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Original Article

Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma

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Abbreviations:

ACQ, Asthma Control Questionnaire;
 AE, adverse event; CI, confidence interval;
 ED, emergency department; FEV₁, forced
 expiratory volume in 1 second; FVC, forced
 vital capacity; GINA, Global Initiative for
 Asthma; ICS, inhaled corticosteroids;
 IgE, immunoglobulin E; IV, intravenous;
 LS, least squares; MCID, minimal clinically
 important difference; mITT, modified
 intent-to-treat; PEF, peak expiratory flow;
 OCS, oral corticosteroids; QoL, quality of life;
 RR, rate ratio; SGRQ, St George's Respiratory
 Questionnaire; SAE, serious adverse event;
 SC, subcutaneous; SE, standard error;
 SoC, standard of care; URTI, upper
 respiratory tract infection

ABSTRACT

Background: The MENSA trial assessed the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma. This report describes the efficacy and safety of mepolizumab in Japanese patients from MENSA.

Methods: A post hoc analysis of the Japanese subgroup from the randomized, double-blind, placebo-controlled, double-dummy, Phase III MENSA trial (NCT01691521). Patients ≥ 12 years with severe eosinophilic asthma received mepolizumab 75 mg intravenously (IV), 100 mg subcutaneously (SC), or placebo, every 4 weeks for 32 weeks. The primary endpoint was the annualized rate of exacerbations. Secondary and other endpoints included annualized rate of exacerbations requiring emergency department (ED) visit/hospitalization, morning peak expiratory flow (PEF), St George's Respiratory Questionnaire (SGRQ) score and eosinophil counts. Adverse events (AEs) were monitored.

Results: In the Japanese subgroup ($N = 50$), the rate of clinically significant exacerbations was reduced by 90% (rate ratio [RR]: 0.10; 95% confidence interval [CI]: 0.02–0.57; $P = 0.010$) with mepolizumab IV and 62% (RR: 0.38; 95% CI: 0.12–1.18; $P = 0.094$) with mepolizumab SC, versus placebo. No exacerbations requiring ED visit/hospitalization were reported with mepolizumab IV; exacerbations were reduced by 73% (RR: 0.27; 95% CI: 0.06–1.29; $P = 0.102$) with mepolizumab SC versus placebo. Compared with placebo, mepolizumab IV and SC numerically increased morning PEF from baseline by 40 L/min and 13 L/min, improved quality of life by greater than the minimal clinically important difference (SGRQ: 9.5 [$P = 0.083$] and 7.9 [$P = 0.171$] points) and reduced eosinophil counts. AE incidence was similar between treatments. Results were broadly consistent with the overall population.

Conclusions: Mepolizumab was efficacious and well tolerated in Japanese patients with severe eosinophilic asthma, producing similar responses to the overall MENSA population.

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Introduction

Severe asthma is defined by the Japanese Asthma Guidelines and Global Initiative for Asthma (GINA) guidelines as asthma requiring high-dose inhaled corticosteroids (ICS) and a second controller medication and/or oral corticosteroids (OCS) for symptom control, or disease that remains uncontrolled despite these therapies.^{1,2} The proportion of Japanese patients with asthma

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characterized as severe is reported to range from 5.7% to 7%,^{3,4} which is similar to the incidence in western countries (5–10%).^{5,6} Severe asthma is a heterogeneous condition, and a subset of patients include those with increased eosinophils, termed severe eosinophilic asthma.^{7,8} These patients experience frequent exacerbations, poor symptom control, decreased quality of life (QoL), and increased risk of lung function decline despite high doses of standard maintenance therapies such as ICS.^{1,8–12}

Mepolizumab is a humanized monoclonal antibody targeting interleukin-5. In clinical trials, mepolizumab has been shown to reduce eosinophil counts,^{7,13,14} the number of asthma exacerbations,^{7,15,16} and OCS maintenance dose^{17,18} in patients with severe eosinophilic asthma compared with placebo, when used as add-on therapy to standard of care (SoC). The global Phase III MENSA trial was conducted in Australia, East Asia, Europe, North America, and South America. It demonstrated that both mepolizumab 75 mg intravenous (IV) and 100 mg subcutaneous (SC) treatment resulted in similar reductions in the rate of clinically significant asthma exacerbations, increased lung function, and improved QoL compared with placebo, when used as add-on therapy to SoC.¹⁵

For the majority of licensed pharmacological therapies, inter-ethnic differences likely to affect treatment responses have been rarely identified.^{19–21} Moreover, the profiles of the majority of monoclonal antibody therapies have demonstrated limited therapeutically relevant ethnic differences, with most licensed doses being the same in Japan and the USA.²² However, differences in patient characteristics between ethnic groups could alter therapeutic responses.^{22,23} Currently, there are data on the pharmacodynamics but no reports on the clinical efficacy and safety of mepolizumab in Japanese patients.²⁴ Therefore, the objective of this subanalysis was to describe the efficacy and safety of mepolizumab in the Japanese subgroup of patients with severe eosinophilic asthma from the MENSA trial.¹⁵

Methods

Study design

This was a post hoc subgroup analysis of the Japanese population from the MENSA trial. Full details of the MENSA trial have previously been reported.¹⁵ In brief, MENSA was a multicenter, randomized, double-blind, placebo-controlled, double-dummy, parallel-group, Phase III trial conducted between October 2012 and January 2014 (NCT01691521; GSK ID: MEA115588). Patients ≥ 12 years of age with a clinical diagnosis of asthma who had experienced two or more asthma exacerbations requiring treatment with OCS in the previous year while on maintenance therapy with high-dose ICS were eligible for inclusion in the study. Following the 1–6-week run-in period, patients were randomized (1:1:1) to receive treatment with mepolizumab 75 mg IV, mepolizumab 100 mg SC, or placebo every 4 weeks for 32 weeks, as add-on therapy to intensive SoC asthma treatment (Fig. 1).¹⁵

Study endpoints

The primary study endpoint was the annualized rate of clinically significant exacerbations, defined as a worsening of asthma requiring systemic corticosteroids administered IV or orally for ≥ 3 days or a single intramuscular dose, or an emergency department (ED) visit or hospitalization. Patients using maintenance systemic corticosteroids were required to have used at least double their existing maintenance dose for ≥ 3 days. Secondary and other endpoints included the annualized rate of severe exacerbations requiring an ED visit and/or hospitalization and the annualized rate

of exacerbations requiring hospitalization. Change from baseline in daily morning peak expiratory flow (PEF) at Weeks 29–32, and the change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV₁) at Week 32 were assessed in a non-centralized manner using individual sites' own spirometry equipment. St George's Respiratory Questionnaire (SGRQ) total score and Asthma Control Questionnaire (ACQ-5) score at Week 32 were also assessed. Additionally, the global response to therapy questionnaire was completed at Week 32 by physicians and patients using a 7-point scale (1 = significantly improved, 7 = significantly worsened). Pharmacodynamic assessment of the change from baseline in blood eosinophil counts was also determined. Safety was assessed by monitoring of adverse events (AE), clinical laboratory testing and vital signs. The levels of anti-mepolizumab and mepolizumab neutralizing antibodies were measured at baseline (Week 0) and Weeks 16, 32, and 40 (12 weeks post-final mepolizumab administration). The anti-mepolizumab antibody assay is a bridging electrochemiluminescent immunoassay. The neutralizing antibody assay is an indirect ligand binding immunoassay using electrochemiluminescent detection.

Statistical analysis

The modified intent-to-treat (mITT) population included all patients randomized to and receiving ≥ 1 dose of study treatment. Two patients who were randomized in error and two patients who were withdrawn due to issues obtaining an IV line were not included in this population; none of these patients were in the Japanese subgroup. The mITT population was the primary analysis population for safety and efficacy endpoints in the overall population and the Japanese subgroup. Statistical analysis methods used for comparisons between treatment groups in the Japanese subgroup were as previously described.¹⁵ The rate of exacerbations used a negative binomial model with covariates of treatment, baseline use of maintenance OCS, exacerbations in the previous year and baseline percent predicted FEV₁. Change from baseline in PEF, FEV₁, and ACQ-5 used a mixed model repeated measures analysis including the above covariates as well as additional ones for baseline, visit, and interaction for visit with baseline and visit with treatment; change from baseline SGRQ used analysis of covariance with the addition of a baseline covariate.

Results

Patients

Of the 576 patients randomized and included in the overall mITT population, 50 (9%) patients from 18 centers in Japan were included in the Japanese subgroup (mean age: 55, range: 14–82 years). Of these patients, 17 received mepolizumab IV, 17 mepolizumab SC, and 16 placebo. In total, 44 (88%) patients (mepolizumab IV, $N = 14$; mepolizumab SC, $N = 15$ and placebo, $N = 15$) in the Japanese subgroup completed the full study. Six patients were withdrawn from the study, with the reason 'withdrawal by subject' in all cases. Of the 6 patients that withdrew, 5 chose not to continue when the original investigator ceased employment at the hospital. Patient demographics and baseline characteristics were broadly similar between the Japanese subgroup and the overall study population (Table 1). However, some differences in the Japanese subgroup included a trend for lower daily OCS dose, higher blood eosinophil counts and decreased reversibility to bronchodilators compared with the overall population. Additionally, in the Japanese subgroup, the mean number (standard deviation [SD]) of exacerbations in the previous year (4.6 [3.6]) was higher than in the overall population (3.6 [2.6]).

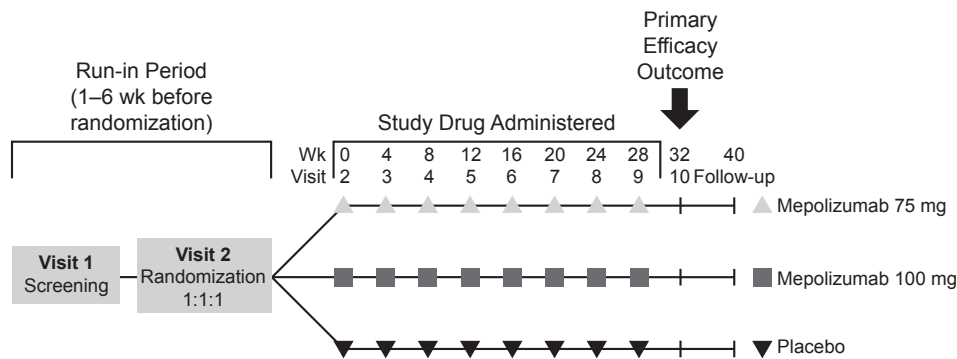


Fig. 1. Summary diagram of the study design.¹⁵ Wk, week. Reproduced with permission from Ortega et al., 2014.¹⁵

Table 1

Summary of patient demographics and baseline characteristics (mITT population).

	Japanese subgroup				Overall population			
	Placebo	Mepolizumab		Total	Placebo	Mepolizumab		Total
		IV	SC			IV	SC	
N = 16	N = 17	N = 17	N = 50	N = 191	N = 191	N = 194	N = 576	
Age (years), mean (range)	50 (15–72)	59 (35–82)	56 (14–76)	55 (14–82)	49 (12–76)	50 (13–82)	51 (12–81)	50 (12–82)
Gender, female, N (%)	10 (63)	12 (71)	10 (59)	32 (64)	107 (56)	106 (55)	116 (60)	329 (57)
Body mass index, mean (SD)	24.3 (4.1)	26.0 (5.1)	22.6 (2.7)	24.3 (4.2)	28.0 (5.6)	27.7 (5.7)	27.6 (6.2)	27.8 (5.8)
Former smoker, N (%)	1 (6)	5 (29)	5 (29)	11 (22)	57 (30)	52 (27)	50 (26)	159 (28)
Asthma duration, (years) mean (SD)	17.4 (11.9)	24.1 (17.1)	18.2 (12.0)	19.9 (14.0)	19.5 (14.6)	19.8 (14.0)	20.5 (12.9)	19.9 (13.8)
Oral corticosteroid use, N (%)	2 (13)	4 (24)	6 (35)	12 (24)	44 (23)	48 (25)	52 (27)	144 (25)
Daily dose (mg), mean (SD)	6.7 (2.4)	5.9 (6.3)	3.5 (1.2)	4.8 (3.7)	15.1 (14.9)	12.0 (9.3)	12.6 (11.1)	13.2 (11.9)
Allergic rhinitis, N (%)	12 (75)	12 (71)	12 (71)	36 (72)	95 (50)	91 (48)	95 (49)	281 (49)
FEV₁, mean (SD)								
Pre-bronchodilator (L)	1.74 (0.67)	1.47 (0.61)	1.60 (0.76)	1.60 (0.68)	1.86 (0.63)	1.86 (0.70)	1.73 (0.66)	1.82 (0.67)
% of predicted	70.1 (20.8)	68.6 (24.0)	70.2 (22.6)	69.6 (22.1)	62.4 (18.1)	61.4 (18.3)	59.3 (17.6)	61.0 (18.0)
% reversibility	24.4 (18.7)	21.6 (16.8)	18.1 (12.0)	21.3 (15.9)	27.4 (20.8)	25.4 (19.6)	27.9 (24.0)	26.9 (21.5)
% pre-bronchodilator FEV ₁ :FVC ratio	69 (15)	66 (14)	66 (18)	67 (16)	64 (13)	64 (13)	63 (13)	64 (13)
Morning PEF (L/min), mean (SD)	285 (132)	231 (119)	243 (87)	252 (114)	277 (106)	269 (112)	255 (108)	267 (109)
ACQ-5 score, mean (SD)	1.5 (1.4)	1.9 (1.2)	1.5 (0.7)	1.6 (1.2)	2.3 (1.2)	2.1 (1.1)	2.3 (1.3)	2.2 (1.2)
SGRQ score, mean (SD)	37.0 (22.9)	35.2 (17.0)	32.4 (12.2)	34.8 (17.5)	46.9 (19.8)	44.4 (19.4)	47.9 (19.5)	46.4 (19.6)
IgE (u/mL), geometric mean (SD logs)	96 (1.7)	191 (2.0)	399 (1.0)	194 (1.7)	150 (1.5)	180 (1.5)	150 (1.5)	159 (1.5)
Blood eosinophil count (cells/μL), geometric mean (SD Logs)	360 (1.154)	440 (1.186)	470 (1.086)	420 (1.124)	320 (0.938)	280 (0.987)	290 (1.050)	290 (0.993)
Asthma exacerbations in previous year								
Mean (SD)	4.8 (3.6)	3.9 (3.1)	5.1 (4.2)	4.6 (3.6)	3.6 (2.8)	3.5 (2.2)	3.8 (2.7)	3.6 (2.6)
Hospitalizations, N (%)	5 (31)	2 (12)	5 (29)	12 (24)	35 (18)	41 (21)	33 (17)	109 (19)
Asthma-related intubations, N (%)	0	1 (6)	1 (6)	2 (4)	3 (2)	10 (5)	8 (4)	21 (4)

ACQ-5, Asthma Control Questionnaire; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IV, intravenous; mITT, modified intent-to-treat; PEF, peak expiratory flow; SC, subcutaneous; SGRQ, St Georges Respiratory Questionnaire; SC, subcutaneous.

Primary endpoint

In the Japanese subgroup, a total of 46 clinically significant exacerbations were reported by 15 patients, with an annual rate of 0.23, 0.88, and 2.32 in the mepolizumab IV, SC, and placebo groups, respectively. In these patients, the relative reduction in the annual rate of clinically significant exacerbations by mepolizumab IV and SC treatment was 90% (rate ratio [RR]: 0.10 [95% confidence interval [CI]: 0.02–0.57]; $P = 0.010$) and 62% (RR: 0.38; [95% CI: 0.12–1.18]; $P = 0.094$), respectively, versus placebo (Table 2; Fig. 2). These results were consistent with the overall population; 47% (RR: 0.53 [95% CI: 0.40–0.72]; $P = <0.001$) and 53% (RR: 0.47 [95% CI: 0.35–0.64]; $P = <0.001$) respectively.

Secondary and other endpoints

Other exacerbations

In the Japanese subgroup, there were few exacerbations requiring ED visits and/or hospitalization: no events in the

mepolizumab IV group, 3 events in the mepolizumab SC group, and 9 events in the placebo group. In the Japanese subgroup, the relative reduction of exacerbations requiring an ED visit and/or hospitalization (annual rate) by mepolizumab SC treatment was 73% (RR: 0.27 [95% CI: 0.06–1.29]; $P = 0.102$) versus placebo (Table 2). Similarly, the relative reduction of exacerbations requiring hospitalization (annual rate) was 65% (RR: 0.35 [95% CI: 0.07–1.84]; $P = 0.213$) with mepolizumab SC treatment versus placebo. Similar results were seen in the overall population.

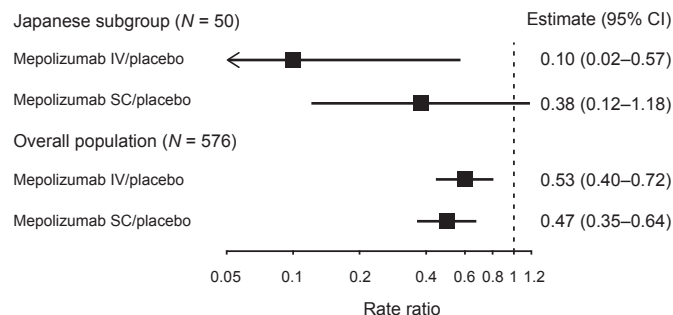
Lung function

Mean (SD) morning PEF at baseline was similar in the Japanese subgroup (252 [114] L/min) and overall population (267 [109] L/min). Mean morning PEF at Weeks 29–32 increased from baseline by 40 L/min and 13 L/min greater than placebo with mepolizumab IV and SC, respectively (Fig. 3A). These improvements, were similar to those in the overall population. Mean (SD) pre-bronchodilator FEV₁ levels at baseline were lower in the Japanese subgroup than the overall population (1.60 [0.68] L

Table 2
Exacerbations requiring hospitalization and/or ED and hospitalization alone (mITT population).

	Japanese subgroup			Overall population		
	Placebo	Mepolizumab		Placebo	Mepolizumab	
		IV	SC		IV	SC
	N = 16	N = 17	N = 17	N = 191	N = 191	N = 194
Clinically significant exacerbations[†]						
Mean exacerbation rate/year	2.32	0.23	0.88	1.74	0.93	0.83
% reduction versus placebo	—	90	62	—	47	53
Rate ratio versus placebo (95% CI)	—	0.10 (0.02–0.057)	0.38 (0.12–1.18)	—	0.53 (0.40–0.72)	0.47 (0.35–0.64)
P-value	—	0.010	0.094	—	<0.001	<0.001
Exacerbations requiring ED visit and/or hospitalization						
Mean exacerbation rate/year	0.67	0 (no events)	0.18	0.20	0.14	0.08
% reduction versus placebo	—	—	73	—	32	61
Rate ratio versus placebo (95% CI)	—	—	0.27 (0.06–1.29)	—	0.68 (0.33–1.41)	0.39 (0.18–0.83)
P-value	—	—	0.102	—	0.299	0.015
Exacerbation requiring hospitalization						
Mean exacerbation rate/year	0.46	0 (no events)	0.16	0.10	0.06	0.03
% reduction versus placebo	—	—	65	—	39	59
Rate ratio versus placebo (95% CI)	—	—	0.35 (0.07–1.84)	—	0.61 (0.23–1.66)	0.31 (0.11–0.91)
P-value	—	—	0.213	—	0.334	0.034

CI, confidence interval; ED, emergency department; IV, intravenous; mITT, modified intent-to-treat; SC, subcutaneous.

[†] A worsening of asthma requiring systemic corticosteroids for ≥ 3 -days, a single intramuscular corticosteroid dose or ED visit/hospitalization.**Fig. 2.** Rate ratio (95% CI) of clinically significant exacerbations in the Japanese subgroup and overall population (mITT population). CI, confidence interval; IV, intravenous; mITT, modified intent-to-treat; SC, subcutaneous.

versus 1.82 (0.67) L, respectively). In the Japanese subgroup, increases in pre-bronchodilator FEV₁ at Week 32 from baseline with mepolizumab IV and SC treatment were smaller than placebo (48 mL and 26 mL versus 145 mL, respectively) (Supplementary Table 1). In contrast, in the overall population, mepolizumab IV and SC treatment significantly increased pre-bronchodilator FEV₁ at Week 32 by 186 mL and 183 mL, respectively, versus 86 mL with placebo. In the Japanese subgroup, the proportion of patients with a ≥ 200 mL increase in pre-bronchodilator FEV₁ was numerically greater with mepolizumab IV and SC versus placebo (Supplementary Fig. 1).

QoL

Baseline mean (SD) SGRQ scores were lower in the Japanese subgroup (34.8 [17.5]) than in the overall population (46.4 [19.6]), indicating a lower impact of asthma on QoL in the Japanese subgroup (Table 1). In the Japanese subgroup, mepolizumab IV and SC treatment decreased SGRQ scores at Week 32 by 9.5 ($P = 0.083$) and 7.9 ($P = 0.171$) points more than placebo, respectively (Fig. 3B). Though these reductions were not statistically significant, they were greater than the minimal clinically important difference (MCID) of a decrease of ≥ 4 points,²⁵ indicating improved QoL in these patients. Significant and clinically relevant reductions in SGRQ scores at Week 32 with mepolizumab were also observed in the overall population (Fig. 3B).

Asthma control

At baseline, mean (SD) ACQ-5 scores were lower in the Japanese subgroup (1.6 [1.2]) than in the overall population (2.2 [1.2]) (Table 1), although still indicative of a lack of control. In the Japanese subgroup, treatment with mepolizumab IV and SC resulted in significant decreases of 0.71 ($P = 0.021$) and 0.70 ($P = 0.024$) points more than placebo in both treatment groups at Week 32 (Fig. 3C). These decreases were greater than the MCID threshold of 0.5.²⁵ Similar improvements were observed in the overall population (Fig. 3C).

Global response to therapy

In the Japanese subgroup at Week 32, there was a trend towards improvement with mepolizumab as indicated by greater proportions of physician-rated response to therapy scores of 'significantly improved' and 'moderately improved' with mepolizumab IV (6% and 29%) and SC (12% and 18%), versus placebo (6% and 19%) (Supplementary Fig. 2A, Supplementary Table 2). A similar trend was seen with patient-rated response to therapy scores at Week 32, with 'significantly improved' and 'moderately improved' reported by a higher proportion of patients receiving mepolizumab IV (24% and 24%) and SC (12% and 29%), versus placebo (6% and 19%) (Supplementary Fig. 2B, Supplementary Table 2).

Blood eosinophil counts

In the Japanese subgroup, geometric mean baseline eosinophil count was higher than in the overall population (420 cells/ μ L and 290 cells/ μ L, respectively) (Table 1). In the Japanese subgroup, eosinophil counts were reduced from baseline by Week 4, relative to placebo; mepolizumab IV reduced counts by 87% (RR: 0.13 [95% CI: 0.06–0.27]; $P < 0.001$) and mepolizumab SC by 85% (RR: 0.15 [95% CI: 0.07–0.31]; $P < 0.001$) (Fig. 4A). In the overall population, eosinophil counts at Week 4 were reduced by 80% with mepolizumab IV (RR: 0.20 [95% CI: 0.17–0.24]; $P < 0.001$) and 80% with mepolizumab SC (RR: 0.20 [95% CI: 0.17–0.23]; $P < 0.001$), relative to placebo (Fig. 4B). Reductions in eosinophil counts with mepolizumab IV and SC were maintained throughout the study in both the Japanese subgroup and overall population (Fig. 4).

Safety

In the Japanese subgroup, there was a trend for a lower overall incidence of AEs during treatment with mepolizumab IV (76%) and

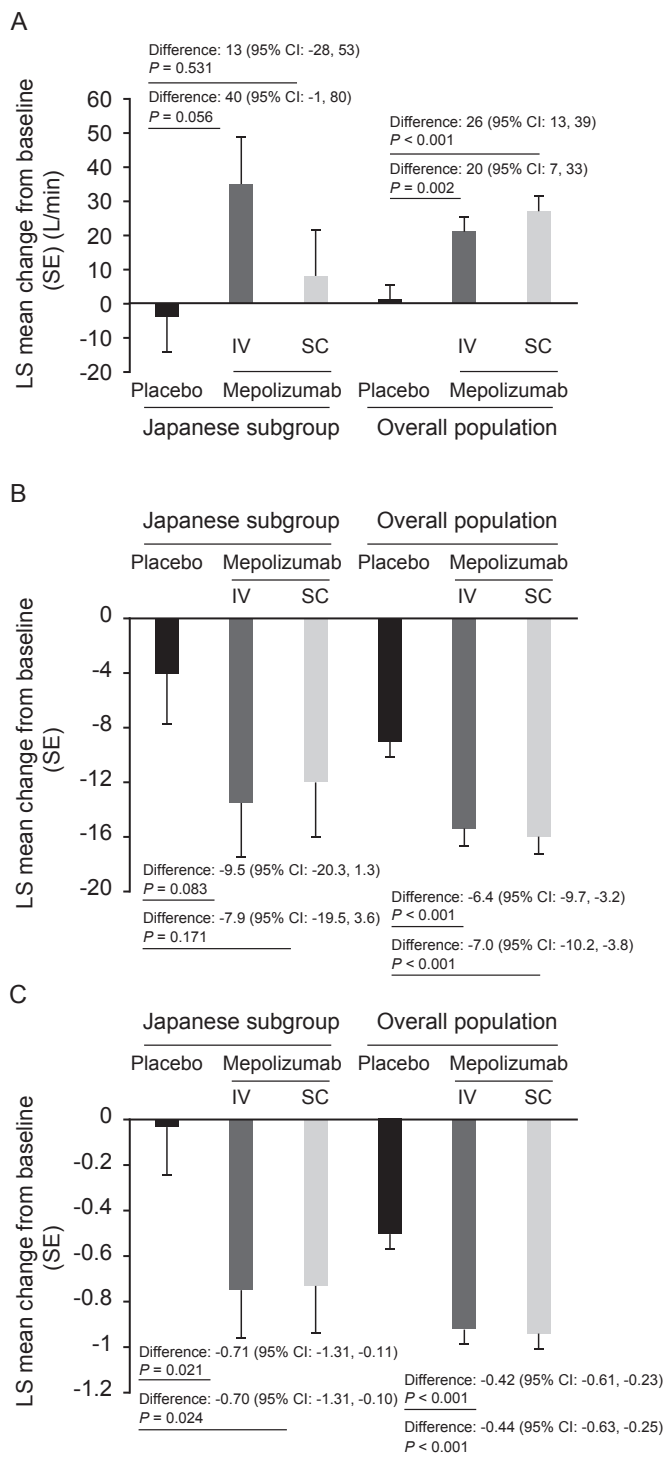


Fig. 3. Change from baseline in A) morning PEF scores at Week 29–32, B) SGRQ total score at Week 32, and C) ACQ-5 score at Week 32 (mITT population). ACQ, Asthma Control Questionnaire; CI, confidence interval; IV, intravenous; LS, least squares; mITT, modified intent-to-treat; PEF, peak expiratory flow; SE, standard error; SGRQ, St Georges Respiratory Questionnaire; SC, subcutaneous.

SC (71%), versus placebo (94%) (Table 3). With the exception of worsening of asthma and nasopharyngitis, all AEs were reported by two or fewer patients in any treatment group. The most frequently reported AE was a worsening or exacerbation of asthma, which had a lower incidence in the mepolizumab IV (29%, $N = 5$) and SC (12%, $N = 2$) groups than the placebo (56%, $N = 9$) group. Nasopharyngitis

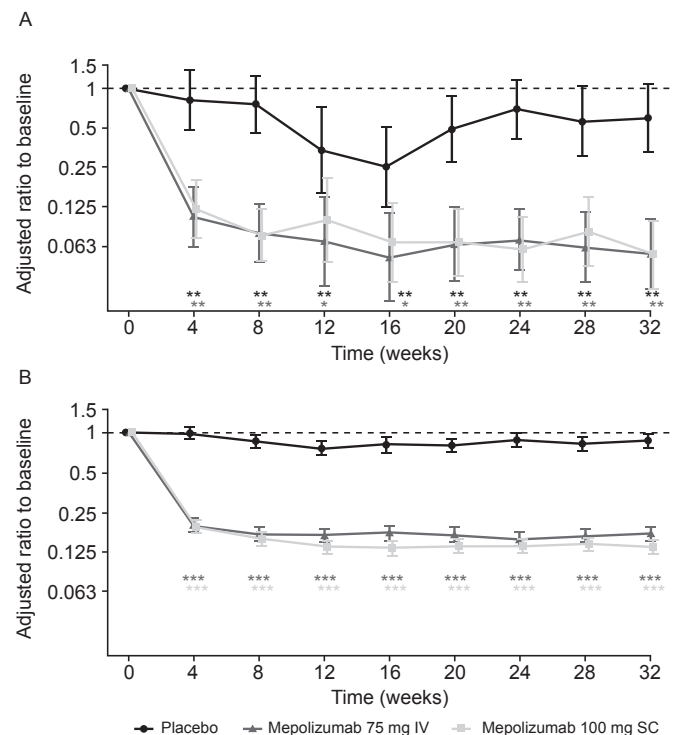


Fig. 4. Ratio to baseline (95% CI) in eosinophil counts in the A) Japanese subgroup and B) overall population (mITT population). Vertical bars represent the 95% CI; $P < 0.05$; $**P < 0.01$; $***P < 0.001$; CI, confidence interval; IV, intravenous; mITT, modified intent-to-treat; SC, subcutaneous.

Table 3
Summary of AEs (mITT population).

	Japanese subgroup			Overall population		
	Placebo	Mepolizumab IV	Mepolizumab SC	Placebo	Mepolizumab IV	Mepolizumab SC
	$N = 16$	$N = 17$	$N = 17$	$N = 191$	$N = 191$	$N = 194$
All AEs, N (%)	15 (94)	13 (76)	12 (71)	158 (83)	161 (84)	152 (78)
Non-asthma event	15 (94)	13 (76)	12 (71)	157 (82)	161 (84)	152 (78)
Worsening of asthma	9 (56)	5 (29)	2 (12)	29 (15)	18 (9)	13 (7)
Treatment-related [†]	3 (19)	1 (6)	2 (12)	30 (16)	33 (17)	39 (20)
Leading to study withdrawal	0	0	0	4 (2)	0	1 (1)
All SAEs, N (%)	4 (25)	1 (6)	4 (24)	27 (14)	14 (7)	16 (8)
Treatment-related [†]	0	0	1 (6)	1 (1)	0	1 (1)
Fatal	0	0	0	1 (1)	0	0
Common AEs in ≥ 2 patients in the Japanese population, N (%)						
Nasopharyngitis	4 (25)	7 (41)	4 (24)	46 (24)	45 (24)	33 (17)
Headache	2 (13)	2 (12)	2 (12)	33 (17)	46 (24)	39 (20)
Diarrhea	2 (13)	0	2 (12)	11 (6)	4 (2)	5 (3)
Constipation	0	1 (6)	2 (12)	3 (2)	1 (1)	5 (3)
Eczema	1 (6)	0	2 (12)	2 (1)	2 (1)	9 (5)
Bronchitis	2 (13)	0	0	18 (9)	14 (7)	9 (5)
Oropharyngeal pain	2 (13)	0	0	15 (8)	12 (6)	7 (4)
Malaise	2 (13)	0	0	2 (1)	0	2 (1)
Migraine	2 (13)	0	0	6 (3)	1 (1)	5 (3)
URTI	0	0	2 (12)	27 (14)	22 (12)	24 (12)

AE, adverse event; IV, intravenous; mITT, modified intent-to-treat; SAE, serious adverse event; SC, subcutaneous; URTI, upper respiratory tract infection.

[†] Assessed by a study investigator while blinded to treatment assignment.

was also common and had a higher incidence in the mepolizumab IV group (41%, $N = 7$) versus mepolizumab SC (24%, $N = 4$) and placebo groups (25%, $N = 4$). The incidence of treatment-related AEs, as assessed by the study investigators, was relatively

similar across treatment groups: mepolizumab IV (6%, $N = 1$), mepolizumab SC (12%, $N = 2$), and placebo (19%, $N = 3$). One patient in the mepolizumab SC group reported an injection site reaction. No patients withdrew due to AEs. In total, 9 patients reported serious AEs (SAEs): 4 patients in the placebo group (asthma hospitalization [$N = 4$], heat stroke [$N = 1$]), 1 patient in the mepolizumab IV group (fractured coccyx) and 4 patients in the mepolizumab SC group (asthma hospitalization [$N = 2$], herpes zoster [$N = 1$], influenza [$N = 1$], gallbladder disorder [$N = 1$]). There were no fatalities. No clinically relevant changes in laboratory evaluations and vital signs were detected. Anti-mepolizumab antibodies were detected in 0, 2 (12%), and 1 (6%) patients in the mepolizumab IV, mepolizumab SC, and placebo groups, respectively. Anti-mepolizumab antibody responses were transient and with low titers. All three patients tested negative for mepolizumab neutralizing antibodies. Safety data for the Japanese subgroup were similar to the overall population, and a summary is shown in Table 3.

Discussion

This is the first report evaluating the efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma. As seen in the overall population¹⁵ the results in the Japanese population demonstrate the efficacy of mepolizumab administered both IV and SC in reducing the number of clinically significant asthma exacerbations, improving lung function, QoL and asthma control, decreasing blood eosinophil counts. A favorable safety profile with mepolizumab was also demonstrated. These results suggest that there is no clinically relevant inter-ethnic difference in the response to mepolizumab.

Japanese patients treated with mepolizumab IV and SC experienced a numerically greater (90% and 62%, respectively) reduction in the annual rate of clinically significant exacerbations than the overall population (47% and 53%, respectively). Furthermore, mepolizumab also demonstrated efficacy in reducing the more severe events, including exacerbations requiring an ED visit and/or hospitalization. Correspondingly, a reduction in blood eosinophil count was seen with mepolizumab in the Japanese subgroup. Overall, these results suggest that mepolizumab is effective in reducing exacerbations in Japanese patients with severe eosinophilic asthma.

Of interest, eosinophil counts were higher at baseline in the Japanese subgroup (420 cells/ μ L) compared with the overall population (290 cells/ μ L). It has been established that increased eosinophil counts are associated with an increased occurrence of asthma exacerbations.^{7,9,15} Accordingly, in the current study the higher baseline eosinophil counts in the Japanese subgroup were associated with a higher number of exacerbations in the previous year than in the overall population. This suggests that patients in the Japanese subgroup had more severe disease. However, OCS use at baseline was lower in the Japanese subgroup than in the overall population, which may also have contributed to the higher eosinophil counts and the greater number of exacerbations in the previous year.

In the Japanese subgroup, mepolizumab improved morning PEF compared with placebo, while results for the effect of mepolizumab on pre-bronchodilator FEV₁ were inconsistent. Smaller increases from baseline in pre-bronchodilator FEV₁ were seen with mepolizumab compared with placebo. Nonetheless, a higher proportion of patients treated with mepolizumab IV and SC demonstrated a ≥ 200 mL increase from baseline in FEV₁ than patients treated with placebo. The absence of an improvement in pre-bronchodilator FEV₁ may be a result of the small sample size or differences in reversibility between populations. In addition,

spirometry was not conducted as a centralized procedure, and sites were allowed to use their own equipment. Previous studies in asthma reported that mepolizumab improved morning PEF,¹³ but did not significantly improve FEV₁.^{13,14,16} However, in more recent trials, where only patients with eosinophilic inflammation and recurrent exacerbations were included, there were improvements in FEV₁ with mepolizumab treatment.^{15,18}

The importance of obtaining and maintaining good asthma control is highlighted in the GINA and Japanese Asthma guidelines.^{1,2} Patients in the Japanese subgroup reported better asthma control at baseline, than the overall population. This observation is unexpected since the Japanese subgroup reported a higher frequency of exacerbations in the prior year compared with the overall population. Previous studies have demonstrated that asthma symptoms and exacerbation rates can be disassociated in some cohorts of patients with severe eosinophilic asthma.^{9,13,16} In the Japanese subgroup mepolizumab treatment resulted in improvement in ACQ-5 scores which were greater than the 0.5 unit MCID.²⁵ Patients with severe eosinophilic asthma experience poor QoL.^{1,7,9,15,16,18} Mepolizumab demonstrated a trend for improvement in QoL which was greater than the 4 unit MCID.²⁵ The improvement in both QoL and asthma control, in addition to the reduction in exacerbations with mepolizumab, was reflected by similar scores on the global response to therapy questionnaire demonstrating the benefits of mepolizumab in both Japanese and overall populations.

The incidence of AEs and SAEs in the Japanese subgroup were similar to other studies of mepolizumab in non-Japanese populations.^{13,17,18} Overall, the incidence of common AEs experienced by patients was similar between routes of administration. Injection site reactions were uncommon, with only one case (7%) reported in the mepolizumab SC group, which was similar to the 9% of patients reporting this AE in the overall population of MENSA.¹⁵ There was no difference between the incidence of nasopharyngitis with mepolizumab SC and placebo in the Japanese subgroup, similar to results in the overall population. However, the incidence of nasopharyngitis was higher in the mepolizumab IV group compared with the other treatment groups in the Japanese subgroup. There were no differences in the immunogenicity profile (anti-mepolizumab antibodies and neutralizing antibodies) of patients treated with mepolizumab in the Japanese subgroup and overall population.

A limitation of this study was the relatively small sample size of Japanese patients in each treatment group. The MENSA¹⁵ trial was conducted across multiple study centers worldwide and consequently individual country sample sizes were small, reducing statistical power for comparing treatment differences within the Japanese subgroup. There may also have been differences between treatment centers in the way that pre-bronchodilator FEV₁ was measured, introducing inter-center variability. However, despite the relatively small sample size, this analysis suggested that the efficacy of mepolizumab in the Japanese population can be considered to be similar to that observed in the overall population.

In conclusion, mepolizumab treatment was efficacious in Japanese patients with severe eosinophilic asthma and had a clinically acceptable safety profile. No clinically relevant inter-ethnic differences between the Japanese and overall study population were found.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2016.11.006>.

Conflict of interest

AO is an employee of GSK. MKa, BM, SY and HOr are employees of GSK and hold stock/shares in GSK. MKo was an employee of GSK during the time of the study. The rest of the authors have no conflict of interest.

Authors' contributions

TS and HOD participated in data acquisition, analysis and interpretation. AO and BM contributed to analysis and interpretation. MKo, SY, and HOr contributed to the study concept and design and analysis and interpretation. MKa contributed to the study concept and design. All authors were involved in preparation and review of the manuscript and approved the final version to be submitted.

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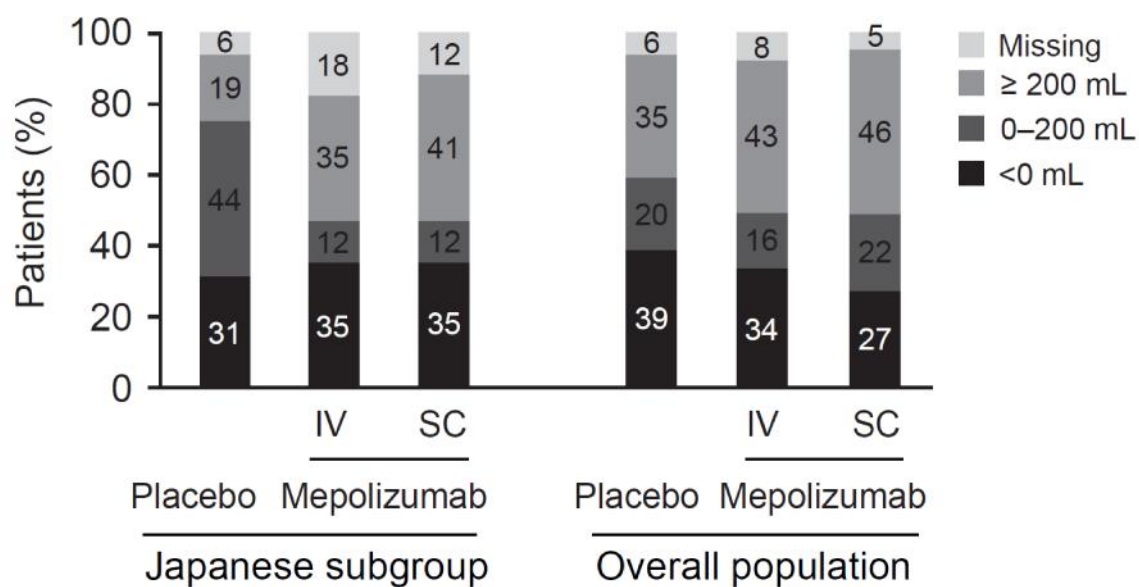
Supplementary Table 1. Change from baseline in pre-bronchodilator FEV₁ at Week 32 (mITT population).

	Japanese subgroup			Overall population		
	Placebo	Mepolizumab		Placebo	Mepolizumab	
	N=16	IV N=17	SC N=17	N=191	IV N=191	SC N=194
Pre-bronchodilator FEV₁ (mL)						
LS mean change from baseline (SE)	145 (81.7)	48 (84.7)	26 (81.0)	86 (31.4)	186 (31.5)	183 (31.1)
Difference from placebo (95% CI)	-	-97 (-336, 142)	-119 (-353, 114)	-	100 (13, 187)	98 (11, 184)
p-value	-	0.418	0.307	-	0.025	0.028

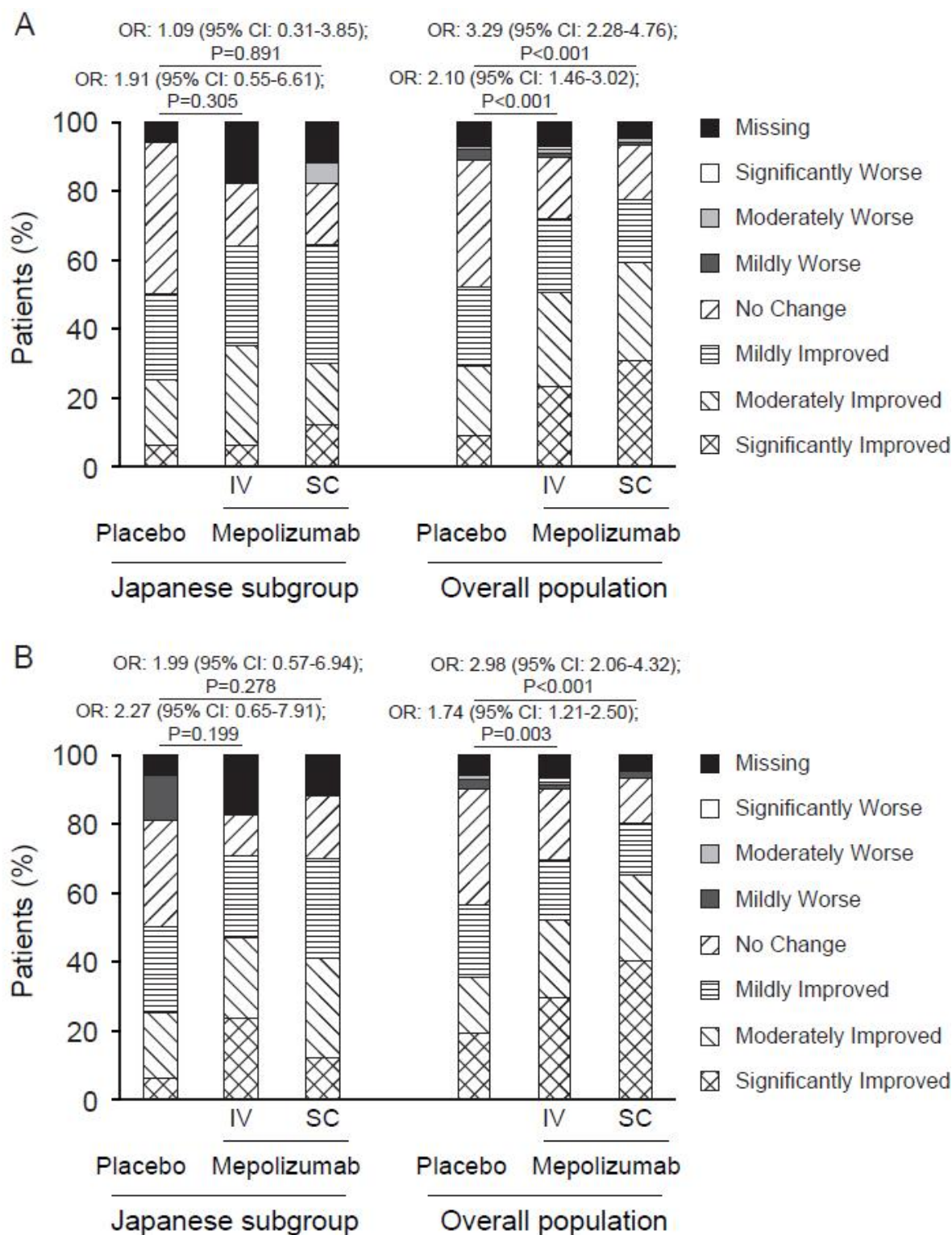
CI, confidence interval; FEV₁, forced expiratory volume in 1 second; IV, intravenous; LS, least squares; mITT, modified intent-to-treat; SE, standard error; SC, subcutaneous.

Supplementary Table 2. Physician and patient assessment of response to therapy (mITT population).

	Japanese subgroup			Overall population		
	Placebo	Mepolizumab		Placebo	Mepolizumab	
	N=16	IV N=17	SC N=17	N=191	IV N=191	SC N=194
Physician assessment of response to therapy						
Significantly improved	1 (6%)	1 (6%)	2 (12%)	18 (9%)	44 (23%)	60 (31%)
Moderately improved	3 (19%)	5 (29%)	3 (18%)	39 (20%)	51 (27%)	56 (29%)
Mildly improved	4 (25%)	5 (29%)	6 (35%)	44 (23%)	41 (21%)	35 (18%)
No change	7 (44%)	3 (18%)	3 (18%)	71 (37%)	36 (19%)	32 (16%)
Mildly worse	0	0	0	5 (3%)	2 (1%)	1 (<1%)
Moderately worse	0	0	1 (6%)	1 (<1%)	2 (1%)	1 (<1%)
Significantly worse	0	0	0	0	1 (<1%)	0
Missing	1 (6%)	3 (18%)	2 (12%)	13 (7%)	14 (7%)	9 (5%)
Patient assessment of response to therapy						
Significantly improved	1 (6%)	4 (24%)	2 (12%)	37 (19%)	57 (30%)	78 (40%)
Moderately improved	3 (19%)	4 (24%)	5 (29%)	31 (16%)	43 (23%)	48 (25%)
Mildly improved	4 (25%)	4 (24%)	5 (29%)	40 (21%)	34 (18%)	30 (15%)
No change	5 (31%)	2 (12%)	3 (18%)	63 (33%)	40 (21%)	26 (13%)
Mildly worse	2 (13%)	0	0	6 (3%)	2 (1%)	3 (2%)
Moderately worse	0	0	0	2 (1%)	1 (<1%)	0
Significantly worse	0	0	0	0	1 (<1%)	0
Missing	1 (6%)	3 (18%)	2 (12%)	12 (6%)	13 (7%)	9 (5%)



Supplementary Figure 1. Proportion of patients with a ≥ 200 mL increase from baseline in pre-bronchodilator FEV₁ at Week 32 (mITT population).
FEV₁, forced expiratory volume in 1 second; IV, intravenous; mITT, modified intent-to-treat; SC, subcutaneous.



Supplementary Figure 2. Physician (A) and patient (B) assessment of response to therapy (mITT population).

CI, confidence interval; IV, intravenous; mITT, modified intent-to-treat; OR, odds ratio; SC, subcutaneous.