Supplementary materials

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

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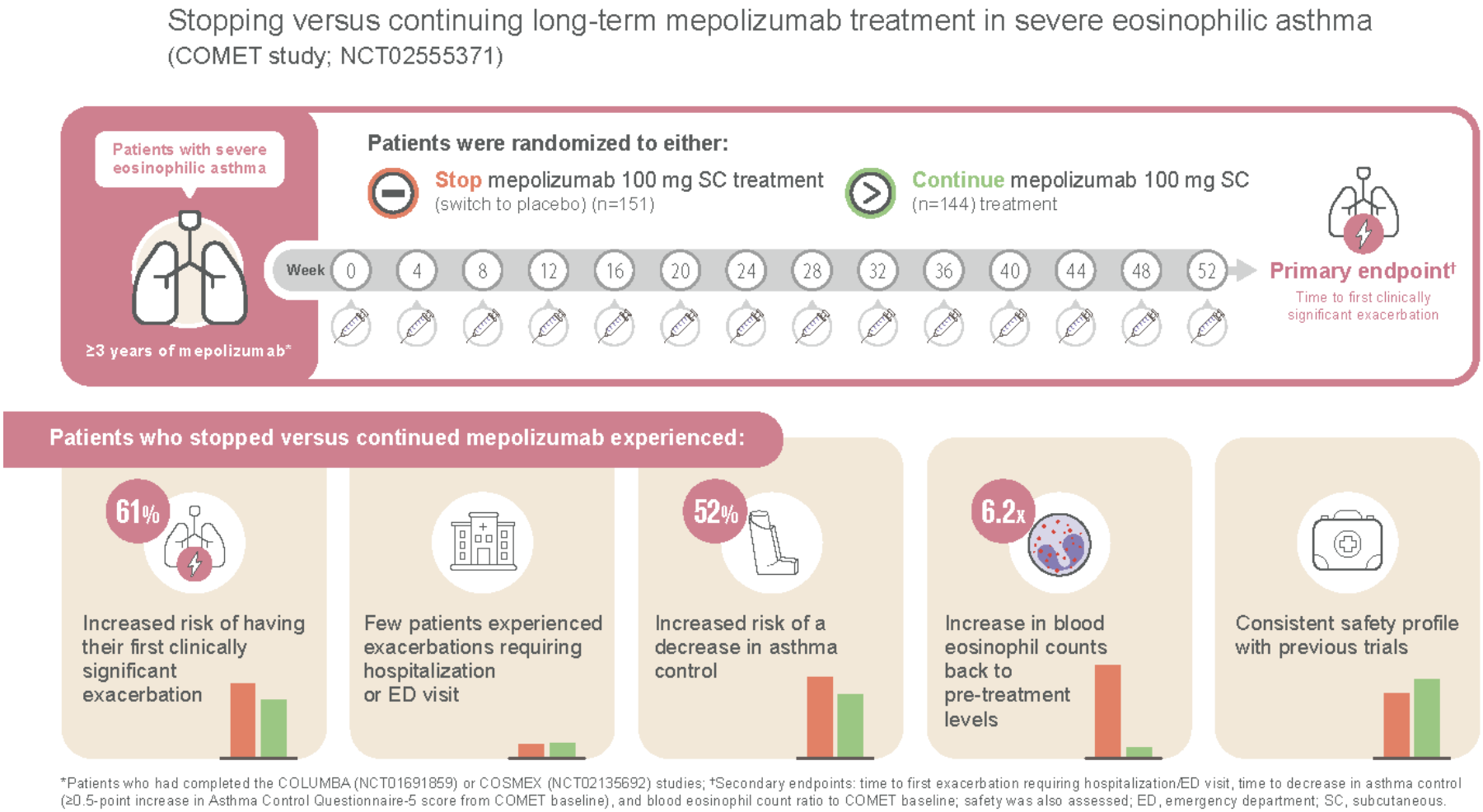
Figure E1. Visual summary of the COMET study.



*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 However, patients meeting protocol-defined QTc or liver event stopping criteria were withdrawn from investigational product, as were those who were pregnant.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	**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

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		related to mepolizumab		MENSA, SIRIUS, or 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 (N=155)	Mepolizumab		Placebo (N=191)	Mepolizumab 100 mg SC (N=69)	Placebo (N=66)	Stopped mepolizumab (switched to placebo) (N=151)	Continued mepolizumab 100 mg SC (N=144)
	75 mg IV (N=153)	250 mg SC (N=152)	750 mg SC (N=156)		75 mg IV (N=191)	100 mg SC (N=194)					
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

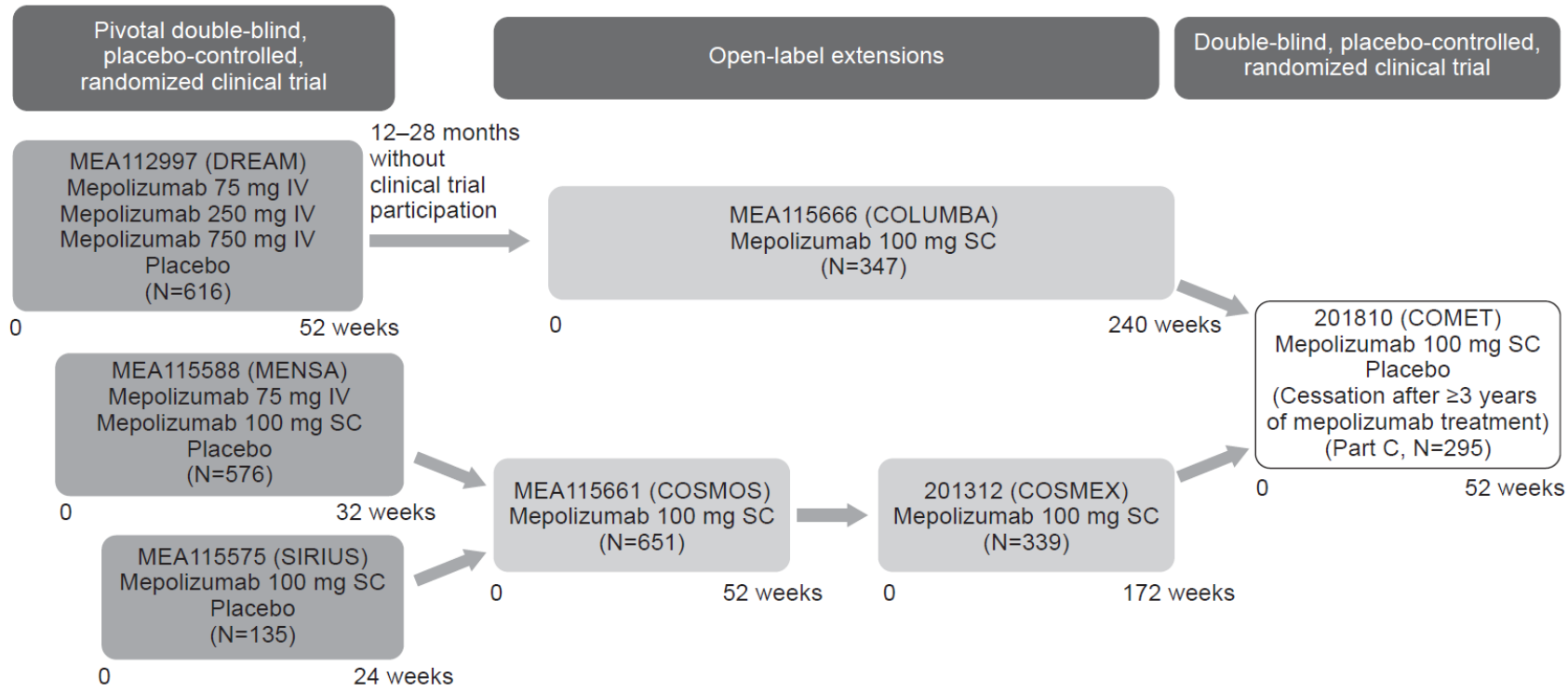
Endocrine disorders	1 (<1)	10.65	1 (<1)	8.73
Blood and lymphatic system disorders	1 (<1)	10.65	0 (0)	0.00
Menopause	1 (<1)	10.65	0 (0)	0.00

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

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

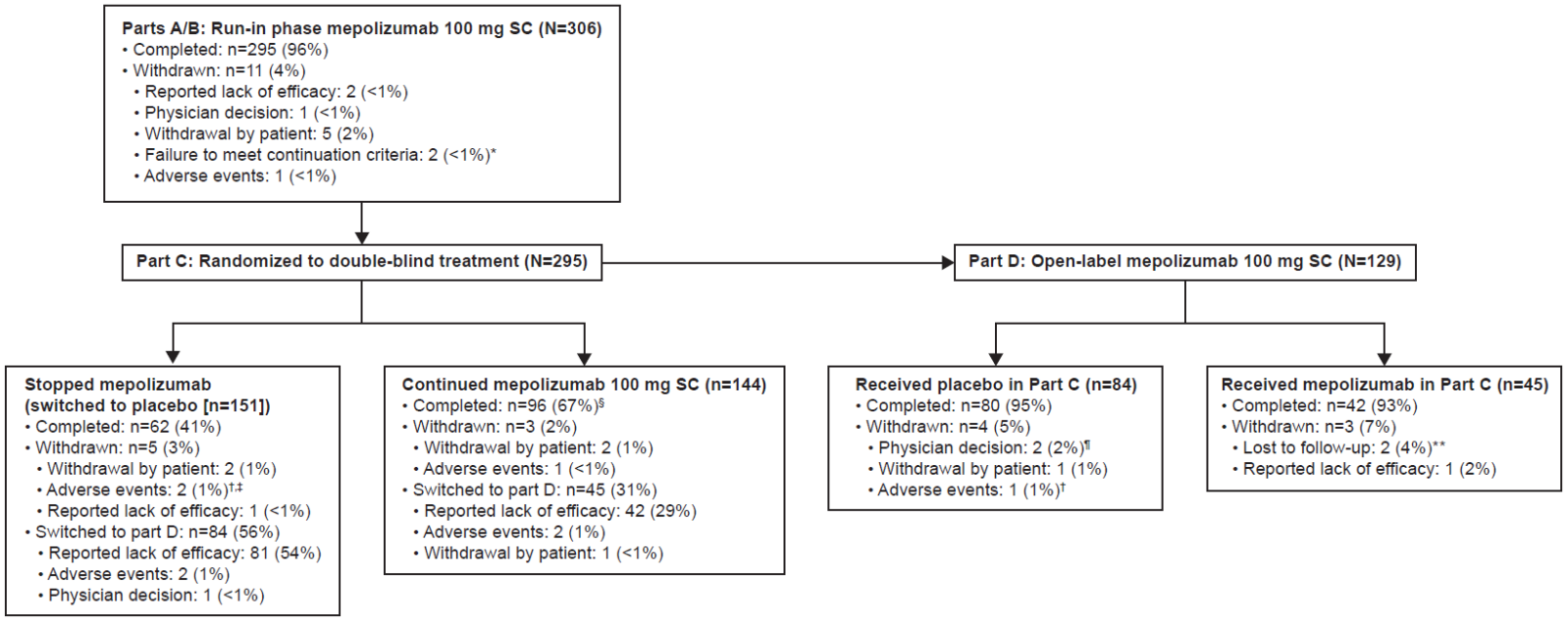
Supplementary Figures

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



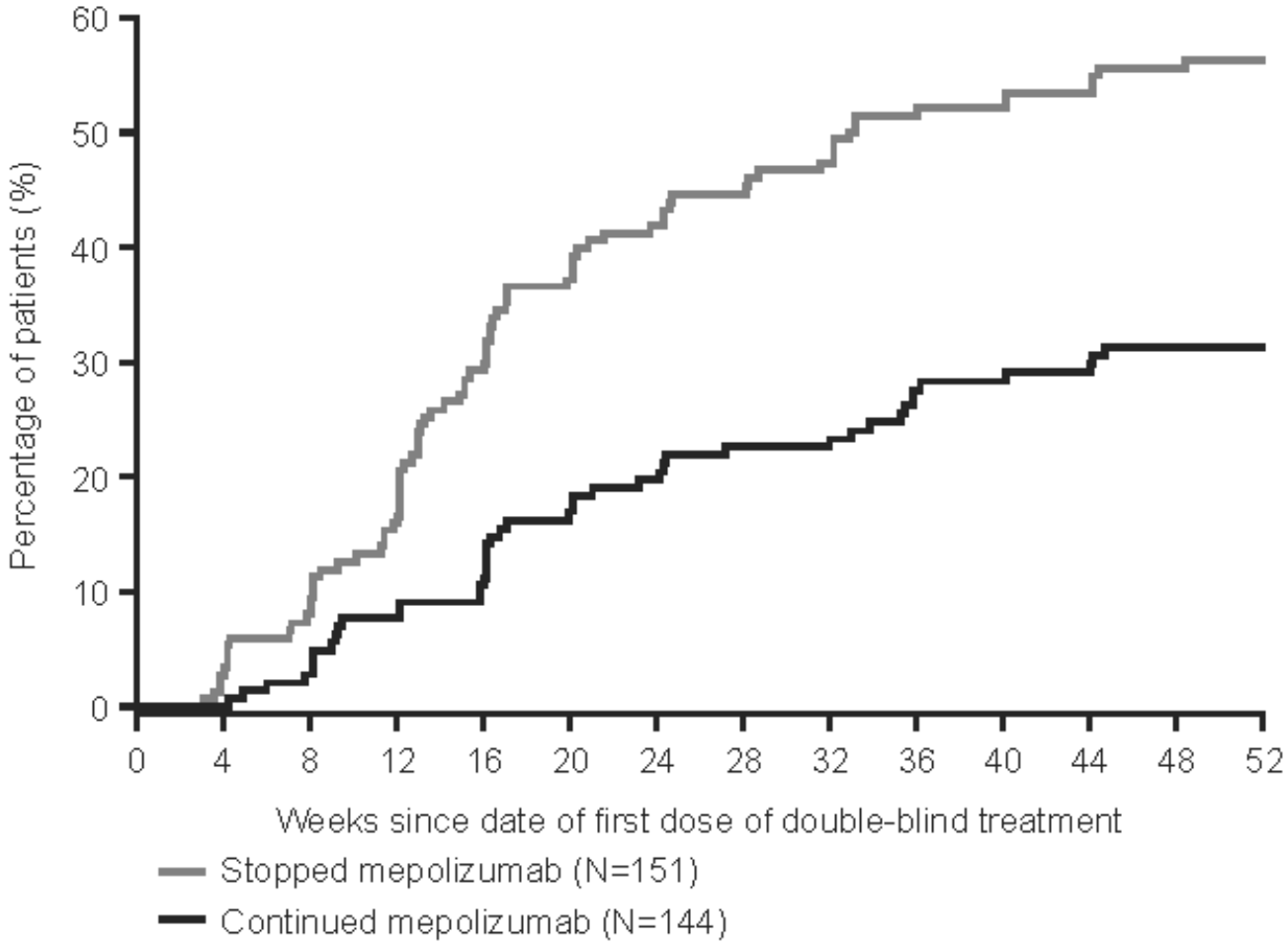
Eligibility criteria for each of the trials are available in **Table E1**. Note that mepolizumab became commercially available in some countries prior to the start of the COMET trial, which may have reduced the number of patients from prior trials enrolling in COMET.
IV, intravenous; SC, subcutaneous

Figure E3. Flow of patients through the COMET study.



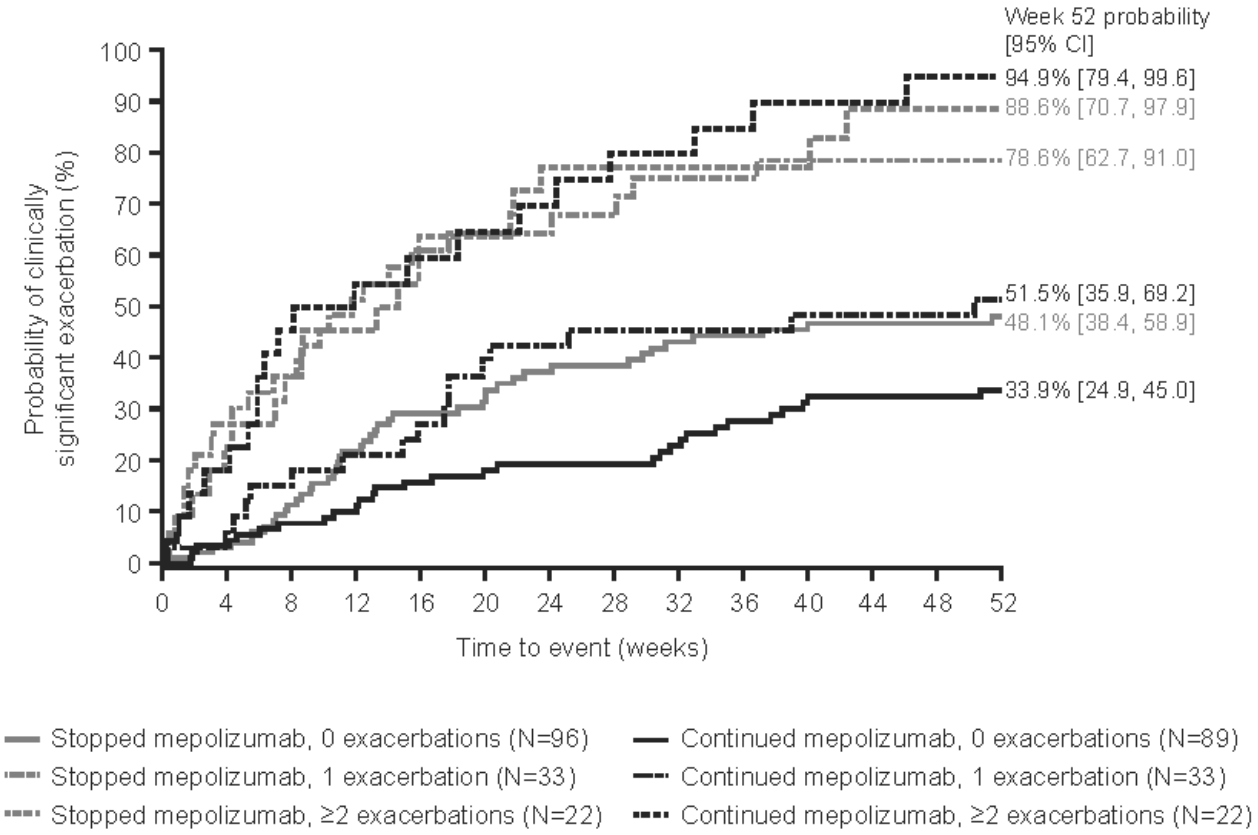
Mepolizumab (100 mg SC) or placebo was administered every 4 weeks. *The patient captured under "Failure to meet continuation criteria" during Parts A/B was withdrawn due to a liver event caused by an AE of Epstein-Barr virus infection resulting in failed randomization/continuation criteria. †There were 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.

References

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