 for difference in ACQ7. Therefore in phase 1 the estimated mean difference in ACQ7 (Flutiform[®] 250 - Seretide[®] 250 Evohaler) and its one sided 95% CI must lie below 0.3 for non-inferiority to be concluded. In phase 2 the estimated mean difference in ACQ7 (Flutiform[®] 125 - Flutiform[®] 250) and its one-sided 95% CI must lie below 0.3 for non-inferiority to be concluded.

4.3. Inclusion-Exclusion Criteria and General Study Population

Phase 1

Patients will be required to meet the following eligibility criteria:

Inclusion criteria:

- Age 18-75
- Able and willing to provide written informed consent and to comply with the study protocol.
- Current diagnosis of asthma (as evidenced by appropriate diagnostic code)
- Received Seretide[®] 250 Evohaler[®] 2 puffs twice daily for the last 6 months
- No asthma exacerbation* in last 3 months
- ≤2 exacerbations* in last 12 months
- No errors in device use after training (during baseline visit)
- Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after discontinuation of study drug. Acceptable methods of contraception include intrauterine device (IUD) known to have a failure rate of less than 1% per year, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, and partner vasectomy.
* Exacerbation defined as acute course of oral steroids, emergency room attendance and/or hospitalisation for asthma

The inclusion criteria requiring patients to be receiving Seretide[®] 250 Evohaler[®] and to have controlled asthma was set for the following reasons:

- No run-in period will be required as patients will already be receiving the control device.

- It is good practice to review current medication and potentially change to a different medication, as patients have had controlled asthma for at least 3 months (demonstrated by absence of exacerbations and controlled asthma using GINA asthma control definitions).

Exclusion criteria

- Other chronic respiratory disease than asthma (e.g. Chronic Obstructive Pulmonary Disease (COPD))
- Uncontrolled asthma (GINA criteria)
- The patient has used a clinical trial investigational drug within the last year before the screening visit
- Hypersensitivity to Flutiform[®], its component Formoterol or its excipients
- Pregnant subjects

Phase 2

Patients completing Phase 1 will be evaluated for eligibility to enter Phase 2 according to the following eligibility criteria.

Inclusion criteria:

- Randomised to Flutiform[®] 250 in Phase 1
- At completion of Phase 1 had stable asthma with no exacerbations in the 12 weeks of the Phase 1 study (exacerbation defined as acute course of oral steroids, emergency room attendance and/or hospitalisation for asthma)

4.4. Randomisation and Blinding

Both phases were open-label studies without blinding, and used a centralised randomisation programme to randomise patients at a ratio of 2:1 to receive either Flutiform[®] 250 treatment or Seretide[®] 250 Evohaler[®] treatment, in phase 1 and at a ratio of 1:1 to receive either Flutiform[®] 250 treatment or Flutiform[®] 125 treatment in phase 2. Blocks of size 6 were used for Phase 1 and blocks of size 4 were used for stage 2 were used. Both randomisations were stratified by:

- Whether patients had 1 or more exacerbations in the 12 months prior to Phase 1 baseline visit
- Practice ID

4.5. Study Variables

Table 1: Study Procedures and Assessments

Procedures and assessments	Phase 1			Phase 2		
	Baseline Phase 1		Visit 2 / Baseline Phase 2	Visit 2	Visit 3	
	Visit 1a Screening	Visit 1b Post-randomisation	Outcome Visit week 12/ Early termination	Screening Week 12	Week 16	Week 24 /Early termination
Informed consent (date)	X			X		
Demographics ^{*j}	X					
Screening Questions ^{*ji}	X			X		
Childbearing Potential ^{*jii}	X					
Pregnancy Test (+ve/-ve)	X					
Spirometry Exam ^{*jiv}	X		X		X	X
GINA ^{*jv}	X		X		X	X
Inhaler technique ^{*jvi}	X					
Eligibility(Y/N)	X			X		
Randomisation (Seretide/Flutiform)	X			X		
MiniAQLQ ^{*jvii}		X	X		X	X
VAS ^{*jviii}		X	X		X	X
ACQ7 ^{*jix}		X	X		X	X
Continuing Phase 2 (Y/N)				X		
FENO ^{*jx}				X	X	X
ACA ^{*jxi}				X	X	X
Eosinophils ^{*jxii}				X		
General Medical history ^{*jxiii}	X					
Concomitant medication history ^{*jxiv}	X					
Adverse event inquiry ^{*jxv}	X		X		X	X
Devise accountability ^{*jxvi}		X	X	X	X	X
Unscheduled Visits ^{*jxvii}			X		X	X
Protocol Violations ^{*jxviii}			X		X	X
Data Entry Completion ^{*jxix}			X			X

*See corresponding numbered section heading in Appendix A for details of data collected.

4.5.1. Description of efficacy variables

- The overall mean from the *Asthma Control Questionnaire* (ACQ7) is measured on a 0 to 6 scale (42 levels), with 0=controlled and 6=severely uncontrolled see section 3.3 for derivation.
- *Forced Expiratory Volume in 1 Second* (FEV₁) (L): Allowed range 0.8L to 6.0L
- *FEV₁ % P*(%): Allowed range 0%-140%
- *Forced Vital Capacity* (FVC) (L): Allowed range 1.0L to 7.0L
- *FVC%P* (%): Allowed range 0%-140%
- *Global Initiative for Asthma Criteria for Asthma Control* (GINA) is measured on a 0 to 2 scale, with 0='Controlled', 1='Partly Controlled' and 2='Uncontrolled'
- The overall mean from the *Mini Asthma Quality of Life Questionnaire* (Mini –AQLQ) is measured on a 0 to 6 scale (90 levels), with 0='no impairment' and 6='maximum impairment' see section 3.3 for derivation.
- The domain means (*symptoms, activities, emotion, environment*) from the *Mini Asthma Quality of Life Questionnaire* (Mini –AQLQ) are measured on a 0 to 6 scale (90 levels), with 0='no impairment' and 6='maximum impairment' see section 3.3 for derivation.
- *Perception of Asthma symptoms* (VAS) is measured on a 0-100 visual analogue scale for how bothersome they find their asthma.
- *Exacerbation whilst in study*: 1='yes', 0='no'
- *Study treatment discontinued*: 1='yes', 0='no'
- *GINA control*: 1='yes', 0='no'
- *Fractional Exhaled Nitric Oxide* (FeNO) (ppb): continuous number
- *Eosinophil* (count x 10⁹/L): allowed range 0 to 20
- *4-week Asthma Control Assessment* (ACA) is measured on a 0 to 2 scale, with 0='Controlled', 1='Partly Controlled' and 2='Uncontrolled'

4.5.2. Study days and study windows

Study days will be numbered relative to randomisation date. Assessments collected from 3 days after or 7 days before will be classed as within the study window. For phase 1, a visit within 77 to 87 days post-randomisation will be identified as the 12-week visit. For phase 2, assessments collected from 21 to 31 days post second-randomisation will be identified as the phase 2 4-week visit, and 77 to 87 days post second-randomisation as the phase 2 12-week visit. Measurements obtained outside the scheduled assessment time will be treated as a protocol violation. If there are multiple assessments that occur within the same assessment window, the one nearest to the exact visit date will be chosen, with preference for the assessment after the exact visit date.

5. Sample Size

Phase 1

When the sample size is 201 (67 Seretide[®] 250 Evohaler[®]: 134 Flutiform[®] 250), a two group t-test of equivalence in means, with a 0.050 one-sided significance level will have 80% power to reject the null hypothesis that the mean ACQ7 scores are not equivalent (based on an acceptable maximum difference of -0.3 in mean ACQ7 score, i.e. lower confidence limit of -0.3 and a common standard deviation of 0.8) when the expected difference in mean ACQ7 score is 0.0.

Assuming a drop-out rate of about 10%, approximately 224 patients (75 Seretide[®]: 149 Flutiform[®]) will be randomised into this study to ensure that a minimum of 201 patients complete all visits and critical assessments. Any patient who withdraws after randomisation will not be replaced.

Phase 2

Based on the expected sample size available following Phase 1, a sample size of 102 (51 Flutiform[®] 250: 51 Flutiform[®] 125), using a two group t-test of equivalence in means, with a 0.050 one-sided significance level will have 59% power to reject the null hypothesis that the mean ACQ7 scores are not equivalent (based on an acceptable maximum difference of -0.3 in mean ACQ7 score, i.e. lower confidence limit of -0.3 and a common standard deviation of 0.8) when the expected difference in mean ACQ7 score is 0.0.

6. General Considerations

6.1. Timing of Analyses

Analyses will be performed on SAS data sets derived from the electronic CRF data. Database lock will occur once the cleaning and approval requirements documented in RIRL SOP 12 have been met and after finalisation and approval of this SAP document.

6.2. Analysis Populations

6.2.1. Non-inferiority Analysis Population

This population will include:

All patients who were randomised, remained on randomised treatment for at least 8 weeks, and did not change treatment at any stage during the follow-up period, and is the population that the primary non-inferiority analyses will be based on, patients will be summarised according to the treatment they were randomised to.

6.2.2. Full Analysis Population

This population will include:

- All patients who were randomised

and is the population that the background and secondary efficacy analyses will be based on, patients will be summarised according to the treatment they were randomised to.

6.2.3. Per Protocol Population

This population will include:

- All randomised patients who completed the phase without any protocol violation

and will be used for a sensitivity analysis for the efficacy analyses.

6.2.4. Safety Population

This will include all randomised patients who received the study devices. Summaries will be given according to which treatment the patient received, regardless of which they were assigned to. This population will be the primary analysis set for the safety analyses.

6.3. Covariate and Subgroups

All analyses will be adjusted for the randomisation stratification variables; experiencing an exacerbation within 12 months prior to starting study and Practice id. For the primary analysis baseline ACQ will also be taken into account.

It is not intended to carry out any subgroup analyses.

6.4. Missing Data

It is intended to carry out the efficacy analyses according to a pragmatic approach, if data for the final visit of the phase are unavailable, making this not possible, the analyses will be carried out in line with the approach of (White IR, 2011) where the main analysis will be conducted under the most plausible assumption about the missing data, followed up by sensitivity analyses to explore the effect of departures from the assumptions made in the main analysis, with all randomised patients being accounted for in at least the sensitivity analyses. The aim of this approach is to check that inferences about the intervention are robust to different assumptions about the reason for missing data, or patient withdrawal. If it is not feasible to assume that data are missing completely at random (MCAR) it is proposed that, to start off with, the initial analysis assumes that data are MCAR conditional on treatment and baseline (ie data are missing at random (MAR)) and an estimation of treatment effect obtained from a likelihood based model (White IR C. J., 2012) fitted using all observed data. Other baseline variables which could affect occurrence of missing data such as age, sex and BMI would also be considered. Sensitivity analyses would then be performed which assume that missing data are related to an unobserved variable (ie data are missing not at random (MNAR)) using selection models (Carpenter JR, 2008).

6.5. Interim Analyses and Data Monitoring

There will not be any interim analyses for this study.

6.6. Multi-centre Studies

Allocation was stratified by GP practice so Practice ID will be included in all analyses. It is expected that there will be some centres with few patients therefore practice will be fitted as a random effect (Kahan, 2013) (Kahan B. , 2014).

The consistency of treatment effects among different investigational centres will be evaluated by a separate model with treatment, centre and a treatment by centre interaction in the model. If there is evidence of an interaction ($p \leq 0.1$), a descriptive summary of treatment differences for each investigational centre will be used to identify the center (or centers) for which the treatment effects are consistent with the remaining centers. This will be an exploratory analysis, which will aid with the interpretation of results, and the treatment effect will still be reported from the main effects.

6.7. Multiple Testing

Reponse to the Asthma Control Questionnaire is the only primary endpoint for both phases and conclusions will be based on the confidence interval of the treatment effect; therefore there is no plan to adjust for multiple testing.

7. Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. All summary tables will be structured with a column for each treatment in the order (Seretide® 250 Evohaler®, Flutiform® 250, all patients for phase 1 and Flutiform® 250, Flutiform® 125, all patients in phase 2) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject.

7.1. Patient Disposition

Phase 1

Data from all patients screened for phase 1, patients screened for phase 1 but not enrolled/randomised (and reason for non-randomisation: *'hypersensitive to drug', '>2 asthma exacerbations in last 12 month', '>0 asthma exacerbations in last 3 months', 'uncontrolled asthma from GINA assessment', 'of childbearing potential but not willing to use accepted method of contraception', 'pregnant', 'errors in used of device after training' or 'other'*), patients who are randomised to phase 1, patients randomised but who do not complete phase 1 (and reason for not completing: *'Lost to follow-up', 'Consent Withdrawn', 'Adverse Event', 'Protocol Violation' or 'Other'*), and patients who complete phase 1 will be summarised using descriptive statistics in accordance with section 7. Patient listings of screening and exclusion/inclusion criteria will be listed in accordance with section 7.

Phase 2

Data from all patients eligible for phase 2, patients screened but not randomised (and reason not randomised: *'not randomised to Flutiform', 'experienced exacerbations in phase 1', 'no consent' or 'other'*), patients who are randomised to phase 2, patients randomised but who do not complete phase 2 (and reason for not completing: *'Lost to follow-up', 'Consent Withdrawn', 'Adverse Event', 'Protocol Violation' or 'Other'*) and patients who complete phase 2 will be summarised using descriptive statistics in accordance with section 7. Patient listings of screening and exclusion/inclusion criteria will be presented in accordance with section 7.

7.2. Protocol violations

Data from all patients who had a protocol violation (and type of violation: *'Inclusion Criteria', 'Exclusion criteria', 'Randomisation criteria', 'Primary objective variable', 'GCP guidelines', 'Non-compliance to study medication', 'Excluded concomitant medication/treatment', 'Not within study window' or 'Other'*) will be summarised separately for phase 1 and phase 2 using descriptive statistics in accordance with section 7. Protocol violations will exclude patients from the per-protocol population. Protocol violations will not affect patients being part of the non-inferiority population (provided they haven't changed treatment), full analysis population or safety population (provided they have received the study device). Patient listings will be presented in accordance with section 7.

7.3. Demographic and Baseline Variables

Age, sex, race, height, weight, BMI, occupation, average units of alcohol consumed per week, smoking status, number of exacerbations in the last 12 months and baseline ACQ7, FEV₁, FEV₁%, FVC FVC%P, GINA, Mini-AQLQ (overall and domains) and VAS will be summarised for the full-analysis population using descriptive statistics in accordance with section 7 for phase 1. Patient listings will be presented in accordance with section 7.

Age, sex, race, height, weight, BMI, occupation, average units of alcohol consumed per week, smoking status, number of exacerbations in the last 12 months and baseline ACQ7, FEV₁, FEV₁%, FVC FVC%P, GINA, Mini-AQLQ (overall and domains), VAS and FENO will be summarised for the full-analysis population using descriptive statistics in accordance with section 7 for phase 2. Patient listings will be presented in accordance with section 7.

7.4. Concurrent Illnesses and Medical Conditions

Concurrent illnesses and medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarised for the full-analysis population using descriptive statistics in accordance with section 7 for phase 1 and phase 2. Patient listings will be presented in accordance with section 7.

7.5. Concurrent Medications

Only medications currently being taken were recorded and will be coded manually, and summarised by therapeutic class and preferred term for the full-analysis population using descriptive statistics in accordance with section 7 for phase 1 and phase 2. Patients will be counted only once in each therapeutic class category, and only once in each preferred term category. Patient listings will be presented in accordance with section 7.

7.6. Treatment Compliance (no change in treatment)

A patient will be determined 'treatment compliant' if according to the device accountability CRF and last visit date they were taking the allocated study medication for at least 8 weeks and until the final visit. Treatment compliance will be summarised for the full-analysis population using descriptive statistics in accordance with section 7.

7.7. Visit Dates

Patient listings of the dates of each visit (including unscheduled visits and reason) will be presented in accordance with section 7.

8. Efficacy Analyses

All summary tables will be structured with a column for each treatment in the order (Seretide® 250 Evohaler®, Flutiform® 250, all patients for phase 1 and Flutiform® 250, Flutiform® 125, all patients for phase 2) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. Results will be presented for each visit where measured. N, mean, standard deviation, median, minimum and maximum will summarise continuous efficacy variables where appropriate, whereas number and percent will summarise categorical efficacy variables.

All analyses of the continuous efficacy variables will be performed as mixed linear models to estimate the treatment effect adjusted for study centre and number of exacerbations in 12 months before Phase 1. Practice ID will be fitted as a random effect. Experiment group non-inferiority will be assessed using one-sided, 95% confidence interval for the treatment effect compared against the pre-defined non-inferiority boundaries. The mean difference in primary outcome measure and its one sided 95% CI will be presented alongside the non-inferiority boundary; for Phase 1 (Flutiform - Seretide) and for Phase 2 (Flutiform 125 – Flutiform 150). For secondary outcomes where non-inferiority is not being assessed the mean difference in outcome measure (Flutiform - Seretide) and its 2-sided 95% confidence intervals will be presented along with the p-value.

All assumptions for models will be assessed by viewing plots of the residual values. If assumptions behind the model cannot reasonably be made, models will be fitted to transformed data. Failing this endpoints will be dichotomised and analysed as a categorical variable.

All analyses of categorical efficacy measures will be performed using logistic regression with treatment group and adjustment for study centre and baseline number of exacerbations.

The non-inferiority analysis population will be used as the analysis set for the primary analyses. The full-analysis population will be used as the analysis set for all secondary efficacy analyses. The Phase 1 and 2 primary analyses will also be analysed using the per-protocol population. Summaries will be presented by treatment group as randomised unless specified otherwise.

An example of the SAS code to examine the treatment effect is given in appendix B, this is subject to change once the exact method for handling missing data has been determined.

In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject.

8.1. Primary Efficacy Analysis

Phase 1

The hypothesis that 12 weeks following allocation, asthma control is non-inferior when allocated Flutiform® 250 compared to Seretide® 250 Evohaler® by less than 0.3 points on the 7-item Asthma Control Questionnaire score (ACQ7), will be examined using confidence intervals in accordance with section 8 with additional adjustment for baseline ACQ. Patient listings will be presented in accordance with section 8.

Phase 2

The hypothesis that 12 weeks following allocation, asthma control is non-inferior when allocated Flutiform® 125 compared to Flutiform® 250 by less than 0.3 points on the 7-item Asthma Control Questionnaire (ACQ7), will be examined using confidence intervals in accordance with section 8 with

additional adjustment for baseline ACQ. Patient listings will be presented in accordance with section 8.

8.2. Secondary Efficacy Analyses

For Phase 1

- a) Sensitivity analyses will be carried out to check inferences about the intervention are robust to different assumptions about the reason for missing data or patient withdrawal.
- b) The primary analysis will also be repeated on the per-protocol population.
- c) The null hypothesis, that 12 weeks following randomisation, there is no difference in outcome for patients allocated Flutiform[®] 250 compared to Seretide[®] 250 Evohaler[®], will be examined in accordance with section 8 for the following secondary outcome measures:
 - i. Lung function – FEV₁
 - ii. Lung function – FEV₁%P
 - iii. Lung function – FVC
 - iv. Lung function – FVC%P
 - v. Mini-AQLQ
 - vi. ‘Perception of Asthma Symptoms’ VAS
 - vii. Mini-AQLQ ‘symptoms’
 - viii. Mini-AQLQ ‘activities’
 - ix. Mini-AQLQ ‘emotions’
 - x. Mini-AQLQ ‘environment’
 - xi. GINA
 - xii. Asthma control – ‘no exacerbations’
 - xiii. Asthma control – ‘no change in treatment’
 - xiv. Asthma control – ‘GINA criteria’
- d) The proportion of patients showing improvement, maintenance or deterioration on the ACQ (using 0.5 as the cut-off) will be presented in accordance with section 8 along with the derived Number-needed-to-treat. (Guyatt GH, 1998;).

Patient listings will be presented in accordance with section 8.

For Phase 2

- a) Sensitivity analyses will be carried out to check inferences about the intervention are robust to different assumptions about the reason for missing data or patient withdrawal.
- b) The primary analysis will also be repeated on the per-protocol population.

- c) The null hypothesis, that at 4 and 12 weeks following randomisation, there is no difference in outcome for patients allocated Flutiform[®] 125 compared to Flutiform[®] 250, will be examined in accordance with section 8 for the following outcome measures:
- i. Lung function – FEV₁
 - ii. Lung function – FEV₁%P
 - iii. Lung function – FVC
 - iv. Lung function – FVC%P
 - v. Mini-AQLQ
 - vi. ‘Perception of Asthma Symptoms’ VAS
 - vii. FeNO
 - viii. Mini-AQLQ – ‘symptoms’
 - ix. Mini-AQLQ – ‘activities’
 - x. Mini-AQLQ – ‘emotions’
 - xi. Mini-AQLQ – ‘environment’
 - xii. GINA
 - xiii. Asthma control – ‘no exacerbations’
 - xiv. Asthma control – ‘no change in treatment’
 - xv. Asthma control – ‘GINA criteria’
- d) The proportion of patients showing improvement, maintenance or deterioration on the ACQ (using 0.5 as the cut-off) will be presented in accordance with section 8 along with the derived Number-needed-to-treat. (Guyatt GH, 1998;).

Patient listings will be presented in accordance with section 8.

8.3. Exploratory

For Phase 2

Relationship between eosinophil levels and FeNO and measures of asthma control will be examined using correlation co-efficients. The correlation co-efficients will be presented in a matrix.

The relationship between between 4-week ACA and GINA and other measures of asthma control will be examined using correlation co-efficients. The correlation co-efficients will be presented in a matrix.

9. Safety Analyses

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. All summary tables will be structured with a column for each treatment in the order (Seretide® 250 Evohaler®, Flutiform® 250, all patients for phase 1 and Flutiform® 250, Flutiform® 125, all patients in phase 2) and will be annotated with the total population size relevant to that table/treatment, including any missing observations. When calculating the incidence of adverse events each subject will only be counted once and any repetitions will be ignored, the denominator will be the total population size.

In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject.

The safety analysis population will be used, and summaries will be presented by treatment group as received regardless of which they were randomised to.

9.1. Extent of exposure

Adherence (see section 3.3) will be summarised for the full-analysis population using descriptive statistics in accordance with section 9. Patient listings of counter values and dispensed date for the three devices at each visit will be presented by site and treatment group for phase 1 and phase 2.

9.2. Adverse events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for i) all adverse events, ii) severity of adverse event, iii) adverse events determined by the investigator to be related to study treatment (see Protocol Section 10.2) (defined as related or with missing relationship), iv) serious adverse events, v) non-serious adverse events and vi) adverse events causing withdrawal from the study.

The incidence of adverse events will be summarised using descriptive statistics by system organ class/body system and preferred term. Patients are counted only once in each system organ class/body system category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non serious adverse events. The number of patients experiencing an adverse event, and number of adverse events per patient will be summarised. The summary statistics will be produced in accordance with section 9.

Patient listings presenting adverse events and severity with indicators for treatment related adverse events and adverse events leading to discontinuation will be produced in accordance with section 9.

9.3. Deaths and Severe Asthma Exacerbations

Listings will be produced according to section 9.

9.4. Pregnancies

Pregnancy tests were only performed at baseline, women were required to use adequate contraception throughout the rest of the trial. Patient listing of baseline pregnancy test results will be presented for Phase 1 and Phase 2.

9.5. Clinical Laboratory Evaluations

Summary statistics for hematology eosinophil count will be presented at Phase 2 Visit 1. The summary statistics will be produced in accordance with section 9. Patient listings will be produced in accordance with section 9.

9.6. Other Safety Measures

No other safety measures were carried out.

10. Reporting Conventions

P-values greater than or equal to 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Percentages will be reported to one decimal place. Estimated parameters, not on the same scale as raw observations (e.g. regression co-efficients) will be reported to 3 significant figures.

11. Technical Details

This statistical analysis plan was based on Study Number OR00213 protocol v.2.3 approved on 17th November 2014. All data listings, summaries and statistical analyses will be carried out using, *SAS version 9.3 (SAS Institute, Cary, NC)*.

A second review statistician will independently reproduce the primary analyses in 8.1, 8.2 and the sensitivity analyses.

12. Summary of Changes to Protocol

Change in Inferiority Boundary

The inferiority boundary for phase 2 has changed from the protocol, in the protocol the boundary for difference in ACQ7 Phase 2 was 0.4 points, to be consistent with the first phase this had been changed to 0.3 points.

Change in Approach for Primary Analyses

Rather than follow an intention-to-treat approach, the primary, non-inferiority analyses will follow a pragmatic approach, including all protocol violators, but excluding those that change treatment. This is to avoid non-inferiority being found as a result of patients having changed back to control rather than the test device truly being non-inferior.

Secondary Outcomes

FEV₁%P, FVC%P and the domain summary for Mini-AQLQ have been added to the secondary outcomes that will be analysed. A descriptive summary for net proportion deteriorating by 0.5 will now be given.

Adjustment for additional covariates

Based on the distribution of the ACQ7 in a previous study ([http://clinicaltrials.gov.ref/NCT02062463](http://clinicaltrials.gov/ref/NCT02062463)) it is expected that it will have a skewed distribution. When baseline ACQ7 is adjusted for, the residuals follow a more normally distributed pattern, it is therefore proposed that baseline ACQ7 is included in the primary analysis models.

Recent research has shown that when randomisation is stratified, stratification factors should be adjusted for in the model in order to preserve power (Kahan B. , 2014). It is therefore proposed that practice id and whether the patient had at least one exacerbation in the 12 months before Phase 1 Visit are included in all models, with practice id fitted as a random effect.

Definite pre-specified covariates could not be identified prior to database lock, as such no other adjusted analyses will be performed.

Missing data

The approach to handling missing data has changed. Both last observation carried forward and imputing marginal means have strong limitations including, importantly for this study, that they underestimate the variability (White IR C. J., 2012). Given that this is primarily a non-inferiority trial, it is felt that the proposed methods would give more robust estimates of the treatment effect and it's variability, should there be missing outcome data which cannot be considered to be missing completely at random.

13. References

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- Guyatt GH, J. E. (1998;). Interpreting treatment effects in randomised trials. . *BMJ : British Medical Journal*. , 316(7132):690-693.
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- Kahan, B. (2014). Accounting for centre-effects in multicentre trials with a binary outcome – when, why, and how? <http://www.biomedcentral.com/1471-2288/14/20>.
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- White IR, H. N. (2011). Strategy for intention to treat analysis in randomised trials with missing outcome data. . *BMJ* , 342:d40.

14. Listing of Tables, Figures and Listings

14.1. Summary Tables

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 1: Patient Disposition	1.1	NA	Disposition	Visit 1 - Visit 3	Treatment	Count	NA	
Phase 2: Patient Disposition	1.2	NA	Disposition	Visit 4 - Visit 6	Treatment	Count	NA	
Phase 1: Protocol Violations	2.1	Full Analysis Phase 1	Violations	Visit 1 - Visit 3	Treatment	Count	NA	
Phase 2: Protocol Violations	2.2	Full Analysis Phase 2	Violations	Visit 4 - Visit 6	Treatment	Count	NA	
Phase 1: Demographics	3.1	Full Analysis Phase 1	Age	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Sex	Visit 1	Treatment	p% (x/n)	NA	
			Race	Visit 1	Treatment	p% (x/n)	NA	
			Height	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Weight	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			BMI	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Occupation	Visit 1	Treatment	p% (x/n)	NA	
			Average Weekly Alcohol Consumption	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Smoking status	Visit 1	Treatment	p% (x/n)	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
			Exacerbations in previous 12 months	Visit 1	Treatment	p% (x/n)	NA	
Phase 2: Demographics	3.2	Full Analysis Phase 2	Age	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Sex	Visit 1	Treatment	p% (x/n)	NA	
			Race	Visit 1	Treatment	p% (x/n)	NA	
			Height	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Weight	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			BMI	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Occupation	Visit 1	Treatment	p% (x/n)	NA	
			Average Weekly Alcohol Consumption	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Smoking status	Visit 1	Treatment	p% (x/n)	NA	
			Exacerbations in previous 12 months	Visit 1	Treatment	p% (x/n)	NA	
Phase 1: Baseline Characteristics	4.1	Full analysis Phase 1	ACQ7	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			ACQ6	Visit 1	Treatment	n, mean, sd, median, max, min	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
			FEV1	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FEV1%P	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FVC	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FVC%P	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			GINA	Visit 1	Treatment	P% (x/n)	NA	
			Mini-AQLQ	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Symptoms	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Activities	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Emotions	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Environment	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			VAS	Visit 1	Treatment	n, mean, sd, median, max, min	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 2: Baseline Characteristics	4.2	Full analysis Phase 1	ACQ7	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FEV1	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FEV1%P	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FVC	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FVC%P	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			GINA	Visit 1	Treatment	P% (x/n)	NA	
			Mini-AQLQ	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Symptoms	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Activities	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Emotions	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			Mini-AQLQ Environment	Visit 1	Treatment	n, mean, sd, median, max, min	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
			VAS	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
			FENO	Visit 1	Treatment	n, mean, sd, median, max, min	NA	
Phase 1: Concurrent Illnesses and Medical Conditions	5.1	Full analysis Phase 1	Medical Conditions	Visit 1	Treatment	p% (x/n)	NA	
Phase 2: Concurrent Illnesses and Medical Conditions	5.2	Full analysis Phase 2	Medical Conditions	Visit 1	Treatment	p% (x/n)	NA	
Phase 1: Concurrent Medication	6.1	Full analysis Phase 1	Medication * Dose?	Visit 1	Treatment	p% (x/n)	NA	
Phase 2: Concurrent Medication	6.2	Full analysis Phase 2	Medication * Dose?	Visit 1	Treatment	p% (x/n)	NA	
Phase 1: Treatment Compliance	7.1	Full analysis Phase 1	Compliance	Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Treatment Compliance	7.2	Full analysis Phase 2	Compliance	Visit 5 & Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Primary Analysis	8.1	Non-inferiority Phase 1	ACQ7	Visit 3	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Mixed model, estimated effect, (1 sided 95% ci & inferiority bound)	
			Net proportion deteriorating by 0.5	Visit 3	Treatment	p% (x/n) NNT	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 2: Primary Analysis	8.2	Non-inferiority Phase 2	ACQ7	Visit 6	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Mixed model, estimated effect, (1 sided 95% ci & inferiority bound)	
			Net proportion deteriorating by 0.5	Visit 6	Treatment	p% (x/n) NNT	NA	
Phase 1: Sensitivity analyses for Primary analysis	9.1	Non-inferiority Phase 1	ACQ7MISS	Visit 3	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Likelihood/Selection model, estimated effect, (1 sided 95% ci & inferiority bound)	
Phase 2: Sensitivity analyses for Primary analysis	9.2	Non-inferiority Phase 2	ACQ7MISS	Visit 6	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Likelihood/Selection model, estimated effect, (1 sided 95% ci & inferiority bound)	
Phase 1: Per-protocol Primary analysis	10.1	Per-protocol Phase 1	ACQ7	Visit 3	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 2: Per-protocol Primary analysis	10.2	Per-protocol Phase 2	ACQ7	Visit 6	Treatment, baseline ACQ7, practice id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 1: Secondary Analyses – lung function	11.1.1	Full analysis Phase 1	FEV1	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FEV1%P	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC%P	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 1: Secondary Analyses - questionnaires	11.1.2	Full analysis Phase 1	Overall Mini-AQLQ	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			VAS	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 1: Secondary Analyses – Mini-AQLQ by domains	11.1.3	Full analysis Phase 1	Mini-AQLQ - symptoms	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Activities	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Emotions	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
			Mini-AQLQ - Environment	Visit 3	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 1: Secondary Analyses – Asthma Control	11.1.4	Full analysis Phase 1	GINA	Visit 3	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
			Asthma Control - no exacerbations	Visit 3	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
			Asthma Control - no change in treatment	Visit 3	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses – lung function	11.2.1	Full analysis Phase 2	FEV1	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FEV1%P	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC%P	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 2: Secondary Analyses - questionnaires	11.2.2	Full analysis Phase 2	Overall Mini-AQLQ	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			VAS	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FENO	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses – Mini-AQLQ by domains	11.2.3	Full analysis Phase 1	Mini-AQLQ - symptoms	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Activities	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Emotions	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Environment	Visit 6	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses – Asthma Control	11.2.4	Full analysis Phase 1	GINA	Visit 6	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
			Asthma Control - no exacerbations	Visit 6	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
			Asthma Control - no change in treatment	Visit 6	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses – lung function	11.3.1	Full analysis Phase 2	FEV1	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FEV1%P	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FVC%P	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses	11.3.2	Full analysis Phase 2	Overall Mini-AQLQ	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			VAS	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			FENO	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 2: Secondary Analyses – Mini-AQLQ by domains	11.3.3	Full analysis Phase 1	Mini-AQLQ - symptoms	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Activities	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Emotions	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
			Mini-AQLQ - Environment	Visit 5	Treatment, site id, baseline exacerbations	NA	Mixed linear model, estimated effect, (p-value & 95% ci)	
Phase 2: Secondary Analyses – Asthma Control	11.3.4	Full analysis Phase 1	GINA	Visit 5	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
			Asthma Control - no exacerbations	Visit 5	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
			Asthma Control - no change in treatment	Visit 5	Treatment, site id, baseline exacerbations	NA	Generalised linear mixed model, estimated effect, (p-value & 95% ci)	
Phase 2: Correlation of Eosinophil with FENO and aspects of Asthma Control	12	Full analysis Phase 2	Eosinophil	Visit 4	FENO & other aspects of asthma control	NA	Correlation co-efficient	
Phase 2: Correlation of 4-week ACA with GINA and aspects of Asthma Control	13	Full analysis Phase 2	4-week ACA	Visit 6	GINA & other aspects of asthma control	NA	Correlation co-efficient	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 1: Extent of exposure	14.1.1	Safety	Adherence (categorised)	Visit 3	Treatment,	P% (x/n)	NA	
Phase 2: Extent of exposure	14.2.1	Safety	Adherence (categorised)	Visit 5 & 6	Treatment,	P% (x/n)	NA	
Phase 1: Adverse events	14.2.1	Safety	≥1 adverse event	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
			No. adverse events	Visit 1 - Visit 3	Treatment	n, mean, sd, median, max, min	NA	
			Adverse Events	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Adverse events	14.2.2	Safety	≥1 adverse event	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
			No. adverse events	Visit 4 - Visit 6	Treatment	n, mean, sd, median, max, min	NA	
			Adverse Events	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Severity of Adverse Events	14.3.1	Safety	Adverse Event Severity	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Severity of Adverse Events	14.3.2	Safety	Adverse Event Severity	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Treatment Related Adverse events	14.4.1	Safety	Adverse Events	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or subgroups	Summary Statistics	Formal Analysis	Footnotes
Phase 2: Treatment Related Adverse Events	14.4.2	Safety	Adverse Events	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Serious Adverse Events	14.5.1	Safety	Adverse Events	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Serious Adverse Events	14.5.2	Safety	Adverse Events	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Non-Serious Adverse Events	14.6.1	Safety	Adverse Events	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Non-Serious Adverse Events	14.6.2	Safety	Adverse Events	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Adverse Events causing discontinuation from study	14.7.1	Safety	Adverse Events	Visit 1 - Visit 3	Treatment	p% (x/n)	NA	
Phase 2: Adverse Events causing discontinuation from study	14.7.2	Safety	Adverse Events	Visit 4 - Visit 6	Treatment	p% (x/n)	NA	
Phase 1: Clinical Laboratory - Eosinophil Count	15.1	Safety	Eosinophil	Visit 1 - Visit 3	Treatment	n, mean, sd, median, max, min	NA	
Phase 2: Clinical Laboratory - Eosinophil Count	15.2	Safety	Eosinophil	Visit 4 - Visit 6	Treatment	n, mean, sd, median, max, min	NA	

14.2. Individual Patient Listings

Listing Title	Number	Population	Footnotes
Phase 1: Screening, by treatment and site	1.1	All patients	
Phase 2: Screening, by treatment and site	1.2		
Phase 1: Patient Disposition, by treatment and site	2.1	All patients	
Phase 2: Patient Disposition by treatment and site	2.2	Full Analysis Phase 1 - randomised to flutiform	
Phase 1: Protocol violations by treatment and site	3.1	All patients	
Phase 2: Protocol violations by treatment and site	3.2	Full Analysis Phase 1 - randomised to flutiform	
Phase 1: Demographics by treatment and site	4.1	All patients	
Phase 2: Demographics by treatment and site	4.2	Full Analysis Phase 1 - randomised to flutiform	
Phase 1: Concurrent Illnesses and Medical Conditions by treatment and site	5.1	Full analysis Phase 1	
Phase 2: Concurrent Illnesses and Medical Conditions by treatment and site	5.2	Full Analysis Phase 2	
Phase 1: Concurrent Medications, by treatment and site	6.1	Full analysis Phase 1	
Phase 2: Concurrent Medications, by treatment and site	6.2	Full Analysis Phase 2	
Phase 1: Visit dates	7.1	Full Analysis Phase 1	
Phase 2: Visit dates	7.2	Full Analysis Phase 2	

Listing Title	Number	Population	Footnotes
Phase 1: Asthma Control Questionnaire by treatment, by treatment and site	8.1	Full analysis Phase 1	To indicate those not included in non-inferiority population
Phase 2: Asthma Control Questionnaire by treatment, by treatment and site	8.2	Full Analysis Phase 2	To indicate those not included in non-inferiority population
Phase 1: Questionnaire (Mini-AQLQ,GINA,VAS,4-week ACA) by treatment and site	9.1.1-9.1.4	Full analysis Phase 1	
Phase 2: Questionnaire (Mini-AQLQ,GINA,VAS, 4-week ACA) by treatment and site	9.2.1-9.2.4	Full Analysis Phase 2	
Phase 1: Spirometry Results by treatment and site	10.1	Full analysis Phase 1	To indicate reason for missing data
Phase 2: Spirometry results by treatment and site	10.2	Full Analysis Phase 2	To indicate reason for missing data
Phase 1: Extent of exposure, by treatment and site	11.1	Safety Phase 1	
Phase 2: Extent of exposure, by treatment and site	11.2	Safety Phase 2	
Phase 1: Adherence, by treatment and site	12.1	Safety Phase 1	
Phase 2: Adherence, by treatment and site	12.2	Safety Phase 2	
Phase 1: Adverse Events by treatment and site	13.1	Safety Phase 1	
Phase 2: Adverse Events by treatment and site	13.2	Safety Phase 2	
Phase 1: Deaths and Severe Asthma Exacerbations by treatment and site	14.1	Safety Phase 1	

Listing Title	Number	Population	Footnotes
Phase 2: Deaths and Severe Asthma Exacerbations by treatment and site	14.2	Safety Phase 2	
Phase 1: Lab Results (Eosinophil) by treatment and site	15.1	Safety Phase 1	
Phase 2: Lab Results (FENO and eosinophil) by treatment and site	15.2	Safety Phase 2	



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The layout of the tables is shown in this document: and listings here: .

Appendix A

i) Demographics

The following data will be collected:

- a) Date of Birth (Age will automatically be calculated from this on the eCRF)
- b) Race: 'White', 'Mixed/Multiple Ethnic Groups', 'Asian/Asian British', 'Black/African/Caribbean/Black British' or 'Other'
- c) Sex: 'Male' or 'Female'
- d) Weight (kg): Range 40kg to 200kg
- e) Height (m): Range 1.4m to 2.2m
- f) Occupation: free text
- g) Average units of alcohol consumed per week (units): Range 0 to 100

ii) Screening Questions

- a) Is the patient hypersensitive to any of the following?: 'Flutiform', 'Formoterol', 'Sodium Cromoglicate', 'Ethanol Anhydrous (absolute ethanol)', 'Aplurane HFA 227', 'The patient is not hypersensitive to any of the above'.
- b) Has the patient suffered from an exacerbation resulting in Emergency room attendance, hospitalisation or acute course of oral steroids in the last 12 months? : Yes or No.
- c) How many exacerbations occurred in the last 12 months?: Count.
- d) How many occurred in the past 3 months?: Count.

iii) Childbearing Potential

- a) Sex: 'Male' or 'Female'
- b) Is the patient of childbearing potential: 'Yes' or 'No'
- c) If not, what is the reason?: 'Bilateral Oophorectomy or Salpingectomy or Tubal Ligation' or '2 years Postmenopausal' or 'Other' and asked to specify
- d) If yes to (ii) what will they be doing to prevent pregnancy?: 'IUD', 'Oral Contraceptives', 'Contraceptive Implant', 'Contraceptive Transdermal', 'Contraceptive Injection', 'Condom and Spermicide', 'Diaphragm and Spermicide', 'Abstinence', 'Partner's Vasectomy', 'Other' and asked to specify

iv) Spirometry Examination

- a) Date (dd/mm/yyyy)
- b) Forced Vital Capacity(L) (FVC): Range 1.0L to 7.0L
- c) Predicted FVC(L): Range 1.0L to 7.0L
- d) Percent predicted FVC(%) (FVC%P): 0% to 140%

- e) Forced Expiratory Volume in 1 Second(L) (FEV_1): Range 0.8L to 6.0L
- f) Predicted FEV_1 (L): 0.8L to 6.0L
- g) Percent Predicted FEV_1 (%) ($FEV_1\%P$): Range 0% to 140%
- h) Ratio of FEV_1 and FVC (FEV_1/FVC): Range 0.1 to 6

v) GINA

Four questions asking about occurrence of asthma events. The first going from '0' to '10+' (coded as 0 to 11), the remaining three referring to how many days in last week range '0 days' to '7 days' (coded as 0 to 7). The GINA score is derived from these and spirometry output and categorises Asthma Control into 0='Controlled', 1='Partly Controlled' or 2='Uncontrolled', see below. This is calculated automatically from the eCRF.

Table 2: Global Initiative for Asthma Criteria for Asthma (GINA) Control

Characteristic	Controlled	Partly Controlled	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice per week	Three or more features of "partly controlled" asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less per week)	More than twice per week	
Lung function (PEF or FEV_1)	Normal	<80% predicted or personal best (if known)	

FEV_1 =forced expiratory flow in 1 second; PEF=peak expiratory flow.

vi) Inhaler Technique

- a) Did the patient demonstrate any errors on Seretide?: 'Yes' or 'No'
- b) Did the patient demonstrate any errors on Flutiform?: 'Yes' or 'No'

vii) Mini-AQLQ

There are 15-questions in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli), each question is scored using a 7 point scale (0-6, 0= no impairment and 6 = maximum impairment). The overall score is the average of the scores for the 15 questions generating a value between 0 and 6.

viii) 'Perception of asthma symptoms' VAS

Patients asked to place an 'X' on the scale denoting how bothersome they find their asthma: score from 0 to 100.

ix) ACQ7

Patients are asked to recall how their asthma has been during the last 7 days and to evaluate their asthma against 5 symptom questions and a rescue bronchodilator use question on a 7-point scale (0 = no impairment, 6 = maximum impairment). The FEV₁ % predicted was graded on a 7 point scale (0 to 6) based on the cut-offs >95%, 95%-90%, 89%-80%, 79%-70%, 69%-60%, 59%-50%, <50%. The questions are equally weighted and ACQ7 score is the mean of the 7 questions, generating a value between 0 (totally controlled) and 6 (severely uncontrolled).

x) FENO

Fractional Exhaled Nitric Oxide (ppb)

xi) 4-week Asthma Control Assessment

The ACA is derived according to section 3.3 and like GINA categorises Asthma Control within the last 4 weeks into 0='Controlled', 1='Partly Controlled' or 2='Uncontrolled'.

xii) Eosinophils ABS

Eosinophils range (count x 10⁹/L): 0 to 20.

xiii) General Medical History

- a) Free text?
- b) Start date: DD-MMM-YYYY, MMM-YYY or YYYY
- c) Stop date: DD-MMM-YYYY, MMM-YYY or YYYY
- d) Ongoing? 1=Yes, 0=No

xiv) Concomitant Medication

- a) Any? 1=Yes, 0=No
- b) Medication: Free text
- c) Dose: Free text
- d) Dose Units: puff, ug, mg, g, mL, gtt, unknown, tablet, cc, patch, Lozenge, application, suppository, Gy, cGy, tbsp, tsp, mEq, IU
- e) Frequency: qd (once a day), bid (Twice a day), tid (Three times a day), qid (Four times a day), 5xd (Five days a day), qs (weekly), qM (once a month), q6h (every six hours), q8h (every 8

hours), q12h (every twelve hours), bis (two times a week), tis (three times a week), PRN, Unknown, Other

- f) Route: Inhaled, Oral, Nasal, Transdermal, Intravenous, Intramuscular, Subcutaneous, Rectal, Sublingual, Ophthalmic, Topical, Transmucosal, Epidural, Intra-Articular, Intraocular, Intralesional, Intradermal, Vaginal, Intrapleural, Intravesical, Intrathecal, Intraperitoneal, Intraosseous, Intracavernous, Intraarticular, Intraarterial, Intracerebral, Parenteral, Enteral, Intravitreal
- g) Start Date: DD-MMM-YYYY
- h) Stop Date: DD-MMM-YYYY
- i) Ongoing: 1=Yes, 0=No
- j) Indication: Free Text

xv) Adverse Events

- a) Any? 1=Yes, 0=No
- b) AE Term: Free Text
- c) Date of onset: DD-MMM-YYYY
- d) Date of resolution: DD-MMM-YYYY
- e) Action taken regarding study medication: Dose not changed, Dose reduced, Dose Increased, Drug Interrupted, Drug Withdrawn, Unknown, Not applicable
- f) Serious AE? Yes, No
- g) Severity: Mild, Moderate, Severe
- h) Outcome: Fatal: Persisted at Death, Fatal: Resulted in Death, Recovering/Resolving, Recovered/Resolved with Sequelae, Recovered/Resolved, Not recovered/not resolved, unknown
- i) Relationship to study drug: related, Not related
- j) Severe Asthma exacerbation?: Yes, No
- k) Action taken: Hospitalised, A&E Attendance, Acute course or Oral Corticosteroids

xvi) Device Accountability

- a) Date Device 1 Dispensed: DDD-MMM-YYYY
- b) Counter value when device 1 dispensed: range 0-120
- c) Device 1 status: Device Returned, Device not due to be Returned Yet, Device was not Returned
- d) Date device 1 was returned: DDD-MMM-YYYY
- e) Counter value when device 1 returned: range 0-120

Same data for devices 2 and 3.

xvii) Unscheduled Visits

- a) Have there been any unscheduled visits? Yes, No

- b) Reason for visit: Adverse Event, Change in concomitant medications, Study drug dispensing, accountability and/or replacement, Laboratory follow-up, Subject Compliance, Other
- c) Other: Free Text
- d) Date of visit: DD-MMM-YYYY

xviii) Protocol Deviations

- a) Event Date: DDMMYYYY
- b) Event Description: DDMMYYYY
- c) Type: 'Inclusion Criteria', 'Exclusion criteria', 'Randomisation criteria', 'Primary objective variable', 'GCP guidelines', 'Non-compliance to study medication', 'Excluded concomitant medication/treatment' or 'Other'
- d) Other: Free Text
- e) Outcome: 'Approved to Continue', 'Participation Terminated' or 'Acknowledged: No Action Taken, Subject Participation Completed'

xix) Data Completion

- a) Date entry stopped: DDMMYYYY
- b) Was the study terminated early: 1=Yes, 0=No
- c) Reason for Early Termination: 'Lost to follow-up', 'Consent Withdrawn', 'Adverse Event', 'Protocol Violation', 'Other'

Appendix B

ACQ if follow-up data complete or MCAR can be assumed

```
ods graphics on;
PROC MIXED data=fflux COVTEST;
  CLASS siteid trtan exacerb;
  MODEL AVAL = trtan exacerb base/ ddfm=kr solution residual;
  RANDOM intercept / subject=siteid solution;
  WHERE paramn=1 & avisitn=3;
  ESTIMATE 'trt diff' trtan 1 -1/ lowertailed CL;
run;
```

Continuous Secondary Outcomes

```
ods graphics on;
PROC MIXED data=fflux COVTEST;
  CLASS siteid trtan exacerb;
  MODEL AVAL = trtan exacerb/ ddfm=kr solution residual;
  RANDOM intercept / subject=siteid solution;
  WHERE paramn=1 & avisitn=3;
  ESTIMATE 'trt diff' trtan 1 -1 / CL;
run;
ods graphics off;
```

Binary outcomes

```
PROC GLIMMIX data=fflux;
  CLASS siteid trtan exacerb;
  MODEL avalcut= trtan exacerb / dist=binary link=logit ddfm=kr solution;
  RANDOM intercept / subject=practice solution;
  WHERE paramn=1 & avisitn=3;
  ESTIMATE 'trt diff' trtan -1 1 / CL;
RUN;
```