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Early View

Original research article

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Stopping vs continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study)

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Take-home

This randomized study demonstrates increased exacerbation risk and a decrease in asthma control in patients with severe eosinophilic asthma who stop mepolizumab treatment after long-term use, when compared with those who continue treatment.

Author contributions: MJG and RGP were involved in the conception or design of the work; WCM, OK, MH, CP, EHB, NK, and MCL were involved in the acquisition of data; all authors were involved in drafting the work or revising it critically for important intellectual content (ie, data analysis and interpretation); and all authors agreed to the submission and to be accountable for all aspects of the work.

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WCM has received funding for clinical research and personal fees for participation in advisory boards from GSK, AstraZeneca and Sanofi Regeneron. OK has received personal fees from AstraZeneca, GSK, Novartis, Boehringer Ingelheim, Sanofi Aventis, and Roche. MH has received personal fees for consultancy services and speaking at conferences, and participation in clinical research projects with AstraZeneca, GSK, Novartis, Roche, Sanofi Regeneron and TEVA; he has a research grant from GSK. CP has received personal fees from GSK, Novartis, Sanofi, and Boehringer Ingelheim. EHB reports grants from GSK and Teva; and personal fees from AstraZeneca, GSK, Novartis, Sanofi/Regeneron, Sterna Biologicals and Chiesi. NK reports that he has nothing to declare. MCL has received grants for clinical trials from Boehringer Ingelheim, GSK, MedImmune, Mereo BioPharm, and Gossamer Bio. SGS, NM, MJG, and RGP are employees of GSK and own stocks/shares. ESB was an employee at GSK at the time of the study.

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Abstract

The long-term efficacy and safety of mepolizumab for treatment of severe eosinophilic asthma are well established. Here, we examine the clinical impact of stopping mepolizumab after long-term use.

COMET (NCT02555371) was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients who had completed COLUMBA (NCT01691859) or COSMEX (NCT02135692) and received continuous mepolizumab treatment for ≥3 years were randomized 1:1 to stop (switch to placebo) or continue subcutaneous mepolizumab 100 mg every 4 weeks for 52 weeks. Primary endpoint: time to first clinically significant exacerbation; secondary endpoints: time to first exacerbation requiring hospitalization/emergency department visit, time to decrease in asthma control (≥0.5-point increase in Asthma Control Questionnaire-5 score from COMET baseline), and blood eosinophil count ratio to COMET baseline. Safety was assessed.

Patients stopping (n=151) versus continuing (n=144) mepolizumab had significantly shorter times to first clinically significant exacerbation (hazard ratio: 1.61 [95% confidence interval: 1.17,2.22]; *P*=0.004) and decrease in asthma control (hazard ratio: 1.52 [1.13,2.02]; *P*=0.005), and higher blood eosinophil counts at Week 52 (270 vs 40 cells/µL; ratio [stopping vs continuing]: 6.19 [4.89,7.83]; *P*<0.001). Differences in efficacy outcomes between groups were observed when assessed from Week 12 (16 weeks after last mepolizumab dose). Exacerbations requiring hospitalization/emergency department visit were rare. Adverse events in patients continuing mepolizumab were consistent with previous studies. For patients who stopped mepolizumab, the safety profile was consistent with other eosinophilic asthma populations.

Patients who stopped mepolizumab had an increase in exacerbations and reduced asthma control versus those who continued.

Clinical trial identifier: 201810/www.clinicaltrials.gov/ct2/show/NCT02555371.

Key words: severe eosinophilic asthma, exacerbations, asthma control, mepolizumab, eosinophils, long-term, discontinuing, continuing, biologic therapy, monoclonal antibody

Introduction

Efficacy and safety of long-term treatment with the targeted, humanized, anti-interleukin-5 (IL-5) monoclonal antibody mepolizumab in patients with severe eosinophilic asthma have been demonstrated for up to 4.5 years in previous double-blinded [1-5] and open-label studies [6-8]. Mepolizumab is approved for the treatment of severe eosinophilic asthma in multiple regions worldwide, and for the treatment of eosinophilic granulomatosis with polyangiitis in adults in the USA and Japan and for the treatment of hypereosinophilic syndrome in patients aged ≥12 years in the USA [9, 10]. Mepolizumab selectively binds to IL-5, inhibiting eosinophilic inflammation [11, 12]; however, it is currently unknown whether the suppression of eosinophilic airway inflammation seen with mepolizumab in severe eosinophilic asthma continues if patients stop treatment, or whether long-term treatment should be recommended for sustained disease control.

A previous 12-month, observational follow-up study of patients who stopped mepolizumab 750 mg intravenous (IV) treatment after 1 year suggested an increase in blood eosinophil counts to pre-treatment levels and a subsequent return to an exacerbating phenotype [13]. Understanding responses after stopping is of interest, as long-term treatment may have a sustained disease modifying effect and potentially permanently reduce eosinophil counts [14]. However, there are no data on the impact of stopping in patients treated with mepolizumab for longer than 1 year, which is important as short-term discontinuation may be required for some patients in clinical practice. Additionally, there are no data on the impact of stopping the licensed mepolizumab dose in adults and adolescents, 100 mg subcutaneously (SC).

The aim of this randomized, placebo-controlled study was to evaluate the clinical impact of stopping mepolizumab 100 mg SC in patients with severe eosinophilic asthma following long-term (≥3 years) exposure by assessing exacerbation rates and other clinical parameters in those who stopped mepolizumab (and switched to placebo) versus those who continued. A visual summary of the COMET study is presented in the **Supplementary Materials, Figure E1**.

Materials and Methods

Study design

COMET (GSK ID 201810; NCT02555371) was a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare stopping versus continuation of long-term mepolizumab treatment in patients with severe eosinophilic asthma.

The study comprised four parts (**Figure 1**). Following screening, patients with <3 years of mepolizumab treatment entered Part A, a variable open-label run-in period of 0 to 132 weeks designed to ensure all patients had received continuous mepolizumab 100 mg SC (in addition to standard of care) for ≥3 years. Once patients had ≥3 years of mepolizumab exposure they entered Part B, which consisted of a fixed open-label run-in of 4 to 8 weeks during which open-label mepolizumab (100 mg SC every 4 weeks plus standard of care) was administered and baseline information was collected. Patients who had ≥3 years of mepolizumab treatment at screening entered Part B directly. Following Part B, patients were randomized 1:1 to stop mepolizumab treatment and switch to placebo (plus standard of care) or receive continued mepolizumab 100 mg SC plus standard of care every 4 weeks for 52 weeks (Part C). Patients with ≥1 clinically significant exacerbation (see **Supplementary Materials**) during Part C were assessed by the study investigator to determine whether the patient should continue taking double-blind study treatment (continue in Part C) or return to open-label mepolizumab 100 mg SC every 4 weeks (switch to Part D [optional, see **Supplementary Materials**]) for the remainder of the study (up to 52 weeks post randomization). No formal criteria for treatment continuation were provided to investigators; the decision was based on the opinion of the treating physician in collaboration with the patient. Patients remained on a stable standard of care asthma therapy from the start of Part B to the end of the study. The reported results focus mainly on the blinded, randomized Part C.

The study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), all applicable patient privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. All patients provided written informed consent prior to study participation.

Patients

Patients with severe eosinophilic asthma who had completed one of the previous open-label studies, COLUMBA (MEA115666; NCT01691859) [7] or COSMEX (201312; NCT02135692) [8], were eligible for COMET (**Supplementary Materials**). To enter the study, patients had to have completed and received continuous mepolizumab treatment (ie, no treatment gaps >12 weeks [84 days, equivalent

to >2 consecutive missed doses] between any two mepolizumab doses), and remained adherent on asthma controller medication/therapy, throughout the previous open-label mepolizumab studies.

Exclusion criteria, randomization criteria for entry to Part C and details of randomization and blinding are listed in the **Supplementary Materials**.

Endpoints and assessments

The primary endpoint was time to the first clinically significant exacerbation during Part C (post randomization). Secondary endpoints were: time to the first exacerbation requiring hospitalization or emergency department (ED) visit; time to a decrease in asthma control, defined as an increase from baseline (start of double-blind treatment in COMET) in Asthma Control Questionnaire-5 (ACQ-5) score of ≥0.5 units [15]; and ratio to baseline in blood eosinophil count at Weeks 12, 24, 36, and 52. Other endpoints included time to the first exacerbation requiring hospitalization, mean change from baseline in ACQ-5 score assessed every 4 weeks until Week 52, and mean change from baseline in health-related quality of life (as assessed by St George's Respiratory Questionnaire [SGRQ] total score) and clinic pre-bronchodilator forced expiratory volume in 1 second (FEV_1) at Weeks 12, 24, 36, and 52. Safety endpoints included adverse events (AEs) and serious AEs; clinical laboratory parameters; 12-lead electrocardiogram (ECG) parameters; and vital signs.

Sample size and statistical analysis

The sample size was based on the primary endpoint of time to first clinically significant exacerbation to test the superiority of continued mepolizumab treatment compared with stopping mepolizumab (randomized to placebo).

The intent-to-treat (ITT) population, used for all efficacy and safety data analyses, comprised all randomized patients who received ≥1 dose of double-blind study treatment. For all change from/ratio to baseline endpoints, baseline was defined as the start of double-blind treatment (randomization) in COMET. Only relevant data from Part C were included in the analysis of the double-blind period, with on-treatment data censored following the discontinuation of double-blind treatment or switch to open-label mepolizumab within Part D. Further details of the sample size and statistical analyses are provided in the **Supplementary Materials**. Additionally, a post hoc analysis was performed to evaluate whether baseline characteristics can identify patients with a greater or reduced treatment effect following stopping or continuing long-term mepolizumab treatment and further information can be found in the **Supplementary Materials.**

Results

Patient population

Patient disposition from previous studies is shown in **Figure E2**. Between January 2016 and November 2017, 306 patients were enrolled in Parts A/B and 295 patients were randomized in Part C (placebo: n=151; mepolizumab: n=144) (**Figure E3**). Of these, 129 patients, 84 who had received placebo in Part C and 45 who had received mepolizumab in Part C, switched to open-label mepolizumab (Part D) following an asthma exacerbation (**Figure E4**); the most common reason for switching in both groups was a reported lack of efficacy in the opinion of the investigator (n=81 and n=42, where n=81 and n=41 reported exacerbation as a sub-reason, respectively). The study was completed in July 2019.

Demographic and disease characteristics at the first Part C visit were similar between the placebo and mepolizumab groups (**Table 1**). The geometric mean blood eosinophil counts were similar in both groups at the start of Part C (placebo 40 cells/μL; mepolizumab 50 cells/μL), and were decreased compared with baseline values before any mepolizumab treatment in DREAM, MENSA, and SIRIUS (230 to 320 cells/μL; **Table E2**). Demographic and disease characteristics were also similar before any treatment with mepolizumab for each group in COMET (e.g. at DREAM, MENSA, and SIRIUS baseline [**Table E3**]).

Prior to randomization in Part C, the median (range) duration of mepolizumab treatment was 44.1 (32–59) months, equating to 1145.2 patient-years of exposure (**Table 1**). Two patients who had 32 months of continuous mepolizumab exposure were randomized prematurely to Part C and subsequently identified as protocol deviations. During the double-blind Part C period, a greater proportion of patients in the placebo arm (56%, n=84/151) switched to open-label mepolizumab treatment (Part D) than in the mepolizumab arm (31%, n=45/144; **Figures E3 and E4)**. Consequently, the total exposure to double-blind treatment was longer for the mepolizumab group (114.6 patient-years) compared with placebo (93.9 patient-years; **Table 1**).

Primary endpoint

Patients who stopped mepolizumab had a significantly shorter time to first clinically significant exacerbation than patients who continued; they had a 61% increase in the risk of experiencing their first clinically significant exacerbation (stopping/continuing mepolizumab HR 1.61 [95% confidence interval (CI) 1.17, 2.22]; *P*=0.004) over the 52-week Part C period (**Figure 2A**). A significantly higher proportion of patients who stopped mepolizumab (placebo group) experienced ≥1 clinically significant exacerbation during Part C compared with those continuing mepolizumab treatment (59%

vs 46%; odds ratio 1.99 [95% CI: 1.19, 3.32]; p=0.009; **Table E4**). The Kaplan–Meier cumulative incidence of patients experiencing an exacerbation was numerically higher with placebo versus mepolizumab, respectively, at each time point: between-treatment differences were detected from Week 12 (31.8% and 20.2%), and grew progressively greater through Week 24 (49.3% and 32.3%), Week 36 (56.0% and 40.3%), and Week 52 (60.7% and 47.1%). Overall, 22 (15%) patients in the placebo group and 19 (13%) patients in the mepolizumab group experienced ≥2 exacerbations while on treatment during Part C.

Secondary and other endpoints

Exacerbations requiring hospitalization or ED visit occurred in 7 (5%) patients who stopped mepolizumab treatment (9 events; 1 patient experienced 3 events requiring ED visit and was never switched to Part D; 6 patients experienced a single exacerbation requiring hospitalization, 5 of whom were immediately switched to Part D). For patients who continued mepolizumab, 10 (7%) experienced a single event of this severity (8 patients had an ED visit, 7 of whom were switched to Part D; the remaining 2 patients required hospitalization and both were immediately switched to Part D).

Patients who stopped mepolizumab treatment had a significantly shorter time to first decrease in asthma control during Part C; they had a 52% increase in risk of having a decrease in asthma control over the 12-month period (stopping/continuing mepolizumab HR 1.52 [95% CI 1.13, 2.02]; *P*=0.005) (**Figure 2B**). The Kaplan–Meier cumulative incidence of patients experiencing a decrease in asthma control was higher with placebo versus mepolizumab, respectively, at each time point: between-treatment differences were detected from Week 12 (44.5% and 39.3%) and increased through Week 24 (69.5% and 49.3%), Week 36 (74.9% and 56.0%), and Week 52 (79.0% and 63.1%). Worsening asthma control, as indicated by increased ACQ-5 scores, was seen from Week 12 (16 weeks after the last dose of open-label mepolizumab) in patients who stopped mepolizumab treatment compared with those who continued, although 95% CIs overlapped at each time point (**Figure 3A**). By Week 52, the difference (95% CI) in ACQ-5 scores for patients stopping versus continuing mepolizumab was 0.23 (-0.02, 0.48; *P*=0.067).

In patients who stopped mepolizumab, least squares (LS) mean (standard error [SE] logs) blood eosinophil counts increased steadily from Week 4 (8 weeks after the last dose of open-label mepolizumab), reaching 270 (0.077) cells/µL by Week 12 (16 weeks after patients' last dose of open-label mepolizumab), while patients continuing mepolizumab maintained their LS mean blood eosinophil count at 40–60 cells/µL (Week 12 stopping vs continuing mepolizumab ratio: 5.21 [95% CI 4.20, 6.46]; *P*<0.001). By Week 52, blood eosinophil counts were 270 (0.091) cells/µL and 40 (0.077)

cells/μL for patients stopping versus continuing mepolizumab, respectively (stopping vs continuing mepolizumab ratio: 6.19 [95% CI 4.89, 7.83]; *P*<0.001) (**Figure 3B**). Absolute blood eosinophil counts are shown in **Table E5**.

Health-related quality of life (change from baseline in SGRQ total score) and lung function (change from baseline in pre-bronchodilator FEV_1) were measured at Weeks 12, 24, 36, and 52, with worsening seen for both endpoints at all time points in patients who stopped mepolizumab; patients who continued mepolizumab experienced sustained benefit in these outcomes, although 95% CIs overlapped at most timepoints (**Figure 3C-D**). By Week 52, the difference (95% CI) in SGRQ total scores and pre-bronchodilator FEV_1 for patients stopping versus continuing mepolizumab was 3.3 (-0.8, 7.5; *P*=0.113) and -56 mL (-139, 27; *P*=0.186).

Post hoc analysis

Our post hoc analysis showed that the number of exacerbations in the year prior to randomization (0, 1, ≥2) was a strong prognostic factor for risk of exacerbation during the 52-week trial period, with an increasing risk of exacerbation during Part C associated with a greater number of exacerbation events in the year prior to randomization. Patients with ≥2 exacerbations in the previous year (n=44) had a higher risk of exacerbation versus those with 0 (n=185) or 1 (n=66) exacerbation (**Figure E5**). Additionally, stopping versus continuing mepolizumab increased the risk of first exacerbation by 74% (HR [95% CI]: 1.74 [1.08,2.80]) and 180% (2.80 [1.44,5.44]), respectively in patients who had 0 or 1 exacerbation in the previous year; however, this increased risk was not seen for patients with ≥2 exacerbations in the previous year (0.88 [0.46,1.67]). No other baseline characteristic assessed identified a differential treatment effect across subgroups.

Safety

The safety profile of mepolizumab was consistent with previous trials (**Table E6**). In part C, a lower proportion of patients on placebo reported AEs than those on mepolizumab (64% vs 78%, respectively); however, exposure per patient-year was lower in the placebo group than in the mepolizumab group (93.94 vs 114.60). Exposure-adjusted rates (per 1000 participant-years) were similar between the treatment arms (placebo, 3097.77; mepolizumab, 2740.01; **Table E7**). A similar proportion of patients in the placebo and mepolizumab groups reported serious AEs (SAEs; 7% vs 6%), none of which were considered by the treating investigator to be related to treatment. Infections were reported in a lower proportion of patients in the placebo group compared with the mepolizumab group (44% vs 58%), with similar exposure-adjusted rates between the treatment arms (1373.24 and 1160.58 per 1000 participant-years, respectively). Local site reactions also

occurred in a lower proportion of placebo-treated versus mepolizumab-treated patients (<1% vs 3%). There were two reported deaths, one during Part C (post treatment, unknown cause) and one during Part D (on-treatment, pneumonia aspiration); both deaths were in patients who received placebo during Part C and both were considered to be unrelated to study treatment.

Discussion

This is the first, randomized study to examine the clinical impact of stopping mepolizumab treatment after long-term use in patients with severe eosinophilic asthma. The time to first clinically significant exacerbation was significantly shorter for those who stopped mepolizumab compared with those who continued mepolizumab treatment. In total, 59% of patients who stopped mepolizumab experienced ≥1 clinically significant exacerbation in the following year, compared with 46% of those who remained on mepolizumab. Worsening of ACQ-5 and SGRQ scores were seen at Week 12 (16 weeks after the last dose of open-label mepolizumab), whereas scores were maintained in those who continued mepolizumab. This suggests a loss of asthma control and quality of life in patients who stop mepolizumab treatment, even after ≥3 years of use. Therefore, the beneficial effects of mepolizumab, evident in the baseline characteristics at the start of double-blind treatment in COMET, are unlikely to be sustained after stopping treatment. These results also highlight the sustained clinical benefit in patients who remain on mepolizumab treatment. Overall, compared with patients who stopped mepolizumab, patients who continued long-term treatment were less likely to experience exacerbations and loss of asthma control, with sustained benefits also shown in health-related quality of life and lung function. The probability of a clinically significant exacerbation and decreased asthma control appeared to increase from around Week 12 (16 weeks after the last dose of open-label mepolizumab) for patients who stopped versus continued mepolizumab.

There were differences in blood eosinophil counts between those who stopped mepolizumab and those who continued, in accordance with the mechanism of action of mepolizumab [9]; these differences were seen as early as Week 4 (8 weeks after the last dose of open-label mepolizumab). Blood eosinophil counts increased slowly; by Week 12 (16 weeks after stopping mepolizumab) they had returned to values similar to baseline at the start of the initial Phase III studies (270 cells/μL vs 230–320 cells/μL) [1, 3, 4]. This is consistent with the publication by Haldar et al., which demonstrated a return to pre-treatment blood eosinophil counts after stopping therapy [13]. Importantly, changes in blood eosinophil counts preceded the separation in efficacy between the placebo and mepolizumab arms during Part C. This supports previous findings demonstrating that the pharmacodynamic effects of mepolizumab on blood eosinophil counts are not sustained after

stopping treatment [13], and further confirms the association between clinical outcomes and blood eosinophil counts [1, 3, 4, 16-19].

Although 59% of patients who stopped mepolizumab experienced ≥1 clinically significant exacerbation in the year after stopping treatment, 41% experienced no clinically significant exacerbations during this period. However, this is consistent with the proportion of patients who experienced no exacerbations while receiving placebo during the previous mepolizumab trials [1, 3-5], and in a similar 12-week trial of dupilumab [20]. For example, in MENSA, 45% of patients receiving placebo did not experience an exacerbation over the 32-week treatment period [4], while the equivalent proportions from SIRIUS (24 weeks), DREAM (52 weeks), MUSCA (24 weeks) and the dupilumab trial (12 weeks) were 32%, 33%, 59%, and 56%, respectively [1, 3, 5, 20]. These findings highlight the frequency of exacerbations in patients with a severe eosinophilic asthma phenotype. The fact that some patients experienced exacerbations while receiving mepolizumab treatment also supports heterogeneity within the phenotype whereby factors other than eosinophils may contribute to exacerbations [21]. Nonetheless, the stability of exacerbating asthma phenotypes over a given time period is currently unknown [22-25], and it is feasible that patients who have a history of severe exacerbations while on standard of care treatment may remain exacerbation free for indeterminant periods and then return to an exacerbating phenotype [26].

In the XPORT study, 48% of patients who stopped omalizumab treatment remained exacerbation free in the following year, similar to the 41% of patients in COMET who did not exacerbate after stopping mepolizumab [27]. As highlighted previously, this is likely due to the variability of exacerbation incidence in the severe eosinophilic asthma population. Additionally, as shown in COMET, a higher proportion of patients who stayed on omalizumab (67%) did not exacerbate in the 1-year study period compared with those who stopped treatment (48%) [27]. This is in line with the 54% of patients who remained exacerbation free while continuing on mepolizumab in COMET.

It may be useful to determine the characteristics or adherence of patients who did not return to an exacerbating phenotype within 12 months of stopping mepolizumab treatment, and indeed to determine whether these patients had any other markers of sustained treatment benefit outside of exacerbations. This information may then be used to determine if there are any patients who can stop mepolizumab without any subsequent loss of control during a 52-week period after a sustained period of treatment, although clinical studies would be needed to confirm. It is therefore of interest that the number of exacerbations in the year prior to COMET randomization was a strong prognostic factor to predict future exacerbation risk, and was the only baseline characteristic assessed that identified a differential treatment effect across subgroups in the risk of exacerbations after stopping

versus continuing mepolizumab. The subgroup of patients with ≥2 exacerbations in the previous year was identified as potentially observing less protection from clinically significant exacerbations with mepolizumab, with no treatment benefit observed in this patient subgroup. It should be stressed however that this subgroup of patients was small and identified following post hoc subgroup analysis, so this finding should be interpreted with caution and considered as hypothesis generating. Further studies are required to understand the impact of discontinuing mepolizumab in patients with ≥2 exacerbations in the previous year whilst receiving continuous treatment.

No new safety concerns were observed in this study population compared with those seen in previous studies [1, 3-8]. Additionally, rates of AEs were similar for patients who stopped mepolizumab and then switched back to mepolizumab treatment following an exacerbation, compared with those who received mepolizumab continuously throughout the study.

One strength of the current study is the monitoring and maintenance of background therapy throughout Part C, with no changes recommended per protocol. However, patients were selected from a population who had completed previous mepolizumab clinical trials; therefore, patient recruitment was biased toward those who responded to mepolizumab, and those without AEs leading to discontinuation from the previous studies. In addition, only around 50% of patients from COLUMBA and COSMEX were enrolled in COMET. Patients may have been reluctant to enroll on a placebo-controlled study, particularly in those countries where mepolizumab became commercially available prior to the start of COMET. In addition, patients may also have experienced an amelioration of disease activity after long term mepolizumab treatment, which may have led to a reduction or discontinuation of their background medications; as patients had to be adherent on asthma controller medication/therapy throughout the previous open-label mepolizumab studies to be eligible for COMET, this may have reduced enrolment. A further limitation was the very small proportion of black patients included in COMET owing to the limited representation of this population in the parent Phase III trials. Additionally, whilst worsening of ACQ-5 and SGRQ scores and worsening FEV_1 were seen at Week 12 for patients who stopped mepolizumab, this study was not designed to be powered to measure statistical significance for these endpoints.

Further, results are based on lower numbers of patients at the later versus earlier time points within Part C with a subset of patients from both arms having discontinued double-blind treatment and switched to Part D. This is likely due to the study design, which called for an investigator assessment for patients who experienced a clinically significant exacerbation during Part C to determine whether a switch to open-label mepolizumab in Part D would be appropriate. This issue was mitigated by the use of a hypothetical estimand strategy applied in the handling of the intercurrent event of

discontinuation of double-blind treatment. The treatment effects reported in Part C therefore refer to the outcomes if all patients had continued to take double-blind treatment throughout the 52-week double-blind period. Analyzing an annualized exacerbation rate during the double-blind treatment period (Part C) was not possible, due to patients being permitted to switch to open-label treatment following their first exacerbation, which meant that repeat exacerbations were not expected by study design.

The investigator assessments during Part C may also have contributed to the low number of exacerbations requiring hospitalization and/or ED visit, as patients may have been switched to open-label mepolizumab before a more severe exacerbation occurred. Due to the rarity of these more severe exacerbation events during Part C, which was consistent with prior trials of mepolizumab [4, 6, 8], any differences between treatment groups should be interpreted with caution. Finally, as this is a double-blind randomized controlled trial, the decisions taken to stop mepolizumab or switch to open-label treatment may not reflect routine clinical practice where the patient's treatment is known, as both patients and physicians were blinded to whether they were on mepolizumab or placebo. Consequently, the finding that of the 45 patients receiving mepolizumab in Part C who switched to Part D, 42 switched due to a reported lack of efficacy (in the opinion of the investigator) should be interpreted with caution. Of these 42 patients, 41 also reported exacerbation as a sub-reason for switching. It is possible that investigators may have switched patients to open-label treatment at the first opportunity (i.e. following their first clinically significant exacerbation) as permitted by study design; this would have enabled patients to return to their established effective therapy, which has been received for at least the previous 3 years. Indeed, most patients who switched to Part D to continue mepolizumab in an open-label setting continued mepolizumab treatment until study end with few withdrawals.

In conclusion, by 12 weeks (16 weeks after the last dose of open-label mepolizumab) patients who stopped long-term (≥3 years) mepolizumab treatment had a shorter time to first clinically significant exacerbation, an increase in blood eosinophil counts back to pre-treatment levels, and a reduction in asthma control, quality of life, and lung function compared with those who continued mepolizumab. These results support continued mepolizumab treatment having sustained clinical benefits in patients with severe eosinophilic asthma and further support that blood eosinophils are a suitable biomarker for treatment response to mepolizumab.

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Data sharing

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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Tables

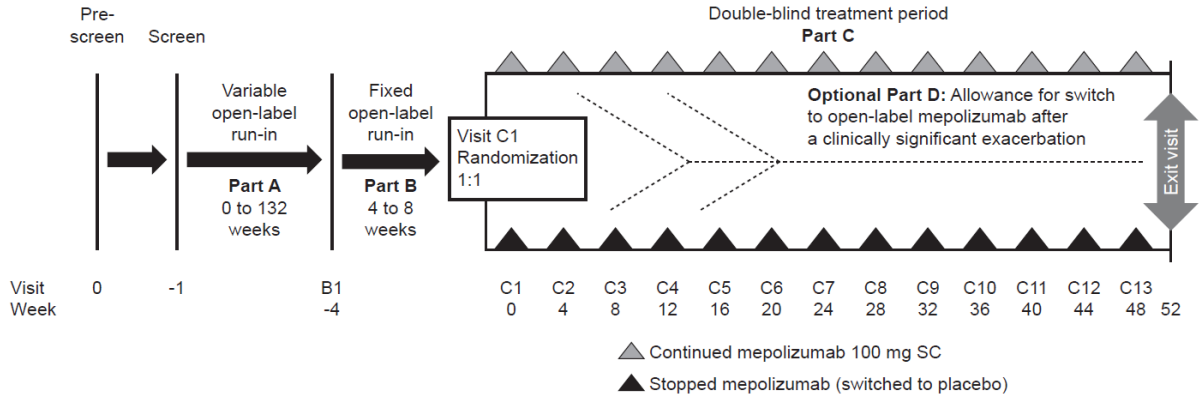
Table 1. Demographics and asthma characteristics of patients on long-term mepolizumab at first clinic visit in Part C and study treatment exposure.

	Stopped mepolizumab (switched to placebo) (N=151)	**Continued mepolizumab 100 mg SC (N=144)**	**Total (N=295)**
Females, n (%)	86 (57)	87 (60)	173 (59)
Age, years, mean (SD)	55.7 (11.42)	56.6 (11.53)	56.1 (11.46)
Race, n (%) Asian Black White	 24 (16) 2 (1) 125 (83)	 24 (17) 5 (3) 115 (80)	 48 (16) 7 (2) 240 (81)
Body mass index, kg/m^2, mean (SD)	28.0 (5.63)	29.1 (6.29)	28.5 (5.98)
Duration of asthma, years, mean (SD)	22.8 (13.82)	25.1 (14.54)	23.9 (14.20)
Current concomitant medication*, n (%) LABA ICS	 145 (96) 146 (97)	 141 (98) 137 (95)	 286 (97) 283 (96)
Using maintenance OCS, n (%) Median (range) dose, mg/day (prednisone equivalent)	17 (11) 5.0 (0.0–20.0)	21 (15) 5.0 (0.0–20.0)	38 (13) 5.0 (0.0–20.0)
Blood eosinophil count, cells/µL, geometric mean (SD of log)	40 (0.870)	50 (0.881)	50 (0.876)
Exacerbations in previous year, mean (SD)	0.6 (1.08)	0.8 (1.51)	0.7 (1.31)
Exacerbations requiring hospitalization or ED visit in the previous year, n (%)	5 (3)	5 (3)	10 (3)
Exacerbations requiring hospitalization in the previous year, n (%)	4 (3)	3 (2)	7 (2)
ACQ-5 score, mean (SD)	1.2 (1.04)	1.4 (1.05)	1.3 (1.05)
SGRQ total score, mean (SD)	32.2 (17.82)	33.1 (17.42)	32.7 (17.60)
Pre-bronchodilator FEV_1, mL, mean (SD)	1921 (655)	1774 (666)	1849 (663)
% predicted pre-bronchodilator FEV_1, mean (SD)	65.5 (19.64)	61.6 (19.08)	63.6 (19.43)
Mepolizumab continuous exposure prior to randomization at Visit C1 Time on mepolizumab, months, median (range) Total exposure, patient-years	 44.1 (36–59) 588.0	 43.6 (32–58) 557.2	 44.1 (32–59) 1145.2
Smoking history, n (%) Never smoked Former smoker	 128 (85) 23 (15)	 123 (85) 21 (15)	 251 (85) 44 (15)
Study treatment exposure during COMET (Part C) Total exposure, patient-years	 93.9	 114.6	 208.5

*Only selected concomitant medications are shown; ACQ, Asthma Control Questionnaire; ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroids; SC, subcutaneous; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Figure Legends

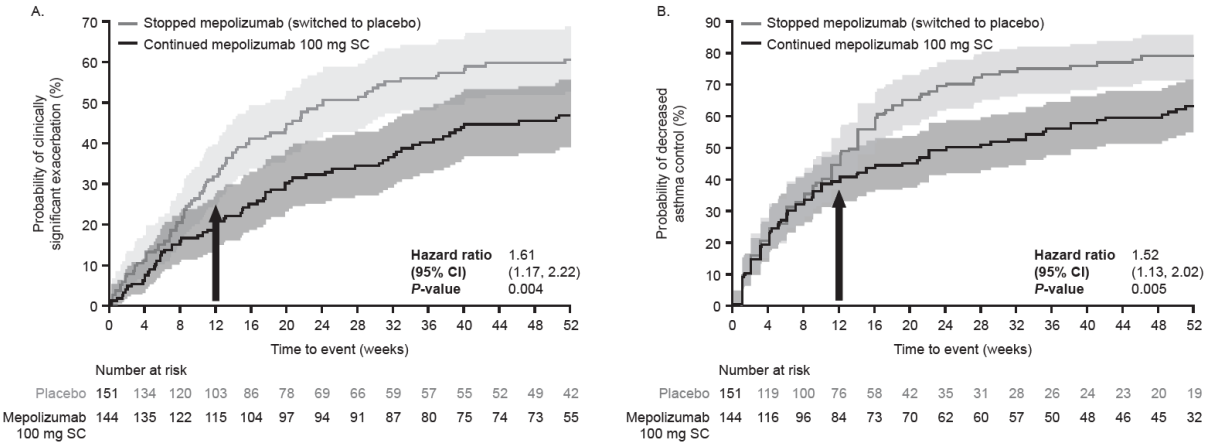
Figure 1. Study design and description of the individual study parts.



Phase	Phase title	Duration	Treatment arms
Part A	Variable open-label run-in	0–132 weeks	Open-label mepolizumab (100 mg SC) every 4 weeks for patients with <3 years mepolizumab treatment
Part B	Fixed open-label run-in	4–8 weeks	Open-label mepolizumab (100 mg SC) every 4 weeks
Part C	Double-blind treatment period	52 weeks	Patients randomized 1:1 to double-blind study treatment: • Mepolizumab 100 mg SC every 4 weeks • Placebo administered SC every 4 weeks
Part D	Open-label switch (optional following exacerbation)	Up to 52 weeks post randomization	Open-label mepolizumab (100 mg SC) every 4 weeks

SC, subcutaneous.

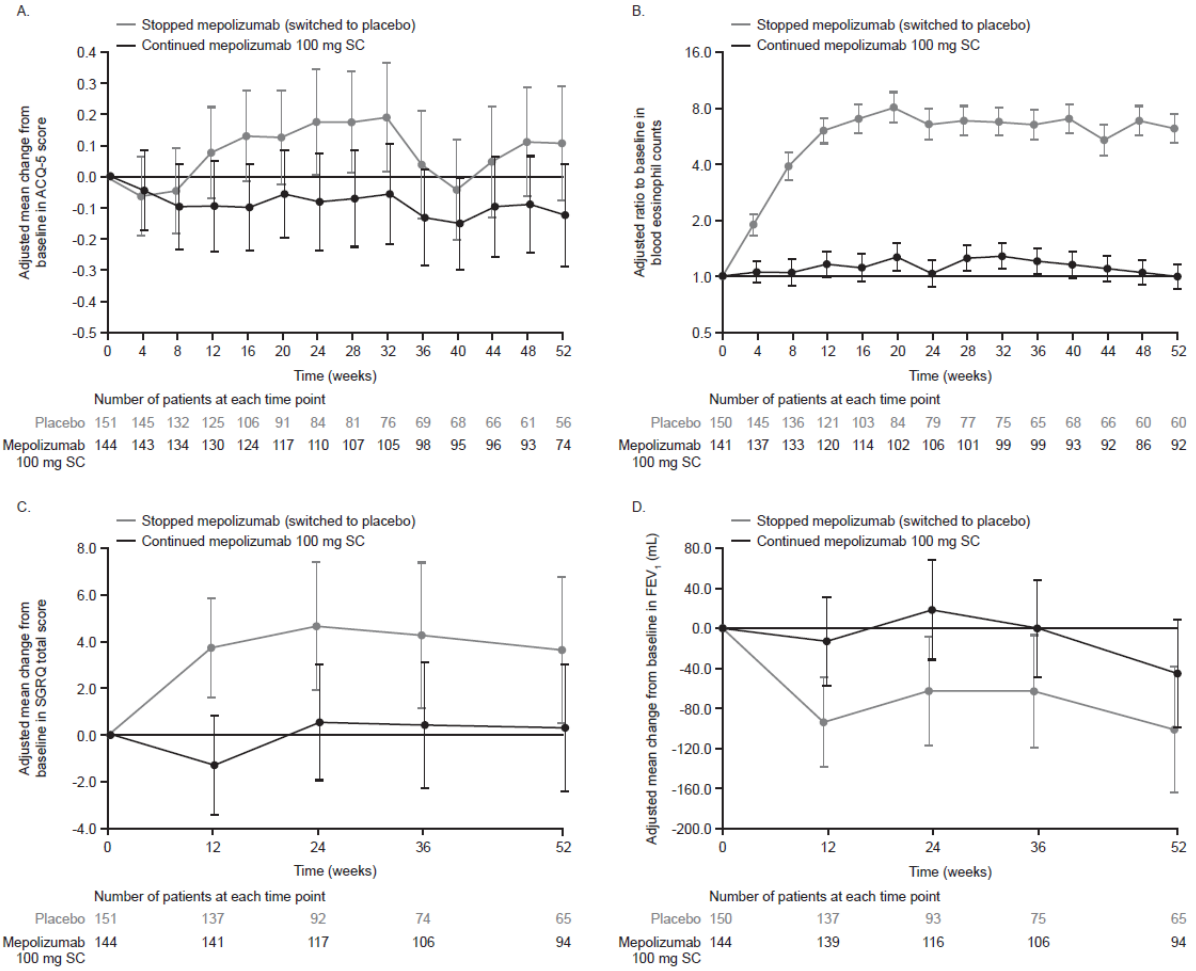
Figure 2. Kaplan–Meier cumulative incidence curve for time to first A) clinically significant exacerbation; B) decrease in asthma control, defined as an increase from baseline in ACQ-5 score of ≥0.5 units [15], and the associated hazard ratios (stopping/continuing mepolizumab) (on-treatment; Part C; blinded treatment).



Week 0 represents 4 weeks following the last dose of open-label mepolizumab. Shaded areas represent 95% CIs. Arrows indicate that the difference between groups was seen from Week 12 onwards (16 weeks after the last dose of open-label mepolizumab).

ACQ-5, Asthma Control Questionnaire-5; CI, confidence interval; SC, subcutaneous.

Figure 3. A) Mean change from baseline (start of double-blind treatment in COMET) in ACQ-5 score, B) ratio to baseline in blood eosinophil count, C) mean change from baseline in SGRQ total score, and D) mean change from baseline in pre-bronchodilator FEV_1 (on-treatment; Part C; blinded treatment).



Week 0 represents 4 weeks following the last dose of open-label mepolizumab. Data are LS means ± 95% CIs in panels A–D. Patient numbers at each given timepoint are shown below each graph. Higher scores on the ACQ-5 indicate worse control (range 0–6); a change of 0.5 points is the minimal clinically important difference [15]. Higher scores on the SGRQ indicate a worse function (range: 0–100); a change of 4 points is the minimal clinically important difference [28].

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LS, least squares; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire.

Supplementary materials

Stopping versus continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study)

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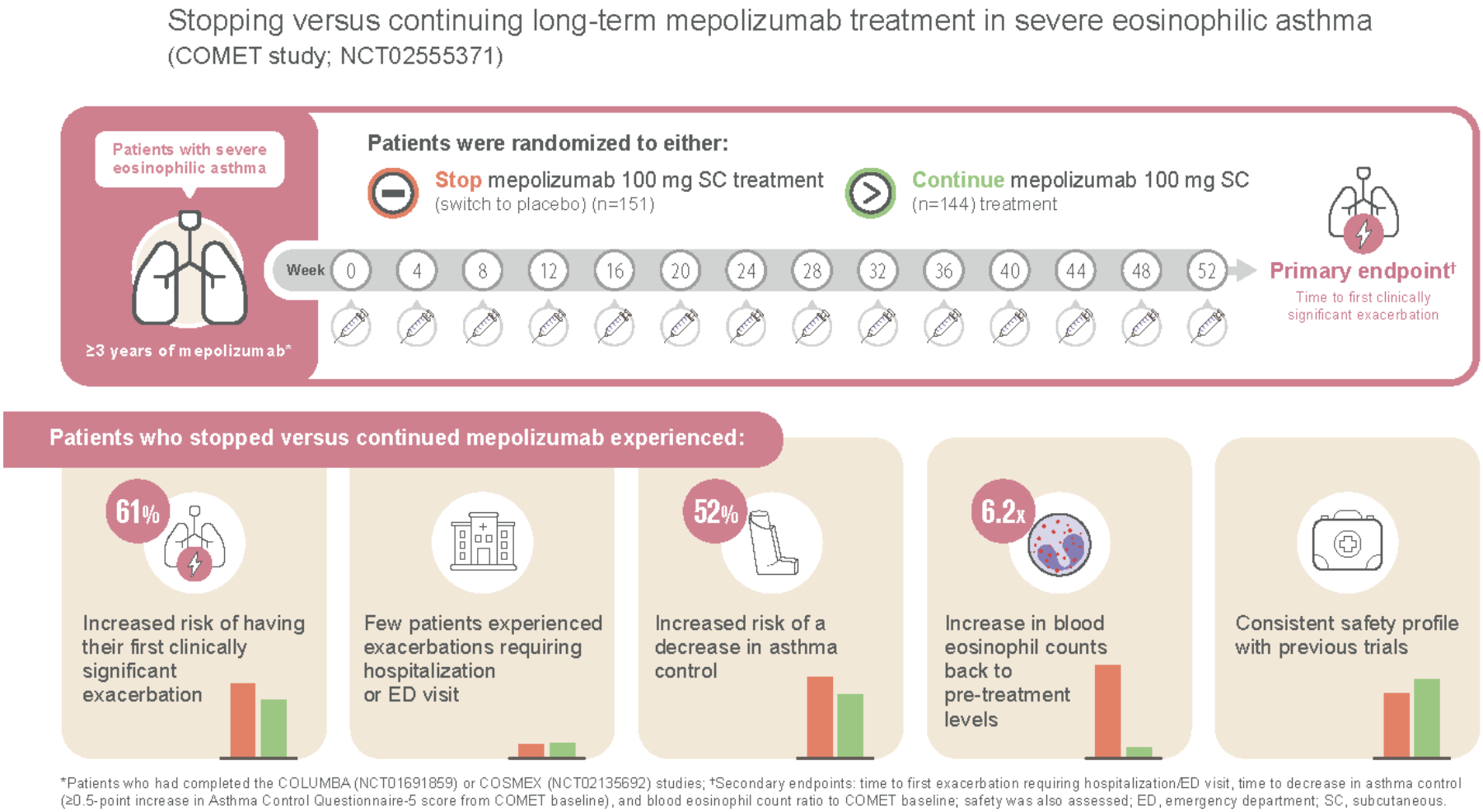
Figure E1. Visual summary of the COMET study.



*Patients who had completed the COLUMBA (NCT01691859) or COSMEX (NCT02135692) studies; †Secondary endpoints: time to first exacerbation requiring hospitalization/ED visit, time to decrease in asthma control (≥0.5-point increase in Asthma Control Questionnaire-5 score from COMET baseline), and blood eosinophil count ratio to COMET baseline; safety was also assessed; ED, emergency department; SC, subcutaneous.

Supplementary Methods

Study design

The trial protocol and statistical analysis plan is available at https://www.gsk-studyregister.com. Study ID 201810.

A clinically significant exacerbation was defined as worsening of asthma that requires use of systemic corticosteroids (≥3 days of intravenous/oral corticosteroid [OCS] or a single intramuscular corticosteroid dose or ≥double existing maintenance dose for ≥3 days) and/or hospitalization or emergency department (ED) visits.

Switching to Part D was optional; alternatively, patients could withdraw from treatment. Patients who permanently discontinued double-blind treatment in Part C or open-label treatment in Part D were not required to withdraw from the study. However, patients meeting protocol-defined QTc or liver event stopping criteria were withdrawn from investigational product, as were those who were pregnant.

Patients

Patients were enrolled by their treating physician or by site staff where delegation was appropriate. Patients were enrolled from 75 centers (mostly hospital-based specialist respiratory centers) across Argentina, Australia, Canada, Europe, Japan, Republic of Korea, Russia, Ukraine, and USA.

COLUMBA [1] was an extension study enrolling patients from the DREAM (MEA112997; NCT01000506) study [2] (following a 12–28-month break without clinical trial participation); COSMEX [3] enrolled patients who had completed the COSMOS (MEA115661; NCT01842607) [4] extension study, which had enrolled patients who had completed either the MENSA (MEA115588; NCT01691521) [5] or SIRIUS (MEA115575; NCT01691508) [6] studies (**Table 1**).

Patients with a clinically significant health deterioration at completion of COLUMBA or COSMEX were excluded, as were those with severe or clinically significant uncontrolled cardiovascular disease or clinically significant ECG abnormality at screening. Additionally, patients who had received any monoclonal antibody (other than mepolizumab) within 5 half-lives of screening were not permitted to participate, nor were current smokers or those with <80% adherence to controller medications during COLUMBA or COSMEX.

Randomization and blinding

Randomization was carried out using an interactive web response system. The randomization sequence was computer generated using validated software, using a permuted-block schedule separately for each country. Mepolizumab and placebo formulations (prepared by pharmacists who were unblinded and aware of study-group assignments but were not involved in study assessments) were identical in appearance and were administered in a blinded manner. Other than the unblinded pharmacists, patients, investigators, other site staff, and the entire study team including those assessing outcomes data were blinded to treatment assignment.

To be eligible for randomization and enter Part C, patients had to have received ≥3 years of continuous mepolizumab treatment, completed details of symptom scores, rescue medication use, peak expiratory flow measurements and nighttime awakenings requiring rescue medication in an eDiary on ≥4 of the 7 days prior to randomization, and have had no changes in the dose or regimen of baseline inhaled corticosteroid (ICS) and/or additional controller medication (except oral corticosteroids [OCS] for treatment of an exacerbation) during Part B. Patients with an asthma exacerbation within 7 days prior to the randomization visit (first visit of Part C) were permitted a 4-week extension to allow for exacerbation resolution.

Those with a known positive neutralizing antibody status were not eligible to be randomized.

Sample size and statistical analysis

A sample size of 300 randomized patients (150 per treatment arm) was estimated to provide 90% power for declaring statistical significance on this endpoint at the two-sided 5% alpha level (one-sided 2.5%), based on a true hazard ratio (HR) of 1.82.

Time to event endpoints were analyzed using Cox proportional hazards models, with adjustment for covariates of region, exacerbations in the year prior to randomization and baseline OCS use (OCS vs. no OCS). Change from baseline (ACQ-5, SGRQ, and FEV_1) and ratio to baseline (eosinophils) endpoints were analyzed using mixed model repeated measures, with adjustment for the aforementioned covariates along with baseline value, visit, and terms for the interaction of visit with baseline value and of visit with treatment group. A pre-specified log transformation was applied to blood eosinophil counts before analysis.

In the analysis of data during the double-blind (Part C) treatment period, a hypothetical estimand strategy was applied in the handling of the intercurrent event of discontinuation of double-blind treatment or switch back to open-label mepolizumab in Part D. As a result, the treatment effects

reported during Part C estimate the outcomes if all patients had continued to take double-blind treatment throughout the 52-week double-blind period.

A post hoc analysis was performed to assess the potential for baseline characteristics to identify patients with a greater or reduced treatment effect following stopping or continuing long-term mepolizumab treatment in the primary endpoint of time to first clinically significant exacerbation. At baseline (prior to COMET randomization) characteristics of interest included exacerbations in the year prior (0, 1, ≥2), use of maintenance OCS (yes/no), blood eosinophil count (<50, 50–<150, ≥150 cells/µL), ACQ-5 score (<0.75, 0.75–<1.50, ≥1.50), presence of nasal polyps (yes/no) and presence of sinusitis (yes/no). Kaplan-Meier cumulative incidence curves were plotted for time to first clinically significant exacerbation by each baseline characteristic of interest. Hazard ratios were estimated separately for each subgroup using a Cox Proportional Hazards Model with covariates of treatment group, region, exacerbations in the year prior to randomization and baseline maintenance OCS therapy (OCS vs. no OCS). Rosenkranz bootstrap model selection was performed to correct subgroup hazard ratios for selection bias [7].

An additional post hoc analysis was performed to provide odds ratios for the proportion of patients with a clinically significant exacerbation during Part C. This analysis used a logistic regression model with terms for treatment group, region, exacerbations in the year prior to randomization (as an ordinal variable) and baseline maintenance OCS therapy (OCS vs no OCS).

Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, USA).

Safety results

There were no clinically important between-group differences in clinical laboratory parameters, 12-lead ECG parameters, or vital signs.

Supplementary Tables

Table E1. Eligibility criteria for prior trials.

Pivotal double-blind, placebo-controlled, randomized clinical trials		**Open-label extensions**			
MEA112997 (DREAM)	• Variability in PEF >20% for ≥3 days during run-in; and/or >12% and 200 mL FEV_1 improvement after 200 µg inhaled salbutamol at screening/baseline/in the prior 12 months; and/or >20% FEV_1 variability between 2 consecutive clinic visits in 12 months; and/or ≤20% FEV_1 reduction with 8 mg/mL inhaled methacholine in the prior 12 months • <80% predicted (adults) or FEV_1 <90% or FEV_1/FVC <0.8 (adolescents) • **≥**2 exacerbations requiring SCS in the prior 12 months • Stable treatment with high-dose ICS (with or without SCS) and required an additional controller • Evidence of eosinophilic inflammation in the prior 12 months (sputum eosinophil count ≥3% or FE_{NO} ≥50 ppb or blood eosinophil count ≥300 cells/µL or asthma deterioration after a ≤25% reduction in maintenance corticosteroid in the prior 12 months)	**MEA115666 (COLUMBA)**	• Received ≥2 doses of randomized treatment during DREAM • Receiving an asthma controller for ≥12 weeks before enrollment in COLUMBA • No neutralizing drug antibodies, mepolizumab-related hypersensitivity, or SAEs possibly related to mepolizumab		
MEA115588 (MENSA)	• FEV_1 <80% predicted (adults) or FEV_1 <90% or FEV_1:FVC ratio <0.8 (adolescents) • FEV_1 reversibility >12% and/or positive results on methacholine or mannitol challenge at screening/baseline or in the prior 12 months and/or ≥20% FEV_1 variability between 2 consecutive clinic visits in 12 months • ≥2 exacerbations requiring SCS in the prior 12 months • High-dose ICS for ≥12 months and ≥3 months of an additional controller • Blood eosinophil count ≥300 cells/µL in the prior 12 months (or ≥150 cells/µL at screening)	**MEA115661 (COSMOS)**	• Completed MENSA or SIRIUS • Received ICS and another controller throughout MENSA or SIRIUS • No mepolizumab-related hypersensitivity or SAEs possibly related to	**201312 (COSMEX)**	• Life-threatening or seriously debilitating asthma • ICS (≥500 µg/day fluticasone propionate or equivalent) for the prior 8 months • Protocol-defined clinical benefit from mepolizumab within MENSA, SIRIUS, or

MEA115575 (SIRIUS)	• ≥6-month history of SCS maintenance treatment (5–35 mg/day) • Blood eosinophil count ≥300 cells/µL in the prior 12 months (or ≥150 cells/µL during optimization phase) • High-dose ICS and an additional controller		mepolizumab		COSMOS

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; PEF, peak expiratory flow; SAE, serious adverse events; SCS, systemic corticosteroid.

Table E2. Demographic and disease characteristics of the study population upon entry in comparison to previous mepolizumab studies.

	DREAM[2] (Intent-to-treat population)				MENSA[5] (Intent-to-treat population)			SIRIUS[6] (Intent-to-treat population)		COMET (Part C population)	
	Mepolizumab			Placebo	Mepolizumab		Placebo	Mepolizumab	Placebo	Stopped mepolizumab (switched to placebo)	Continued mepolizumab
	75 mg IV (N=153)	250 mg SC (N=152)	750 mg SC (N=156)	(N=155)	75 mg IV (N=191)	100 mg SC (N=194)	(N=191)	100 mg SC (N=69)	(N=66)	(N=151)	100 mg SC (N=144)
Blood eosinophil count, cells/µL, geometric mean (SD of log)	250 (0.952)	230 (1.201)	250 (0.933)	280 (1.011)	280 (0.987)	290 (1.050)	320 (0.938)	250 (1.245)	230 (1.001)	40 (0.870)	50 (0.881)
Exacerbations in previous year, mean (SD)	3.7 (3.1)	3.4 (2.4)	3.5 (2.8)	3.7 (3.8)	3.5 (2.2)	3.8 (2.7)	3.6 (2.8)	3.3 (3.4)	2.9 (2.8)	0.6 (1.1)	0.8 (1.5)
Exacerbations requiring hospitalization in the previous year, n (%)	35 (23)	36 (24)	39 (25)	40 (26)	41 (21)	33 (17)	35 (18)	14 (20)	9 (14)	4 (3)	3 (2)
ACQ-5 score, mean (SD)	2.3 (1.1)	2.4 (1.1)	2.3 (1.2)	2.6 (1.1)	2.1 (1.1)	2.3 (1.3)	2.3 (1.2)	2.2 (1.3)	2.0 (1.2)	1.2 (1.0)	1.4 (1.1)
AQLQ score or SGRQ total score, mean (SD)*	4.2 (1.2)	4.2 (1.2)	4.2 (1.2)	4.1 (1.2)	44.4 (19.4)	47.9 (19.5)	46.9 (19.8)	49.6 (17.8)	45.0 (18.4)	32.2 (17.8)	33.1 (17.4)
Pre-bronchodilator FEV_1, mL, mean (SD)	1808 (637)	1854 (672)	1950 (674)	1899 (653)	1860 (702)	1730 (659)	1860 (631)	1897 (660)	2005 (822)	1921 (655)	1774 (666)
Using maintenance OCS											

n (%)	46 (30)	50 (33)	47 (30)	45 (29)	48 (25)	52 (27)	44 (23)	69 (100)	66 (100)	17 (11)	21 (15)
Daily dose, median, mg (prednisone equivalent)	10.0	10.0	12.5	10.0	10.0	10.0	10.0	10.0	12.5	5.0	5.0

Higher scores on the ACQ-5 indicate worse control (range 0–6); a change of 0.5 points is the minimal clinically important difference[8]. Higher scores on the AQLQ indicate a better quality of life (range: 1–7); a change of 0.5 points is the minimal clinically important difference[9]. Higher scores on the SGRQ indicate a worse quality of life (range: 0–100); a change of 4 points is the minimal clinically important difference[10].

*DREAM used AQLQ as the quality of life questionnaire; other studies used SGRQ.

ACQ, Asthma Control Questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1 second; IV, intravenous; OCS, oral corticosteroids; SC, subcutaneous; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table E3. Demographics and asthma characteristics of patients at DREAM/MENSA/SIRIUS baseline according to COMET randomized treatment group

	Stopped mepolizumab (switched to placebo) (N=151)	**Continued mepolizumab 100 mg SC (N=144)**
Females, n (%)	86 (57)	87 (60)
Age, years, mean (SD)	50.3 (11.45)	51.4 (11.62)
Race, n (%) Asian Black White	 24 (16) 2 (1) 125 (83)	 24 (17) 5 (3) 115 (80)
Body mass index, kg/m^2, mean (SD)	27.9 (5.76)	28.7 (6.41)
Duration of asthma, years, mean (SD)	17.4 (13.8)	19.8 (14.7)
Using maintenance OCS, n (%) Median (range) dose, mg/day (prednisone equivalent)	48 (32) 10.0 (2.0–40.0)	50 (35) 10.0 (3.0–40.0)
Blood eosinophil count, cells/μL, geometric mean (SD of log)	300 (1.011)	290 (1.053)
Exacerbations in previous year, mean (SD)	3.5 (1.94)	3.4 (2.55)
Exacerbations requiring hospitalization or ED visit in the previous year, n (%)	74 (49)	56 (39)
Exacerbations requiring hospitalization in the previous year, n (%)	51 (34)	41 (28)
ACQ-5 score, mean (SD)	2.2 (1.20)	2.3 (1.06)
SGRQ total score, mean (SD)	52.0 (18.79)	49.1 (17.74)
Pre-bronchodilator FEV_1, mL, mean (SD)	1861 (701)	1773 (626)
% predicted pre-bronchodilator FEV_1, mean (SD)	59.7 (18.41)	58.8 (16.64)
Smoking history, n (%) Never smoked Former smoker	 119 (79) 32 (21)	 106 (74) 38 (26)

Post hoc analyses

ACQ, Asthma Control Questionnaire; ED, emergency department; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; SC, subcutaneous; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table E4. Analysis of proportion of patients with a clinically significant exacerbation (on treatment, Part C; blinded treatment)

	Stopped mepolizumab (switched to placebo) (N=151)	**Continued mepolizumab 100 mg SC (N=144)**
Clinically significant exacerbations, n (%)	89 (59)	66 (46)
No clinically significant exacerbations, n (%)	62 (41)	78 (54)
Comparison: stopped mepolizumab/continued mepolizumab Odds ratio (95% CI) *P*-value	1.99 (1.19, 3.32) 0.009	

Post hoc analysis

CI, confidence interval; SC, subcutaneous.

Table E5. Blood eosinophil counts during Part C
(on-treatment; Part C; blinded treatment).

	Stopped mepolizumab (switched to placebo) (N=151)	**Continued mepolizumab 100 mg SC (N=144)**
Blood eosinophil count, cells/µL, LS mean (SE of log)		
Week 4	80 (0.066)	50 (0.068)
Week 8	170 (0.085)	50 (0.087)
Week 12	270 (0.077)	50 (0.078)
Week 16	310 (0.092)	50 (0.088)
Week 20	360 (0.094)	60 (0.086)
Week 24	290 (0.095)	50 (0.084)
Week 28	300 (0.091)	60 (0.082)
Week 32	300 (0.088)	60 (0.078)
Week 36	290 (0.093)	50 (0.079)
Week 40	310 (0.093)	50 (0.082)
Week 44	240 (0.097)	50 (0.084)
Week 48	300 (0.091)	50 (0.079)
Week 52	270 (0.091)	40 (0.077)

LS, least squares; SC, subcutaneous; SE, standard error.

Table E6. AEs and AEs of special interest reported during the COMET study (on-treatment).

	Part A/B (open label)	Part C (blinded treatment)		Part D (open label)	
	Mepolizumab 100 mg SC (N=306)	Stopped mepolizumab (switched to placebo) (N=151)	Continued mepolizumab 100 mg SC (N=144)	Mepolizumab 100 mg SC (prev. placebo) (N=84)	Mepolizumab 100 mg SC (prev. mepo) (N=45)
Any AE					
Any AE	73 (24)	96 (64)	112 (78)	64 (76)	38 (84)
Any AE related to study treatment	0	1 (<1)	5 (3)	2 (2)	2 (4)
Any AE leading to treatment discontinuation	3 (<1)	2 (1)*,†	2 (1)†	1 (1)	0
Any SAE					
Any SAE*	7 (2)	10 (7)	9 (6)	10 (12)	4 (9)
Any SAE related to study treatment	0	0	0	0	0
Any fatal SAE	0	0*	0	1 (1)	0
AEs of special interest					
Systemic reactions	0	0	0	0	0
Anaphylaxis	0	0	0	0	0
Local site reactions	0	1 (<1)	5 (3)	1 (2)	0
All infections‡	47 (15)	66 (44)	84 (58)	39 (46)	26 (58)

Serious infections	4 (1)	2 (1)	2 (1)	2 (2)	0
Opportunistic infections[§]	2 (<1)	2 (1)	2 (1)	1 (1)	0
Neoplasms[‡]	2 (<1)	3 (2)	5 (3)	0	0
Malignancies[¶]	2 (<1)	0	2 (1)	0	0
Cardiac disorders[‡]	1 (<1)	2 (1)	1 (<1)	2 (2)	1 (2)
Serious CVT events**	0	1 (<1)	0	0	0
Serious ischemic events[††]	0	0	0	0	0

Data are n (%). *One participant reported a post-treatment fatal SAE of "Death" (unknown cause) leading to treatment discontinuation during Part C (stopped mepolizumab group). [†]Two additional participants randomized to continued mepolizumab group and 1 additional participant randomized to stopped mepolizumab group discontinued blinded treatment due to an AE during Part C but are not included in this table. [‡]Infections from infections and infestations SOC. Neoplasms from neoplasms benign, malignant, and unspecified (including cysts and polyps) SOC. Cardiac disorders from cardiac disorders SOC. [§]Identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy (Winthrop, 2015) [11]. [¶]Identified from neoplasms benign, malignant, and unspecified (including cysts and polyps) SMQs. **Serious CVT events identified from cardiac disorders SOC, vascular disorders SOC, and SMQs. [††]Subset of serious CVT events identified through SMQs.

AE, adverse event; CVT, cardiac vascular & thromboembolic; prev.; previous SAE, serious adverse event; SC, subcutaneous; SMQs, standard MedDRA queries; SOC, system organ class.

Table E7. AEs and exposure-adjusted AEs (on-treatment; Part C; blinded treatment).

	Stopped mepolizumab (switched to placebo)		**Continued mepolizumab 100 mg SC**	
	n (%) (N=151)	**Event rate* (Pt.-years=93.94)**	**n (%) (N=144)**	**Event rate* (Pt.-years=114.60)**
Any event	96 (64)	3097.77	112 (78)	2740.01
Infections and infestations	66 (44)	1373.24	84 (58)	1160.58
Respiratory, thoracic, and mediastinal disorders	30 (20)	447.10	23 (16)	287.96
Musculoskeletal and connective tissue disorders	16 (11)	276.78	19 (13)	261.78
Gastrointestinal disorders	17 (11)	234.20	14 (10)	157.07
Nervous system disorders	13 (9)	159.68	16 (11)	174.52
Injury, poisoning, and procedural complications	10 (7)	117.10	10 (7)	95.99
General disorders and administration site conditions	4 (3)	42.58	9 (6)	113.44
Skin and subcutaneous tissue disorders	4 (3)	42.58	9 (6)	104.71
Vascular disorders	2 (1)	21.29	10 (7)	95.99
Metabolism and nutrition disorders	4 (3)	63.87	4 (3)	43.63
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (2)	42.58	5 (3)	43.63
Immune system disorders	4 (3)	53.23	2 (1)	26.18
Reproductive system and breast disorders	2 (1)	21.29	4 (3)	43.63
Eye disorders	3 (2)	42.58	2 (1)	17.45
Investigations	1 (<1)	21.29	3 (2)	26.18
Renal and urinary disorders	1 (<1)	21.29	3 (2)	26.18
Cardiac disorders	2 (1)	21.29	1 (<1)	17.45
Psychiatric disorders	1 (<1)	10.65	3 (2)	26.18
Ear and labyrinth disorders	2 (1)	21.29	1 (<1)	8.73
Hepatobiliary disorders	2 (1)	31.94	0 (0)	0.00

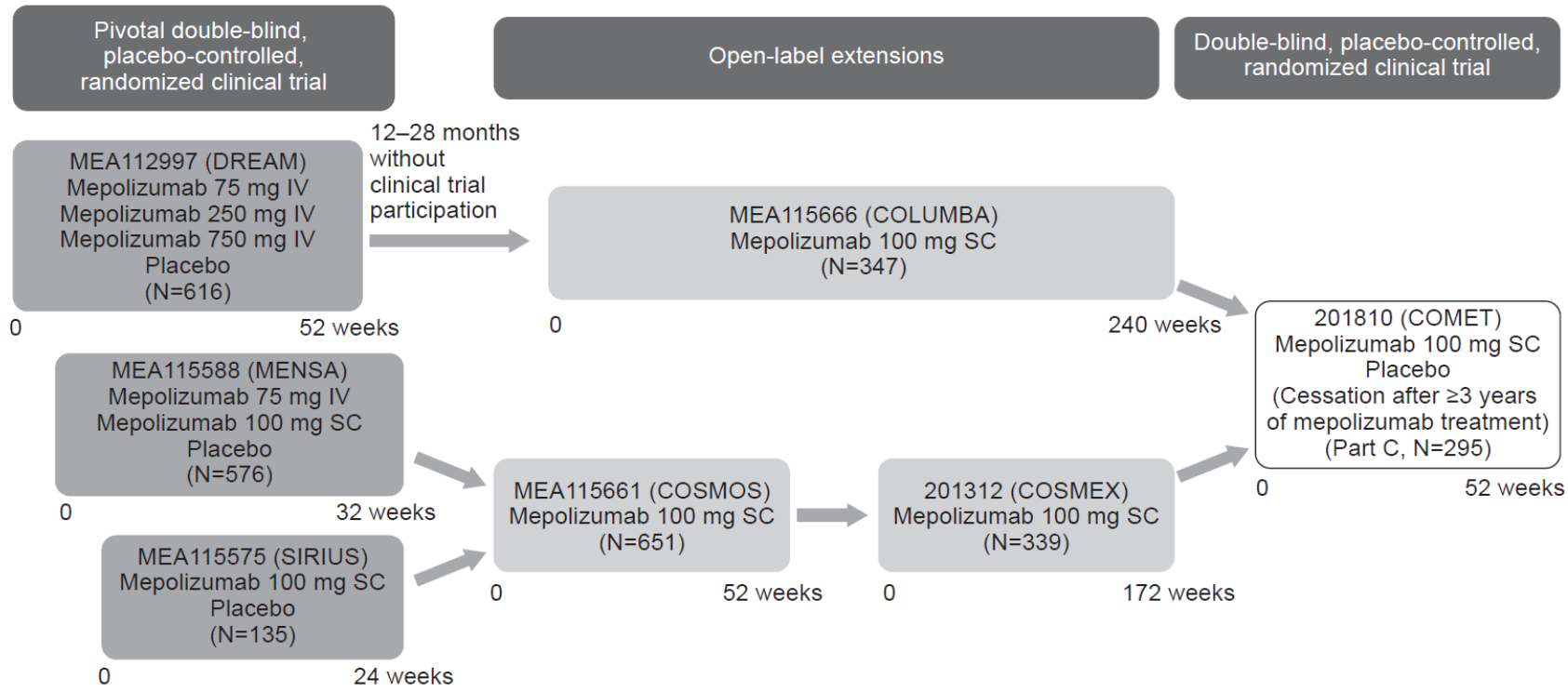
Endocrine disorders	1 (<1)	10.65	1 (<1)	8.73
Blood and lymphatic system disorders	1 (<1)	10.65	0 (0)	0.00
Menopause	1 (<1)	10.65	0 (0)	0.00

*Rate reflects number of events per 1000 patient-years of exposure.

AE, adverse event; Pt.-years, patient-years; SC, subcutaneous.

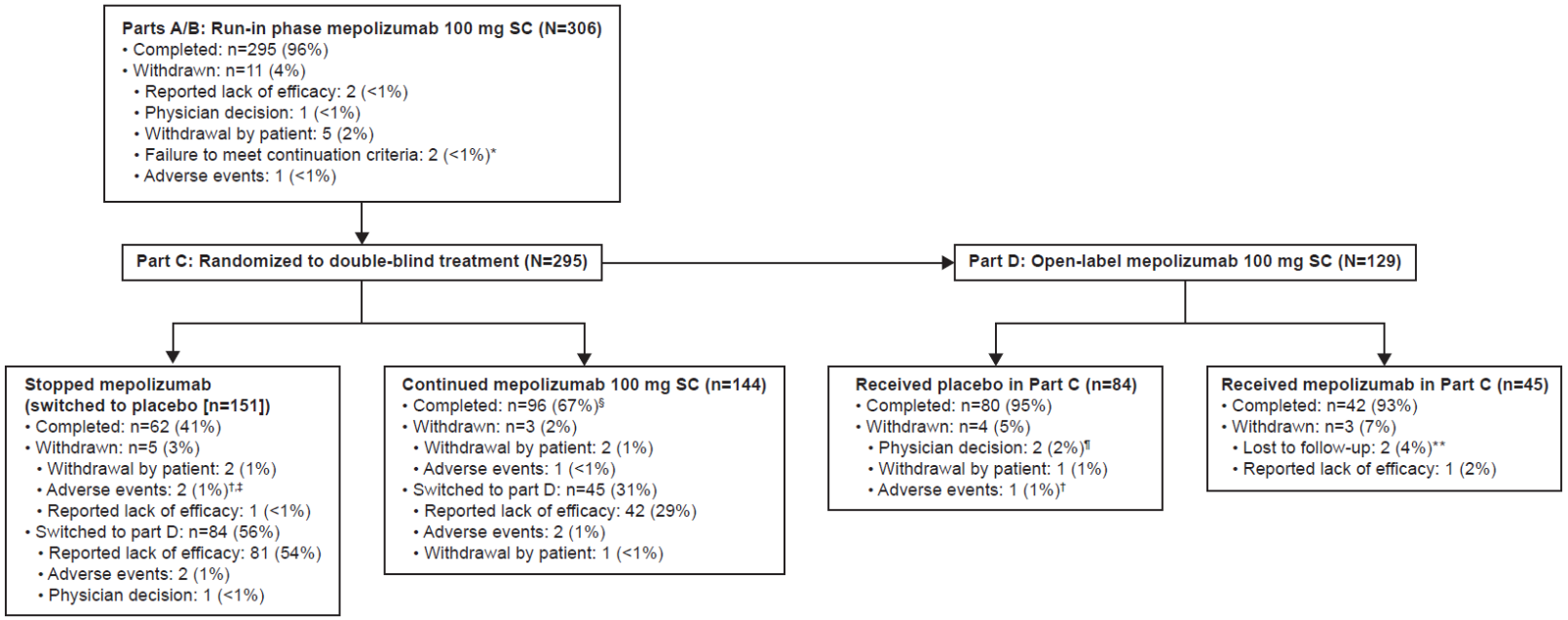
Supplementary Figures

Figure E2. Flow of patients through previous parent studies prior to enrollment into COMET.



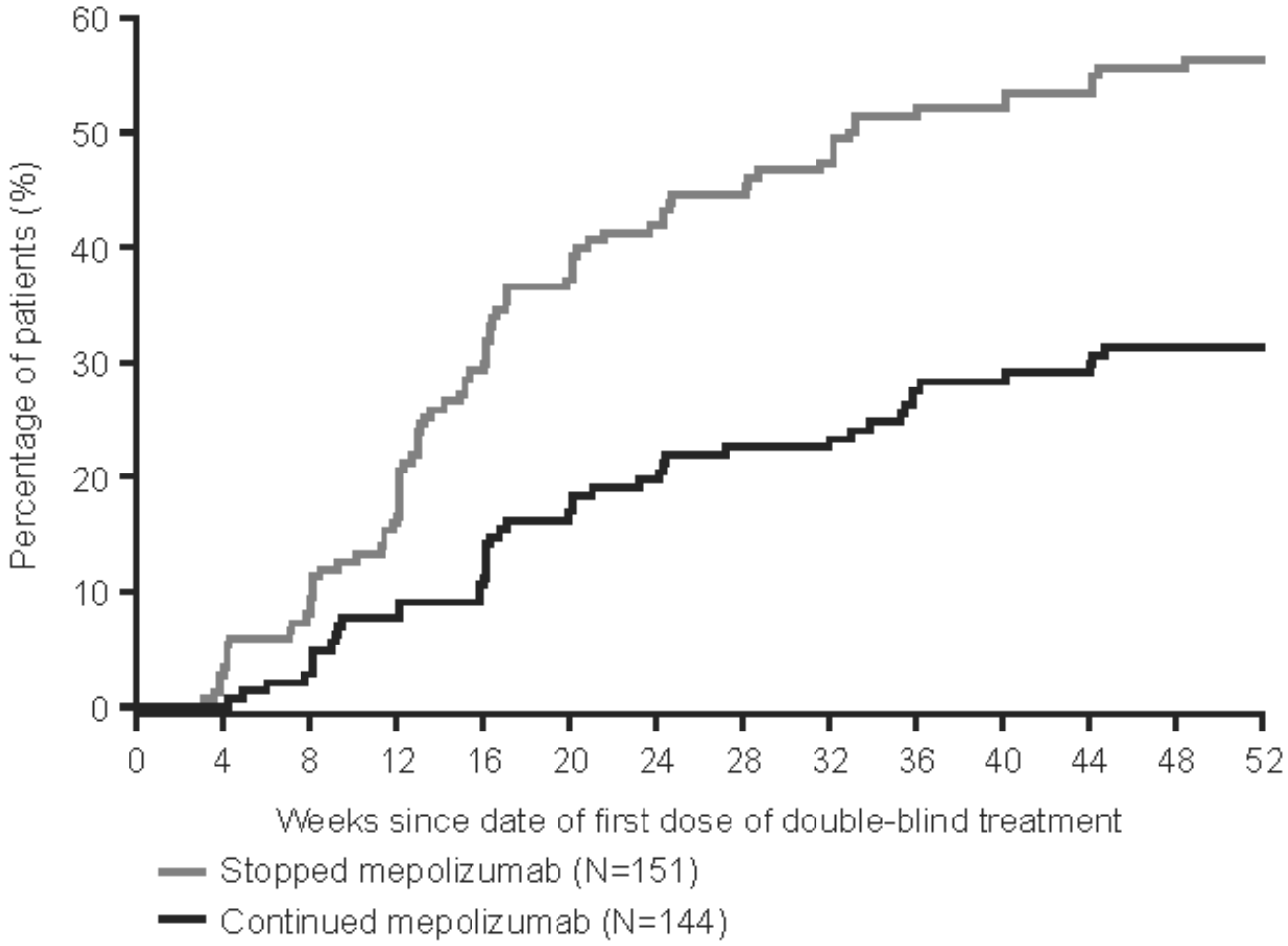
Eligibility criteria for each of the trials are available in **Table E1**. Note that mepolizumab became commercially available in some countries prior to the start of the COMET trial, which may have reduced the number of patients from prior trials enrolling in COMET.
IV, intravenous; SC, subcutaneous

Figure E3. Flow of patients through the COMET study.



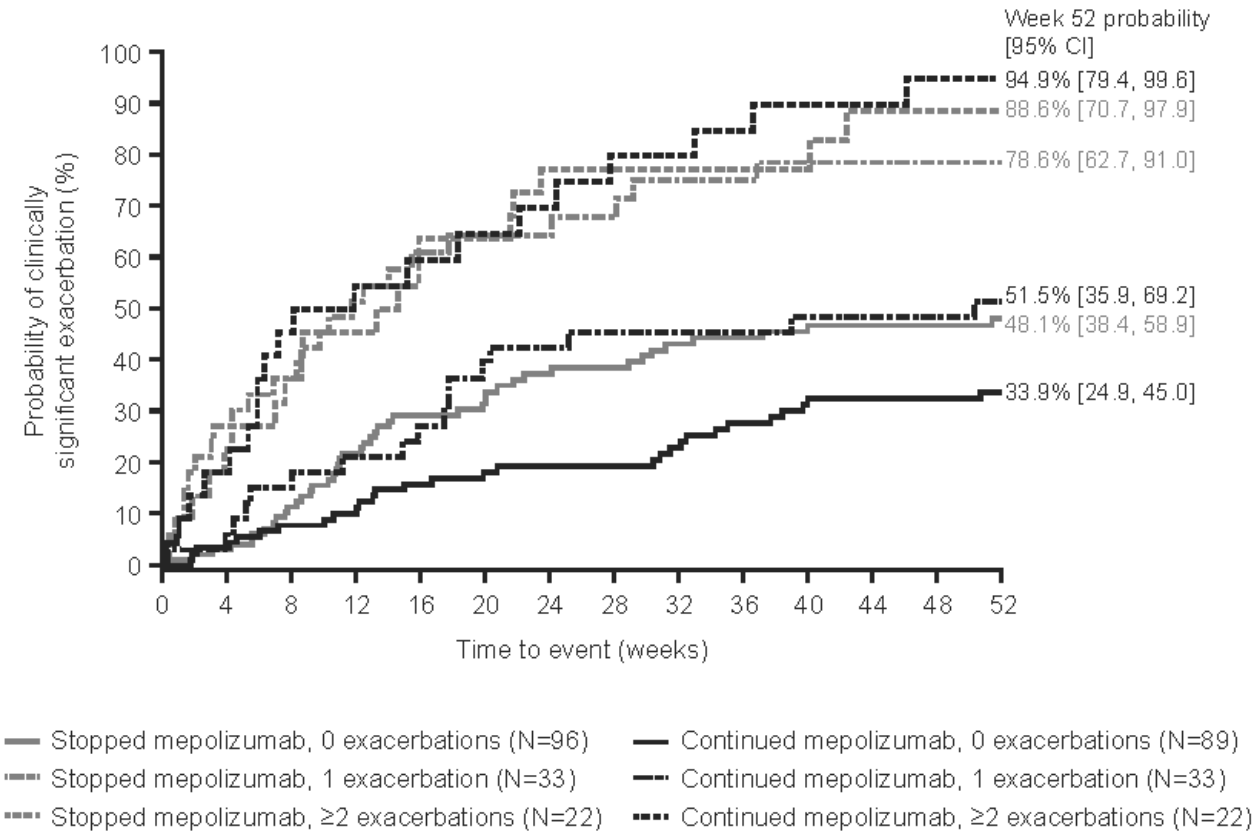
Mepolizumab (100 mg SC) or placebo was administered every 4 weeks. *The patient captured under "Failure to meet continuation criteria" during Parts A/B was withdrawn due to a liver event caused by an AE of Epstein-Barr virus infection resulting in failed randomization/continuation criteria. †There were two reported deaths, both unrelated to study treatment; one post treatment during Part C (placebo group) and one on-treatment during Part D (in a patient who had received placebo during Part C). ‡One patient (randomized to placebo in Part C) was withdrawn from study within Part C due to an AE of eosinophilic granulomatosis with polyangiitis with onset during Parts A/B. §Two patients discontinued double-blind treatment during Part C (continued mepolizumab arm) and remained in the study off-treatment, completing all remaining scheduled visits in Part C following pregnancy and an AE, respectively. Additionally, two patients discontinued double-blind treatment during Part C with the reason for treatment discontinuation reported as AE/exacerbation. However, these events were only captured on the exacerbation page of the electronic case report form and were not reported as AEs. ¶One patient discontinued Part D treatment due to patient decision (burden of procedures) and subsequently left the study due to physician decision. **One patient completed Part D open-label study treatment and was later lost to follow-up. AE, adverse event; SC, subcutaneous.

Figure E4. Time to switching to open label mepolizumab treatment (Part D)



Patient population includes all patients who were randomized to Part C. Of these, 129 patients, 84 who had stopped mepolizumab in Part C and 45 who had continued mepolizumab in Part C, switched to open-label mepolizumab (Part D) following an asthma exacerbation.

Figure E5. Kaplan-Meier cumulative incidence curves for time to first clinically significant exacerbation by exacerbations in the year prior to randomization (0, 1, ≥2)



Post hoc analysis

CI, confidence interval.

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