Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype

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Background: Mepolizumab is approved for patients with severe asthma with an eosinophilic phenotype aged 12 or more (United States) or 6 or more (European Union) years, but its long-term use in children aged 6 to 11 years has not yet been assessed.
Objective: We sought to assess the long-term safety, efficacy, and pharmacodynamics of mepolizumab in children aged 6 to 11 years with severe asthma with an eosinophilic phenotype.
Methods: In this open-label, uncontrolled, repeat-dose extension study (NCT02377427), children aged 6 to 11 years with severe asthma with an eosinophilic phenotype (blood eosinophil counts ≥150 cells/μL at screening or ≥300 cells/μL in the previous year) received a body weight–dependent dose of subcutaneous mepolizumab of 40 mg (<40 kg) or 100 mg (≥40 kg) over 52 weeks. End points included the incidence of adverse events (AEs) and immunogenicity (primary), absolute blood eosinophil counts (cells per microliter; secondary), and annualized exacerbation rates and asthma control questionnaire/childhood asthma control test scores (exploratory).
Results: Over 52 weeks, 30 children received mepolizumab; 27 (90%) and 7 (23%) experienced on-treatment AEs and serious AEs, respectively. No serious AEs were treatment related. There were no fatal AEs. No specific patterns of AEs were evident, and no anti-drug antibody or neutralizing antibody responses were reported. Compared with baseline values, mepolizumab treatment reduced blood eosinophil counts and asthma exacerbations and improved asthma control across all treatment groups.
Conclusion: Long-term safety, pharmacodynamic, and efficacy data from this study support a positive benefit-risk profile for mepolizumab in children with severe asthma with an eosinophilic phenotype and were similar to data in studies in adults and adolescents. (J Allergy Clin Immunol 2019;144:1336-42.)

Key words: *Pediatric asthma, eosinophilia, mepolizumab*

Asthma is a common pediatric condition affecting approximately 11% of children aged 6 to 12 years.[1,2] Although the majority of children and adolescents with asthma are able to control their symptoms with available standard of care, up to 16% have severe asthma and require regular treatment with high-dose inhaled corticosteroids plus a second controller and/or chronic systemic corticosteroids (for ≥50% of the year) to manage their condition.[3,4] These children have diverse and often overlapping phenotypes and might continue to experience poor disease control despite additional treatment.[1,4,5] In adults a subset of patients with severe asthma present with an eosinophilic phenotype characterized by airway infiltration with eosinophilic inflammatory cells, leading to poor asthma control, frequent exacerbations, and reduced lung function.[4,6] This phenotype is associated with a greater severity of symptoms, placing patients at greater risk of near-fatal asthma attacks and hospitalizations or emergency department (ED) visits.[6] The eosinophilic phenotype is not well described in children; however, eosinophils have been identified as the predominant inflammatory cells in the airways of children with asthma.[7,8] Eosinophils persist in the airway tissue of children with severe asthma despite use of high-dose inhaled corticosteroids and are associated with significant airway remodeling.[5,7] Given the burden on caregivers of children with chronic illness,

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

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Abbreviations used
ACQ-5: Asthma Control Questionnaire, 5-item
ACQ-7: Asthma Control Questionnaire, 7-item
ADA: Anti-drug antibody
AE: Adverse event
AESI: Adverse event of special interest
ED: Emergency department
MCID: Minimal clinically important difference
PK: Pharmacokinetics
SAE: Serious adverse event

pediatric severe asthma with an eosinophilic phenotype is likely to carry a substantial health burden and reduce quality of life for patients and their caregivers.[9,10]

Mepolizumab is a humanized mAb that targets IL-5, a key regulator of eosinophil proliferation, activation, and survival.[11] It was approved in 2015 by the European Medicines Agency as an add-on treatment for patients 18 years and older with severe asthma with an eosinophilic phenotype and in 2018 was approved for patients 6 years of age and older.[12] In the United States mepolizumab is currently approved only for adults and adolescents 12 years of age and older.[13]

To characterize the pharmacokinetics (PK), pharmacodynamics, safety, and efficacy of mepolizumab in children 6 to 11 years of age with severe asthma with an eosinophilic phenotype, a 2-part study (GSK ID 200363; NCT02377427) was conducted in which patients received 40 or 100 mg of subcutaneous mepolizumab every 4 weeks according to body weight.[14] The first part of the study (part A) focused on the PK and pharmacodynamics of mepolizumab, whereas the second part (part B) focused on long-term safety and pharmacodynamics.

Part A associated mepolizumab treatment with a favorable safety profile in children 6 to 11 years of age.[14] Average exposure (PK) of subcutaneous mepolizumab for children was within the acceptable range of adult target exposure, although overall, it was greater than predicted based on adult models.[14] Mepolizumab treatment resulted in a marked and predictable reduction in blood eosinophil counts compared with baseline.[14]

The primary objective of part B was to assess the long-term safety of mepolizumab over an additional 52-week treatment period in patients who successfully completed part A. The secondary objective was to characterize the long-term pharmacodynamics of mepolizumab.

METHODS

Treatments and study design

This was an open-label, uncontrolled, repeat-dose extension to a phase II study (GSK ID 200363/NCT02377427) conducted in children with severe asthma with an eosinophilic phenotype. Details of the study design have been previously published by Gupta et al.[14] In Part A children 6 to 11 years of age with severe asthma with an eosinophilic phenotype (peripheral blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL within the previous 12 months), 2 or more exacerbations in the previous 12 months, and a well-documented requirement for regular treatment with medium or high doses of inhaled corticosteroids (>200 μg/d fluticasone propionate or equivalent plus a second controller)[15] were enrolled to receive 3 doses of mepolizumab every 4 weeks. Children received subcutaneous mepolizumab for 12 weeks at 40 mg if they weighed less than 40 kg or at 100 mg if they weighed 40 kg or more and were monitored for 8 weeks after treatment completion. Children who completed all doses and assessments in part A were given the option to continue receiving mepolizumab in part B. In this second part children recommenced treatment to receive a further 13 doses of mepolizumab at 4-week intervals (overall study weeks 20-72).

Based on their weight at the beginning of part B (overall study week 20), children received 40 mg of mepolizumab subcutaneously if they weighed less than 40 kg or 100 mg subcutaneously if they weighed 40 kg or more. Children weighing less than 40 kg at the beginning of part B were weighed at each visit, and their dose was adjusted to 100 mg permanently once their weight reached 40 kg. On completion of all part B doses, children were given the option to continue mepolizumab treatment within a subsequent long-term access program (GSK ID 201956/NCT00244686).[16] For those who chose not to transition into the long-term access program, a follow-up visit was conducted 12 weeks after their last part B dose of mepolizumab (overall study week 80).

Before inclusion in part B, children agreed to continue receiving mepolizumab, and their parents/legal guardians were required to provide consent. The study was performed in accordance with Good Clinical Practice guidelines, ethical principles outlined in the Declaration of Helsinki 2008, and institutional review board approvals/processes. Anonymized individual participant data and study documents can be requested from www.clinicalstudydatarequest.com.

End points and assessments

Part B primary end points were the incidence of adverse events (AEs), clinically significant changes in vital sign measurements and laboratory parameters, and the frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies. On-treatment, posttreatment, and drug-related AEs; serious adverse events (SAEs; including fatalities); and adverse events of special interest (AESIs) were recorded at every visit. The AESIs for mepolizumab included systemic (allergic and nonallergic) reactions, local injection-site reactions, cardiac disorders (serious cardiac, vascular, thromboembolic, and serious ischemic events), infections, neoplasms, and malignancies. Vital signs were assessed at every study visit. Immunogenicity samples were collected before dosing at overall study weeks 44 and 68 and at follow-up week 80 for participating patients. To characterize the long-term pharmacodynamics of mepolizumab, the secondary end point of absolute blood eosinophil count (cells per microliter) was recorded at overall study weeks 32, 44, 56, 68, and 72 and follow-up week 80.

Exploratory end points included asthma exacerbation frequency over the treatment period plus changes from baseline in Asthma Control Questionnaire, 7-item (ACQ-7) or 5-item (ACQ-5), and Childhood Asthma Control Test (C-ACT) scores at overall study weeks 32, 44, 56, 68, 72, and 80. An exacerbation was defined as disease worsening that required systemic corticosteroids and/or an ED visit and/or hospitalization. Annualized exacerbation rates were compared with those calculated over the 12 months preceding mepolizumab administration in part A. Analysis of ACQ-5 data was performed using the 5 symptoms item responses of the ACQ-7 questionnaire.

Comparison with adult/adolescent studies

Asthma exacerbation rates and changes from baseline in ACQ-5 scores at the end of treatment were compared with those of the corresponding adult and adolescent data from mepolizumab phase II b/3 trials (Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma [DREAM; MEA112997/NCT01000506], Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma [MENSA; MEA115588/NCT01691521], Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma [MUSCA; 200862/NCT02281318], and the Steroid Reduction with Mepolizumab Study [SIRIUS; MEA115575/NCT01691508]) to contextualize the exploratory efficacy data observed in this study.[17-19]

Statistical analysis

This article contains a complete analysis of the long-term data collected within part B; all part A data have been published previously.[14] The sample size for part A was determined by the number of children needed for adequate PK and pharmacodynamic evaluations based on previous studies.[14] Therefore

TABLE I. Summary of patients' demographics and baseline characteristics

	Mepolizumab, 40 mg (n = 16)	Mepolizumab, 100 mg (n = 10)	Mepolizumab, 40/100 mg* (n = 4)	Mepolizumab, total (n = 30)
Derived age† (y)	7.5 (1.6)	10.0 (1.3)	9.3 (1.5)	8.6 (1.9)
Sex, no. (%)				
Male	12 (75)	5 (50)	3 (75)	20 (67)
Female	4 (25)	5 (50)	1 (25)	10 (33)
Race, no. (%)				
Asian	5 (31)	1 (10)	1 (25)	7 (23)
Black or African American	2 (13)	3 (30)	2 (50)	7 (23)
White	8 (50)	6 (60)	1 (25)	15 (50)
Multiple	1 (6)	0	0	1 (3)
Weight‡ (kg)	27.5 (3.9)	52.5 (6.6)	34.1 (7.8)	36.2 (12.5)
Body mass index‡ (kg/m^2)	16.1 (1.3)	23.5 (2.7)	16.8 (4.0)	18.5 (4.0)
Pre-BD lung function§				
FEV_1 (mL)	1381 (370)	1940 (310)	1583 (541)	1594 (444)
Predicted normal FEV_1 (%)	89.5 (15.14)	92.3 (6.94)	87.7 (28.50)	90.2 (14.84)
FVC	1759 (387.0)	2436 (448.4)	2098 (329.7)	2030 (499.2)
FEV_1/FVC ratio	0.79 (0.109)	0.80 (0.091)	0.74 (0.148)	0.79 (0.107)
No. of exacerbations requiring corticosteroids in 12 mo before screening, median (range)§	2.5 (2-6)	2.0 (2-10)	4.5 (3-8)	2.5 (2-10)
Patients with an exacerbation requiring hospitalization in 12 mo before screening, no. (%)§	8 (50)	2 (20)	2 (50)	12 (40)
Blood eosinophil count (cells/μL), geometric mean (SD log)§	306 (0.807)	331 (0.910)	506 (0.085)	336 (0.789)
ACQ-7 score§	1.83 (1.01)	1.39 (0.96)	2.64 (1.23)	1.79 (1.06)
ACQ-5 score§	1.94 (1.03)	1.42 (1.09)	2.75 (1.59)	1.87 (1.17)
C-ACT score§	16.4 (5.3)	20.4 (3.2)	15.8 (4.3)	17.6 (4.9)

Data are means (SDs), unless otherwise stated.

BD, Bronchodilator; *FVC*, forced vital capacity.

*These patients weighed less than 40 kg and received 40 mg of mepolizumab at the start of part B and were moved to the 100 mg treatment group when their weight reached 40 kg or greater.

†Only year of birth was collected, with age derived by using an imputed birth date of June 30th.

‡Data are from the latest value recorded before the first dose of mepolizumab in part B of the study.

§Data are from the latest value recorded before the first dose of mepolizumab in part A of the study.

the study population for part B was determined by the number of children enrolled and treated in part A who were eligible for and willing to participate in Part B. All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). End points were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range).

AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated. For blood eosinophil counts, the ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (half the minimum nonzero result) was imputed before log-transformation. For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient population

Of the 36 children enrolled in part A, 30 (83%) consented to take part in part B; 2 eligible children decided not to enter part B, and 4 were not eligible because they did not complete part A (see Fig E1 in this article's Online Repository at www.jacionline.org). A total of 29 (97%) children completed part B; 1 was withdrawn from the study because of a protocol deviation of poor compliance with study visits and study medication. Demographic and baseline characteristics are shown in Table I. The mean age was 8.6 (SD, 1.9) years, and 20 (67%) of the children were male. At the start of part B, the mean weight was 36.2 kg (SD, 12.5); 4 children weighing less than 40 kg at part B screening reached 40 kg or greater during part B, resulting in permanent adjustment of their mepolizumab dose from 40 to 100 mg administered subcutaneously. In part B most children (90%) received all 13 treatments and spent an average of 355 days on treatment, with exposure to mepolizumab amounting to 29.2 patient years.

Safety

Across all part B treatment groups, on-treatment AEs were reported in 27 (90%) children (Table II), the most frequent of which were bronchitis (9 children), headache (8 children), and asthma exacerbation (7 children). Of the 27 children experiencing on-treatment AEs during the 52-week treatment period, 8 (27%) experienced an on-treatment AE that was considered related to mepolizumab by the investigator; these included headache (4 children), upper abdominal pain (3 children), and pyrexia (2 children). The majority of on-treatment AEs were moderate in intensity. Eight on-treatment AEs did not resolve by the end of the study; one of these (mild upper abdominal pain) was considered related to mepolizumab.

TABLE II. Summary of AEs and immunogenicity

	Patients, no. (%)			
	Mepolizumab, 40 mg (n = 16)	Mepolizumab, 100 mg (n = 10)	Mepolizumab, 40/100 mg* (n = 4)	Mepolizumab, total (n = 30)
Any AE	15 (94)	8 (80)	4 (100)	27 (90)
On-treatment† AEs	15 (94)	8 (80)	4 (100)	27 (90)
Posttreatment‡ AEs	5 (31)	4 (40)	0	9 (30)
Treatment-related§ on-treatment AEs	4 (25)	3 (30)	1 (25)	8 (27)
AEs leading to discontinuation of treatment or withdrawal	0	0	0	0
Most frequent on-treatment AEs (>10% of total population)				
Bronchitis	5 (31)	3 (30)	1 (25)	9 (30)
Headache	4 (25)	3 (30)	1 (25)	8 (27)
Asthma	4 (25)	2 (20)	1 (25)	7 (23)
Nasopharyngitis	3 (19)	1 (10)	2 (50)	6 (20)
Upper respiratory tract infection	2 (13)	2 (20)	1 (25)	5 (17)
Influenza	3 (19)	0	1 (25)	4 (13)
Any SAE	4 (25)	2 (20)	1 (25)	7 (23)
On-treatment† SAEs	4 (25)	2 (20)	1 (25)	7 (23)
Posttreatment‡ SAEs	1 (6)	1 (10)	0	2 (7)
Treatment-related§ on-treatment SAEs	0	0	0	0
Fatal SAEs	0	0	0	0
On-treatment AESIs				
Systemic reactions	1 (6)	1 (10)	0	2 (7)
Allergic hypersensitivity (anaphylactic shock‖ and generalized rash)	1 (6)	1 (10)	0	2 (7)
Nonallergic	0	0	0	0
Local injection-site reactions	0	0	0	0
All infections	11 (69)	7 (70)	4 (100)	22 (73)
Serious	0	1 (10)	0	1 (3)
Opportunistic	0	1 (10)	0	1 (3)
Neoplasms	0	0	0	0
Malignancies	0	0	0	0
Cardiac disorders	0	0	0	0
Serious CVT events	0	0	0	0
Serious ischemic events	0	0	0	0
ADA assay result				
Negative	16 (100)	10 (100)	4 (100)	30 (100)
Positive#	0	0	0	0

AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms.
CVT, Cardiac, vascular, and thromboembolic.
*These patients weighed less than 40 kg and received 40 mg of mepolizumab at the start of part B and were moved to the 100 mg treatment group when their weight reached 40 kg or greater.
†Any AE commencing within 4 weeks of the last dose of mepolizumab.
‡AEs commencing more than 4 weeks after the last mepolizumab dose.
§As assessed by the treating investigator.
‖Anaphylactic shock was due to a previously diagnosed peanut allergy and was not considered related to mepolizumab treatment by the investigator.
#A patient's results were considered "positive" if they had at least 1 positive postbaseline ADA assay result within part B of the study.

Nine on-treatment SAEs, none of which were considered related to mepolizumab by the investigator, were reported in 7 (23%) children; these resolved without interruption of mepolizumab treatment. Asthma exacerbation (5 children) was the only on-treatment SAE reported in more than 1 child. On-treatment SAEs reported by 1 child each included anaphylactic shock, epistaxis, and pneumonia. The SAE of anaphylactic shock occurred in a 6-year-old boy in the group receiving 40 mg of mepolizumab subcutaneously 27 days after his fifth part B dose of mepolizumab and was determined to be caused by a previously diagnosed peanut allergy. The SAE of pneumonia occurred in a 10-year-old girl 25 days after her second part B dose of mepolizumab. Two additional SAEs were reported after treatment (wheezing and asthma exacerbation) and were not considered related to mepolizumab treatment. No fatal SAEs were reported (Table II). A comparison of these SAE rates with those from adult and adolescent studies is shown in Table E1 in this article's Online Repository at www.jacionline.org.

On-treatment AESIs are outlined in Table II. Two children reported systemic reactions; 1 (anaphylactic shock) was judged by the investigator to be a serious event and is described above. One child in the group receiving 100 mg of mepolizumab subcutaneously (a 10-year-old boy) had an event of moderate-intensity body rash with pruritis 3 days after his final dose of mepolizumab in part B. This was judged to be related to mepolizumab treatment but was not deemed serious. On-treatment infections were reported in 22 (73%) children, the

TABLE III. Summary of blood eosinophils (cells/μL)

Time point in part B (within the overall study)	Blood eosinophils (cells/μL), geometric mean (SD log)			
	Mepolizumab, 40 mg (n = 16)	Mepolizumab, 100 mg (n = 10)	Mepolizumab, 40/100 mg* (n = 4)	Mepolizumab, total (n = 30)
Baseline† (week 0)	306 (0.807)	331 (0.910)	506 (0.085)	336 (0.789)
Week 12 (week 32)	52 (0.820)	58 (0.796)	37 (0.696)	52 (0.784)
Week 24 (week 44)	51 (0.712)	63 (0.772)	74 (1.495)	58 (0.839)
Week 36 (week 56)	48 (0.642)	57 (0.597)	29 (0.767)	48 (0.656)
Week 48 (week 68)	47 (1.090)	71 (0.647)	55 (1.473)	55 (0.995)
Week 52 (week 72)	48 (0.858)	44 (1.020)	49 (0.166)	47 (0.841)
Week 60 (week 80‡; follow-up)	164 (0.973)	199 (1.666)	NA	179 (1.274)

NA, Not available.

*These patients weighed less than 40 kg and received 40 mg of mepolizumab at the start of part B and were moved to the 100 mg treatment group when their weight reached 40 kg or greater.

†Baseline was defined as the latest value recorded before the first dose of mepolizumab in part A.

‡Week 80 was not applicable to patients transitioning to the long-term access program.

most frequent of which (n > 3 children) included bronchitis, nasopharyngitis, upper respiratory tract infection, and influenza. One child (a 10-year-old girl) had an event of pneumonia 25 days after her second part B dose of mepolizumab, which was not judged to be related to mepolizumab treatment. One child (a 10-year-old boy) had 2 on-treatment events of oral herpes, which were not judged to be related to mepolizumab treatment or to represent invasive disease/opportunistic infection. No children reported local injection-site reactions, neoplasms, malignancies, or cardiac events. Throughout part B, there were no apparent treatment-related changes in clinical laboratory parameters, electrocardiographic results, or vital signs (data not shown).

Immunogenicity

No anti-drug antibody (ADA) or neutralizing antibody responses were reported throughout part B (Table II). Of the 2 children with positive ADA responses in part A, one did not continue into part B, and the other was ADA negative throughout part B.

Pharmacodynamics

The baseline geometric mean blood eosinophil count (collected before the first mepolizumab treatment in part A) across all 30 patients enrolled in part B was 336 cells/μL. Geometric mean blood eosinophil counts were reduced to approximately 50 to 60 cells/μL at the first time point measured in part B (preceding the fourth part B dose of mepolizumab, Table III), and this reduction was sustained through the cessation of treatment at overall study week 72 (Fig 1 and Table III). In children followed up to week 80 (12 weeks since the last dose), blood eosinophil counts began to increase toward but did not reach baseline values (Fig 1 and Table III).

Efficacy

Asthma control improved relative to baseline through part B, as indicated by improvements in ACQ-7, ACQ-5, and C-ACT scores (see Fig E2 and Table E2 in this article's Online Repository at www.jacionline.org). Before receiving mepolizumab in part A, children's mean ACQ-7, ACQ-5, and C-ACT scores were 1.79 (95% CI, 1.39-2.19), 1.87 (95% CI, 1.44-2.31), and 17.6 (95% CI, 15.8-19.4), respectively. Part B improvements in asthma control were greatest at week 36 (overall study week 56), with mean scores reaching 0.79 (95% CI, 0.51-1.06), 0.79 (95% CI, 0.51-1.07), and 22.0 (95% CI, 20.7-23.3), respectively. At week 52, 4 weeks after the last dose of mepolizumab, mean scores were 1.14 (95% CI, 0.79-1.49), 1.08 (95% CI, 0.64-1.52), and 20.5 (95% CI, 18.8-22.2), respectively.

A minimal clinically important difference (MCID) of at least 0.5 points from baseline ACQ-7 and ACQ-5 scores was met by 55% and 59% of children, respectively, at week 52 (overall study week 72, see Table E2). This was similar to ACQ-5 score improvements observed in older patients, with 42% to 59% of adults and adolescents achieving MCIDs from baseline ACQ-5 scores at the end of mepolizumab treatment (see Table E3 in this article's Online Repository at www.jacionline.org).

Fourteen (47%) children had 1 or more on-treatment exacerbations during part B (see Table E4 in this article's Online Repository at www.jacionline.org), 5 of whom required an ED visit or hospitalization. Annualized on-treatment exacerbation rates were lower than baseline for all treatment groups, with the annualized on-treatment rate (1.09 events/y [95% CI, 0.63-1.89 events/y]) representing a 69% decrease from the 12 months before part A screening (a mean of 3.5 events). On-treatment exacerbation rates reported for children in part B are similar to those reported in adults and adolescents receiving mepolizumab, which range from 0.51 to 1.44 events/y (see Table E3). Overall, 28 (93%) children experienced at least a 25% reduction, 24 (80%) experienced at least a 50% reduction, and 18 (60%) experienced at least a 75% reduction in exacerbations (see Table E4). Children reported greater on-treatment rates of exacerbations requiring hospitalization than adults and adolescents, with children reporting a mean of 0.21 events/y (95% CI, 0.08-0.55 events/year) and adults and adolescents reporting means of 0.02 to 0.10 events/year (see Tables E3 and E4).

DISCUSSION

This was a long-term (52-week) study of mepolizumab in children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. The safety data (including SAEs) from part B demonstrate that mepolizumab was well tolerated, with a safety profile consistent with that of part A[14] and similar to that observed in previous studies of adults and adolescents.[17-20]

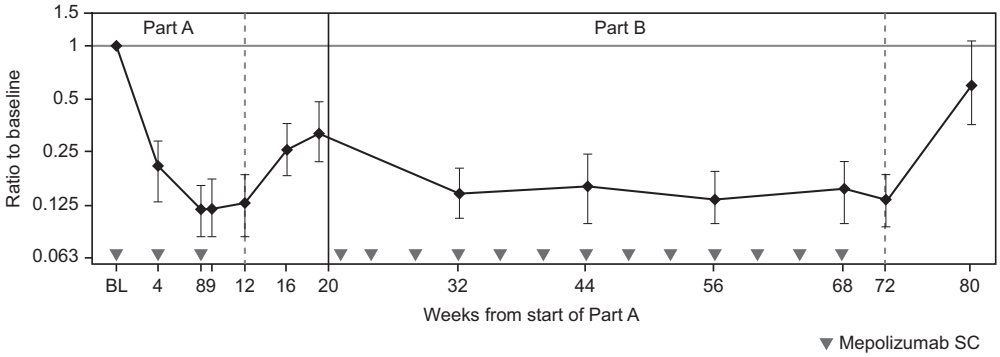

FIG 1. Geometric mean ratio to baseline (defined as the latest value recorded before the first dose of mepolizumab in part A) of blood eosinophil counts throughout parts A and B. *Vertical bars* represent 95% CIs, and *dashed lines* indicate the start of the follow-up period in each study part. Week 80 was not applicable to patients transitioning to the long-term access program. *BL*, Baseline; *SC*, subcutaneous.

Mepolizumab consistently reduced blood eosinophil counts, whereas exploratory analyses suggested improvements in asthma control similar to those observed in adults and adolescents.[17-19]

The safety and tolerability of mepolizumab in part B of the study was consistent with that in part A. No new safety concerns were observed after long-term treatment with mepolizumab in children compared with adults and adolescents with severe asthma and an eosinophilic phenotype.[14,17-19,21] Also in line with previous long-term observations in adults and adolescents,[21] the incidence of reported local injection-site reactions decreased over time; 5 children reported reactions in part A, and no reactions were reported in part B. Positive immunogenicity samples were infrequent across parts A and B, with no positive immunogenicity results in part B. This is consistent with the low immunogenicity observed in adults and adolescents after treatment with mepolizumab, suggesting a low or limited immune response to mepolizumab in children.[17-19,21,22]

In terms of pharmacodynamic responses, blood eosinophil counts began to increase after cessation of treatment at the end of part A; in previous adult and adolescent studies this response has been associated with a worsening of asthma symptoms (as indicated by ACQ-7 and ACQ-5 scores).[22,23] After reinitiation of mepolizumab treatment in part B, blood eosinophil counts again began to decrease. The sustained reduction in blood eosinophil counts (to 50 cells/μL) observed during the 12-week dosing phase of mepolizumab in part A[14] was reproduced during the long-term, 52-week dosing phase in part B. This reduction in blood eosinophil counts after treatment with 40 or 100 mg of subcutaneous mepolizumab is also consistent with blood eosinophil counts achieved in adult/adolescent studies (approximately 40 cells/μL) across a 10-fold range of doses (75–750 mg) and differing administration routes (subcutaneous or intravenous), suggesting that higher doses might not reduce blood eosinophil counts further.[17,19,24]

In the exploratory analysis of efficacy data, reduced on-treatment exacerbation rates observed in children appear to be consistent with those noted previously in adults and adolescents,[17-19] with mean annualized rates reduced to approximately 1 event/y after mepolizumab treatment in both age groups with this highly exacerbating asthma phenotype. As expected, there was a greater frequency of on-treatment asthma exacerbations during part B compared with part A because of the longer study duration of part B. However, annualized exacerbation rates in part B were considerably lower than rates in the 12 months before screening for each treatment group, with 80% of children at least halving their exacerbation rates compared with pretreatment values.

Although annualized exacerbation rates recorded before and during mepolizumab treatment within this study are similar to those previously reported in adults and adolescents, the hospitalization rate appears to be higher.[17-19,21] This is likely due to differences in hospitalization criteria for children and adolescents compared with adults[25,26] because the children enrolled in this study presented with baseline markers of disease (eg, blood eosinophil counts and lung function) similar to those reported in the equivalent adult and adolescent studies. This also highlights that as a vulnerable patient population, children with severe asthma with an eosinophilic phenotype are more likely to be hospitalized than adults presenting with similar symptoms during an exacerbation.[27]

Improvements in asthma control were observed in children receiving mepolizumab treatment (as indicated by ACQ and C-ACT scores). At the end of treatment, approximately 40% to 60% of both children and adults/adolescents met MCIDs indicative of disease improvement.[17-19] Additionally, consistency observed across ACQ-7, ACQ-5, and C-ACT responses throughout both parts of this study provides reassurance that asthma control parameters evaluated by using ACQ and C-ACT questionnaires proportionately reflect symptom control in children with severe asthma, as suggested by previous comparisons of these tools.[28]

There are several limitations to this study that should be acknowledged. This was an open-label study in children aged 6 to 11 years to assess the PK, pharmacodynamics, and safety profiles of mepolizumab in children with severe asthma with an eosinophilic phenotype, and therefore no direct comparator was available. A double-blind, placebo-controlled randomized trial is difficult to perform in this patient population because of the rarity of the disease phenotype in this age group.[12] Moreover, it can be a difficult decision for parents to enroll their children in a clinical trial, making enrollment particularly challenging. Therefore the efficacy data from this study have been compared with those of the corresponding adult/adolescent program, in which these challenges are less prevalent, and consequently, a more adequate sample size could be enrolled.[17-19] This comparison can be

considered relevant because consistent eligibility criteria were applied across the studies, irrespective of age.

When reviewing the results, it should be noted that the small sample size and uncontrolled design of this study limited further assessments of efficacy. Additionally, because the part B follow-up period was not required for children transitioning to the long-term access program (Study 201956), the posttreatment observation period for these children was of limited length.

In conclusion, the results of this long-term study suggest that mepolizumab is well tolerated after 52 weeks of continuous treatment in children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. Importantly, safety data generated by part B indicate that mepolizumab administered at a body weight–dependent dose of 40 or 100 mg administered subcutaneously has an acceptable safety profile for long-term use in children with peripheral blood eosinophil counts of 150 cells/μL or greater (or ≥300 cells/μL in the previous 12 months). Although limited, the uncontrolled efficacy data in children 6 to 11 years of age appeared to be consistent with adult/adolescent efficacy data. The PK in part A and the pharmacodynamics and safety profiles of mepolizumab in both parts of this study appear to be similar to those found in adults and adolescents, supporting the extrapolation of mepolizumab treatment efficacy data from adults and adolescents to children.

Clinical implications: These safety, pharmacodynamic, and efficacy data support long-term mepolizumab use in children 6 to 11 years of age with severe asthma with an eosinophilic phenotype and are similar to those reported in adults/adolescents.

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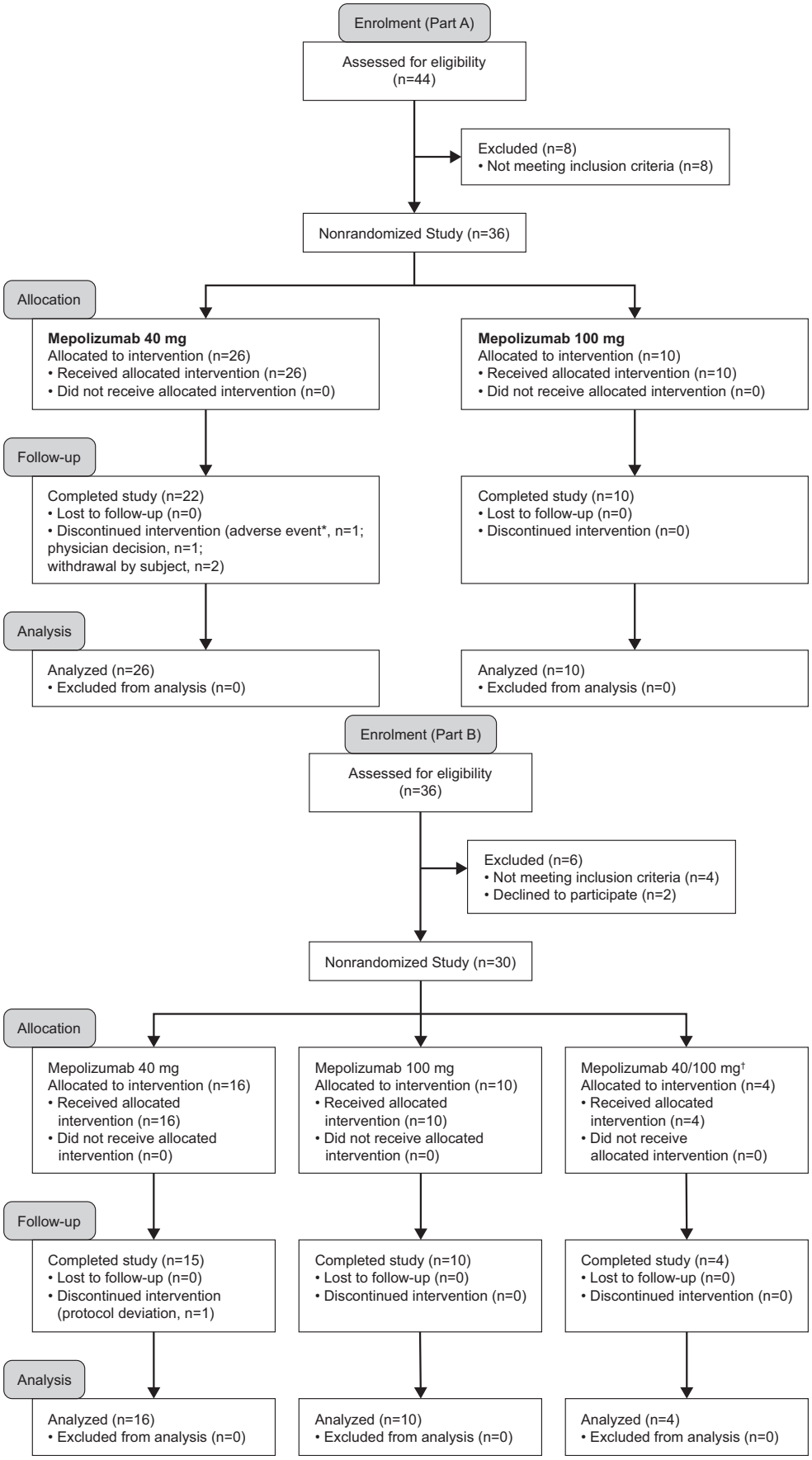

FIG E1. Summary of patient disposition for parts A and B. Treatment group allocated according to body weight: 40 mg (<40 kg) and 100 mg (≥40 kg). *Child withdrew because of an AE of asthma. †These patients weighed less than 40 kg and received 40 mg of mepolizumab at the start of part B and were moved to the 100 mg mepolizumab subcutaneous treatment group when their weight reached 40 kg or greater.

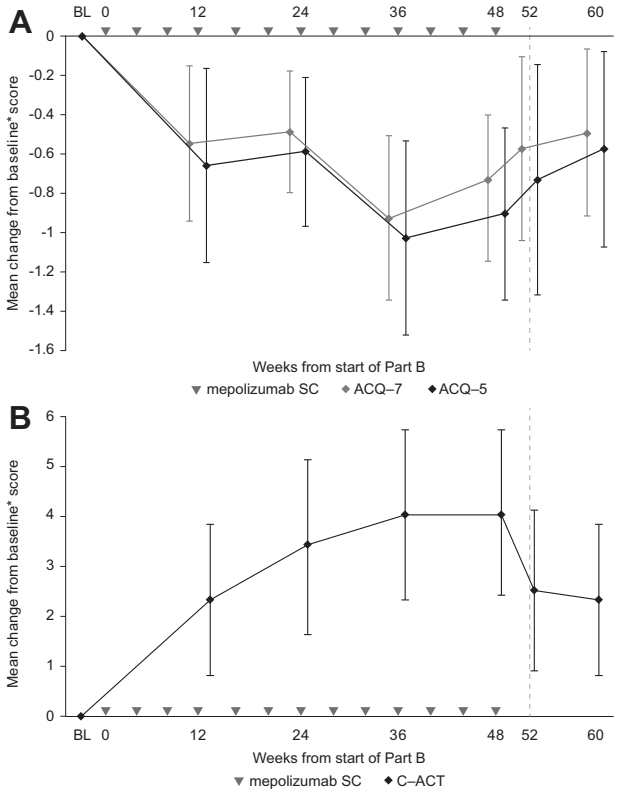

FIG E2. Mean change from baseline (defined as the latest value recorded before the first dose of mepolizumab in part A) in ACQ-7 and ACQ-5 scores **(A)** and C-ACT scores **(B)** throughout part B. *Vertical bars* represent 95% CIs, and *dashed lines* indicate the start of the part B follow-up period. Week 60 was not applicable to patients transitioning to the long-term access program. *BL*, Baseline; *SC*, subcutaneous.

TABLE E1. Comparison of SAEs in study 200363 and adolescent/adult data from the mepolizumab clinical development program[E1,E2,E3,E4]

	Study size	Study duration (wk)	Placebo	Mepolizumab (all doses)
Patients experiencing SAEs, no. (%)				
Children				
200363, part B	30	52*	NA	7 (23)
Adults/adolescents				
DREAM	616	52	25 (16)	63 (14)
MENSA	576	32	27 (14)	30 (8)
MUSCA	551	24	22 (8)	15 (5)
SIRIUS	135	24	12 (18)	1 (1)
Patients experiencing treatment-related SAEs, no. (%)				
Children				
200363, part B	30	52*	NA	0
Adults/adolescents				
DREAM	616	52	0	2 (<1)
MENSA	576	32	1 (<1)	1 (<1)
MUSCA	551	24	1 (<1)	0
SIRIUS	135	24	0	0

DREAM, Mepolizumab for Severe Eosinophilic Asthma; *MENSA*, Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma; *MUSCA*, Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma; *NA*, not applicable; *SIRIUS*, Steroid Reduction with Mepolizumab Study.
*Duration of study B only (total duration of parts A and B was 80 weeks).

TABLE E2. Summary of exploratory efficacy end points during part B

Time point in part B (within the overall study)	Mean change from baseline* (95% CI)	Patients meeting MCID from baseline,* no. (%)
ACQ-7		
Week 12 (week 32)	−0.54 (−0.94 to −0.15)	15/29 (52)
Week 24 (week 44)	−0.49 (−0.79 to −0.18)	13/28 (46)
Week 36 (week 56)	−0.93 (−1.34 to −0.51)	19/29 (66)
Week 48 (week 68)	−0.77 (−1.15 to −0.40)	18/29 (62)
Week 52 (week 72)	−0.57 (−1.04 to −0.10)	16/29 (55)
Week 60 (week 80†; follow-up)	−0.49 (−0.92 to −0.07)	12/23 (52)
ACQ-5		
Week 12 (week 32)	−0.66 (−1.15 to −0.16)	17/29 (59)
Week 24 (week 44)	−0.59 (−0.97 to −0.21)	14/28 (50)
Week 36 (week 56)	−1.03 (−1.52 to −0.53)	20/29 (69)
Week 48 (week 68)	−0.90 (−1.34 to −0.47)	19/29 (66)
Week 52 (week 72)	−0.73 (−1.32 to −0.14)	17/29 (59)
Week 60 (week 80†; follow-up)	−0.57 (−1.07 to −0.08)	11/23 (48)
C-ACT		
Week 12 (week 32)	2.3 (0.8 to 3.8)	NA
Week 24 (week 44)	3.4 (1.6 to 5.1)	NA
Week 36 (week 56)	4.0 (2.3 to 5.7)	NA
Week 48 (week 68)	4.0 (2.4 to 5.7)	NA
Week 52 (week 72)	2.5 (0.9 to 4.1)	NA
Week 60 (week 80†; follow-up)	2.3 (0.8 to 3.8)	NA

The MCID of ACQ scores was defined as a 0.5-point or greater reduction.
NA, Not available.
*Baseline was defined as the latest value recorded before the first dose of mepolizumab in part A.
†Week 80 was not applicable to patients transitioning to the long-term access program.

TABLE E3. Comparison of efficacy data from study 200363 and adolescent/adult data from the mepolizumab clinical development program[E1,E2,E3,E4]

	Study size	Study duration (wk)	Placebo	Mepolizumab (all doses)
Annualized rate of on-treatment exacerbations (95% CI)				
Children				
200363, part B	30	52*	NA	1.09 (0.63-1.89)
Adults/adolescents				
DREAM	616	52	2.40 (1.95-2.95)	1.28 (1.11-1.48)
MENSA	576	32	1.74 (1.44-2.11)	0.88 (0.74-1.04)
MUSCA	551	24	1.21 (1.01-1.46)	0.51 (0.39-0.65)
SIRIUS	135	24	2.12 (1.66-2.70)	1.44 (1.08-1.93)
Annualized rate of on-treatment exacerbations requiring hospitalization (95% CI)				
Children				
200363, part B	30	52*	NA	0.21 (0.08-0.55)
Adults/adolescents				
DREAM	616	52	0.18 (0.10-0.32)	0.10 (0.06-0.16)
MENSA	576	32	0.10 (0.05-0.20)	0.05 (0.02-0.09)
MUSCA	551	24	0.07 (0.03-0.15)	0.02 (0.01-0.07)
SIRIUS	135	24	Not estimable†	Not estimable†
≥0.5-Point reduction from baseline in ACQ-5 score at end of treatment,‡ no. (%) of patients				
Children				
200363, part B	30	52*	NA	17/29 (59)
Adults/adolescents				
DREAM	616	52	77/153 (50)	222/452 (49)
MENSA	576	32	85/186 (46)	202/373 (54)
MUSCA	551	24	116/276 (42)	161/274 (59)
SIRIUS	135	24	19/66 (29)	29/69 (42)

DREAM, Mepolizumab for Severe Eosinophilic Asthma; *MENSA*, Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma; *MUSCA*, Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma; *NA*, not available; *SIRIUS*, Steroid Reduction with Mepolizumab Study.

*Duration of study part B only (total duration of study parts A and B was 80 weeks).

†Insufficient events reported to estimate an exacerbation rate.

‡Patients with missing ACQ-5 scores at baseline have been excluded.

TABLE E4. Summary of on-treatment exacerbations

	Mepolizumab, 40 mg (n = 16)	Mepolizumab, 100 mg (n = 10)	Mepolizumab, 40/100 mg* (n = 4)	Mepolizumab, total (n = 30)
Any exacerbation				
Children, no. (%)	8 (50)	3 (30)	3 (75)	14 (47)
No. of events	11	12	8	31
Annualized rate				
Mean rate/year (95% CI)	0.76 (0.34-1.68)	1.20 (0.51-2.83)	1.98 (0.58-6.79)	1.09 (0.63-1.89)
Reduction from baseline,† no. (%)				
≥25%	14 (88)	10 (100)	4 (100)	28 (93)
≥50%	13 (81)	8 (80)	3 (75)	24 (80)
≥75%	10 (63)	7 (70)	1 (25)	18 (60)
100%	8 (50)	7 (70)	1 (25)	16 (53)
Exacerbations requiring hospitalization/ED visit				
Children, no. (%)	2 (13)	2 (20)	1 (25)	5 (17)
No. of events	2	5	1	8
Exacerbations requiring hospitalization				
Children, no. (%)	2 (13)	2 (20)	1 (25)	5 (17)
No. of events	2	3	1	6
Annualized rate				
Mean rate/y (95% CI)	0.14 (0.03-0.62)	0.30 (0.08-1.08)	0.25 (0.03-2.19)	0.21 (0.08-0.55)

*These patients weighed less than 40 kg and received 40 mg of mepolizumab at the start of part B and were moved to the 100 mg treatment group when their weight reached 40 kg or more.

†Baseline defined as the exacerbation rate calculated from the 12 months before screening in part A of the study.