NDA/BLA Multi-Disciplinary Review and Evaluation

Application type	sBLA
Application number(s)	125526/S-12, 761122/S-2, 761122/S-3
Priority or standard	Standard
Submit date(s)	11/16/2018, 7/29/2019, 8/28/2019
Received date(s)	11/16/2018, 7/29/2019, 8/28/2019
PDUFA goal date	9/16/2019
Division/Office	Division of Pulmonary, Allergy and Rheumatology Products
Review completion date	9/9/2019
Established/proper name	mepolizumab
(Proposed) trade name	Nucala
Pharmacologic class	Interleukin-5 antagonist monoclonal antibody (IgG1 kappa)
National drug code	0173-0881-01 and 0173-0881-61
Applicant	GlaxoSmithKline
Dosage form	Lyophilized Powder for Subcutaneous Injection and Liquid Formation for Subcutaneous Injection via Autoinjector or Safety Syringe Device
Applicant proposed dosing regimen	40 mg administered subcutaneously once every 4 weeks
Applicant proposed indication(s)/population(s)	Add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype
Recommendation on regulatory action	Approval
Recommended indication/dosing regimen	Unchanged

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OPDP = Office of Prescription Drug Promotion
OSIS = Office of Study Integrity and Surveillance
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DMEPA = Division of Medication Error Prevention and Analysis
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Glossary

ACQ	Asthma Control Questionnaire
ADA	antidrug antibody
AE	adverse event
AUC	area under the curve
BLA	Biologic License Application
C-ACT	Childhood Asthma Control Test
CFR	Code of Federal Regulations
CI	confidence interval
CSE	clinically significant exacerbations
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
IgE	immunoglobulin E
IL5	human interleukin 5
IV	intravenous
PD	pharmacodynamic
PK	pharmacokinetic
PMR	postmarketing requirement
Q4W	every 4 weeks
RR	rate ratio
SAE	serious adverse event
SC	subcutaneous
SE	standard error

1. Executive Summary

1.1. Product Introduction

GlaxoSmithKline submitted an efficacy supplement S-012for biologic license application (BLA) 125526 to expand the treatment indication down to 6 years of age for the add-on maintenance treatment of severe asthma, and with an eosinophilic phenotype. Mepolizumab is a human interleukin 5 (IL5) antagonist monoclonal antibody. IL5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. It was approved in 2015 and was the first-in-class. Mepolizumab is currently approved for 1) add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, and 2) treatment of adult patients with eosinophilic granulomatosis with polyangiitis.

For asthma in adolescent and adults, the approved dosage is 100 mg administered subcutaneously ever 4 weeks. For eosinophilic granulomatosis with polyangiitis, the approved dosage is 300 mg administered subcutaneously every 4 weeks. In June 2019, mepolizumab was approved in two new presentations– a prefilled safety syringe device and an autoinjector for adolescents and adults for home use under a separate BLA 761122. The Applicant is seeking a new dose of 40 mg administered subcutaneously every 4 weeks for 6 to 11 year olds for the original lyophilized powder in a single-dose vial for reconstitution administered by a healthcare provider. The recently approved prefilled safety syringe device and autoinjector will not be used for 6-11 year olds; however, a prior approval labeling supplement (S-002) was submitted to provide labeling revisions to the United States Product Insert (USPI), Patient Information and the Instructions for Use. Additionally, as the efficacy supplement fulfills pediatric PMRs under BLA 125526, an additional prior approval supplement (S-003) was submitted to BLA 761122 to satisfy the PMRs under BLA 761122. For further details see Labeling Recommendations and Postmarketing Requirements and Commitments.

Mepolizumab is currently approved in over 40 countries including the European Union and Japan. The application is submitted in electronic Common Technical Document format.

Through the review, severe asthma with an eosinophilic phenotype will be referred to as severe eosinophilic asthma.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on an overlap in the clinical presentation of both adult and pediatric severe eosinophilic asthma, consistency in the therapeutic approach, consistency of the mepolizumab mechanism of action, and relevance of the clinical endpoints, efficacy in children 6 to 11 years of age was extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older. The extrapolation was supported by pharmacokinetic (PK) analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks and a similar pharmacodynamic response. Refer to the original review for BLA 125526 for review of efficacy in ≥12-year-olds.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This efficacy supplement for mepolizumab proposes to expand the indication in patient with severe asthma, and with an eosinophilic phenotype, down to patients 6 years of age and older. To support the efficacy and safety of mepolizumab for the proposed indication, the Sponsor submitted Trial 200363, an open-label clinical trial in children6 to 11 years of age, with severe asthma and an eosinophilic phenotype (defined as having a blood eosinophil count ≥300 cells/uL in the past 12 months or ≥150 cells/uL at visit 1). Trial 200363 was conducted to investigate the pharmacokinetics (PK), pharmacodynamics (PD), and long-term safety of mepolizumab administered SC to subjects with severe asthma with an eosinophilic phenotype aged 6 to 11 years. Thirty-six (36) subjects received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of mepolizumab administered subcutaneously once every 4 weeks for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 subjects received mepolizumab for an additional 52 weeks (long phase).

Based on an overlap in the clinical presentation of both adult and pediatric severe eosinophilic asthma, consistency in the therapeutic approach, consistency of the mepolizumab mechanism of action, and relevance of the clinical endpoints, efficacy for 6- to 11-year-olds is extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older, based on pharmacokinetic analyses demonstrating comparable systemic exposure for the proposed dose of 40 mg administered subcutaneously every 4 weeks to the approved 100 mg SC dose in patients ≥12 year of age. The pharmacodynamic response was also comparable.

The safety profile of mepolizumab is well-established since its approval in 2015. The safety profile in 6- to 11-year-olds, as demonstrated in the submitted clinical trial, was similar to that observed in adults and adolescents 12 years of age and older. Mepolizumab is the first anti-human interleukin 5 (anti-IL5) proposed for children less than 12 years of age and the first biologic approved for children less than 12 years of age with severe eosinophilic asthma. The overall risk-benefit is favorable for the approval of mepolizumab down to age 6 as add-on maintenance treatment of patients with severe asthma, and an eosinophilic phenotype.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction leading to chronic symptoms despite current standard of care treatment. While many exacerbations may be managed with oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death. Severe uncontrolled asthma accounts for approximately 5% of all patients with asthma. While there are no clinical guidelines that specifically define severe eosinophilic asthma, the estimated prevalence is ≤ 3% of all patients with asthma.	While asthma is a common condition, severe asthma with an eosinophilic phenotype represents a small percentage of the overall asthma population. Nonetheless, patients with severe uncontrolled asthma experience the greatest burden of disease with significant morbidity and deleterious effects on quality of life and daily activity as well as potential for mortality.
Current Treatment Options	There are four biologics currently approved for the treatment of asthma. Omalizumab is an anti-immunoglobulin E (IgE) for treatment of allergic asthma and approved down to the age of 6 for moderate to severe persistent asthmatics. For severe eosinophilic asthma, there are three additional approved biologics (b) (4) (b) (4) (two against IL5, one against IL4Rα) with varying dosing regimens (every 2 weeks up to every 8 weeks), routes of administration (SC and IV), and administration requirements (healthcare professional vs patient/caregiver). This would be the first anti-IL5 approved down to the age of 6 years. Currently treatment options for this age group includes inhaled corticosteroids and long-acting beta agonists and oral anti-leukotrienes.	While anti-IgE therapy is approved for moderate-to-severe asthma in children down to 6 years of age, it is limited to allergic asthma (defined by perennial aeroallergen sensitivity) and by weight and serum IgE restrictions. This would be the first anti-IL5 approved in children 6 to 11 years of age for severe asthma with an eosinophilic phenotype, and would expand the treatment options for this age group.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Based on an overlap in the clinical presentation of both adult and pediatric severe eosinophilic asthma, consistency in the therapeutic approach, consistency of the mepolizumab mechanism of action, and relevance of the clinical endpoints, efficacy for 6- to 11-year-olds is extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks and a similar pharmacodynamic response. The pediatric study was not designed to assess efficacy given the small sample size, duration, and uncontrolled design. However, exploratory efficacy analyses were supportive. There was a trend towards a ≥0.5 reduction from baseline in Asthma Control Questionnaire 7 (ACQ-7) score over the treatment period along with an increase in total Childhood Asthma Control Test (C-ACT) scores in all groups, suggesting an improvement in asthma control. The rates of annual on-treatment exacerbations were also lower than baseline values for each treatment group. A Bootstrap analysis showed consistency of the annualized asthma exacerbation incidence rates observed in the treatment group of the 6-11 year old trial with adults/adolescents trials. This was further supported by a Bayesian Dynamic Borrowing with a Mixture Prior approach which offers a numerical model to predict efficacy with increasing prior weights indicating greater confidence in the extrapolation strategy.	Efficacy was extrapolated for patients 6-11 years of age from the adolescent and adult trials based on pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks, a similar pharmacodynamic response, and exploratory efficacy results from the pediatric study. Mepolizumab would be the first biologic for the treatment of severe eosinophilic asthma, in subjects 6 to 11 years old and would represent a clinically relevant, beneficial treatment for this difficult to treat patient population.
Risk and Risk Management	The safety profile of mepolizumab is well established since its approval in 2015. The safety profile in 6- to 11-year-olds was similar to that observed in adults and adolescents 12 years of age and older.	The risk analysis is similar to the approved product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable	
	x	Clinical outcome assessment (COA) data, such as		8.1.1.3.5	
		x	Patient reported outcome (PRO)		
		□	Observer reported outcome (ObsRO)		
		□	Clinician reported outcome (ClinRO)		
		□	Performance outcome (PerfO)		
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify):			
□	**Patient experience data that were not submitted in the application, but were considered in this review:**				
	□	Input informed from participation in meetings with patient stakeholders			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Other: (Please specify):			
□	**Patient experience data was not submitted as part of this application.**				

2. Therapeutic Context

2.1. Analysis of Condition

Asthma is a disease that is the result of chronic inflammation of the lungs that presents as wheezing, shortness of breath, chest tightness, and coughing. Chronic inflammation of the lungs can also lead to airway remodeling, resulting in permanent decrease in lung function.[1,2] The European Academy of Allergy and Clinical Immunology estimates that asthma affects 300 million people worldwide.[3] Clinical presentations of asthma can vary from mild intermittent to severe persistent. Uncontrolled asthma can make it difficult for patients to partake in daily life activities due to frequent respiratory symptoms that can occur with and without exertion. Patients with poorly controlled asthma are also more prone to exacerbations that may require oral steroids, emergency room visits, and hospitalizations. Given the significant prevalence along with the various phenotypes, there has been an urge to find targeted therapies to treat the underlying pathology. One particular asthma phenotype of interest is the eosinophilic phenotype. This phenotype can be seen in both adults and children. Determining the prevalence of severe asthma in children is difficult, particularly with an eosinophilic phenotype, due to the lack of a widely accepted definition and nonstandard collection of data variables across studies to characterize patients. A prevalence of 1.9% was reported for children ages less than 14 years of age from a UK General Practice Research database.[4] Asthmatics with high eosinophil counts and eosinophilic airway inflammation has been suggested to increase the risk of severe or difficult to control airway.[5] Thus, severe eosinophilic asthma represents disproportionate percentage of health care utilization and costs associated with asthma. Due to this disproportion, many researchers and pharmaceutical companies are targeting this phenotype for drug development.

2.2. Analysis of Current Treatment Options

Mepolizumab was approved in November 2015 and was the first interleukin-5 antagonist monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma 12 years and older, and with an eosinophilic phenotype. Since then, other anti-IL5 biologics have come on the market, including reslizumab and benralizumab, all approved for the same indication (b) (4). Other biologics approved for the treatment of asthma include Xolair (an anti-IgE for moderate-to-severe persistent asthma in patients 6 years of age

[1] GINA (Global Initiative for Asthma). Global Strategy for Asthma Management and Prevention, 2018. Available at https://ginasthma.org. Accessed 25 May 2018
[2] NAEPP (National Asthma Education and Prevention Program Expert Panel) Report 3.
[3] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004;59(5):469–78.
[4] Prescribing patterns of asthma controller therapy for children in UK primary care: a cross-sectional observational study: BMC Pulmonary Medicine 201; 10:29R
[5] Bousquet J, Chanez P, Yves Lacoste J, Barneon G, et al. Eosinophilic Inflammation in Asthma. N Engl J Med 1990; 323:1033-1039

and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids) and dupilumab (an anti-IL4 receptor alpha antagonist for add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma). Other small molecule treatment options for pediatric asthmatics include systemic and inhaled corticosteroids, leukotriene modifiers, and long-acting beta-agonist bronchodilators. Mepolizumab is proposed as the first anti-human interleukin 5 (anti-IL5) for children 6 to 11 years of age and the first biologic approved for children 6 to 11 years of age with severe asthma with an eosinophilic phenotype.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mepolizumab was first approved in November 2015 for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Mepolizumab was later approved for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis in December 2017. Mepolizumab is also approved in the European Union Member States, Japan, and over 10 other countries as of December 2018.

Following approval of mepolizumab for patients with severe eosinophilic asthma aged 12 years and older, two postmarketing requirements (PMR 2979-1 and PMR 2979-2) were issued for children 6 to 11 years of age. The requirement of studies in ages 0 to 5 years were waived because necessary studies are impossible or highly impracticable as severe asthma with eosinophilic phenotype is unlikely to exist in sufficient numbers to allow for a study to be conducted. .

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 1. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
Agreed iPSP	Jun 13, 2014	Deferral <12 year of age Conduct PK/PD study in 6-11 year olds along with evaluating safety, tolerability, and include ACQ
Late-cycle meeting	Aug 6, 2015	Division suggested a 12-month open-label extension study in addition to the 12-week PK/PD study to assess long-term safety
Adult approval	Nov 4, 2015	Mepolizumab approved for adult asthma indication PREA requirement for 6-11-year-olds: Trial 200363 -Part A: 12-week randomized, open label PK/PD study -Part B: 12-month long safety and PD extension study
Type C	Mar 1, 2018	FDA suggested flat dose of 40 mg instead of weight based dosing for pediatric indication after reviewing Study Report for Part A of Trial 200363

iPSP= initial pediatric study plan; ACQ = Asthma Control Questionnaire; FDA = Food and Drug Administration; PD = pharmacodynamic; PK = pharmacokinetic; PREA = Pediatric Research Equity Act

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Office of Scientific Investigations (OSI) inspections were not deemed necessary for this supplement.

4.2. Product Quality

With this supplement, the Applicant introduced a new dosage strength of mepolizumab (40 mg) for the lyophilized powder in a single-dose vial for reconstitution. Cross-reference is made tothe original BLA for the chemistry, manufacturing, and control drug substance information as there are no changes to the drug substance with this application. The data provided in the supplement support the conclusion that the proposed control strategy for the new presentation combined with in-process, release, and stability testing ensure process consistency and drug substance, (b) (4) and drug product with appropriate quality attributes. For more information, refer to the separate Chemistry, Manufacturing and Controls review.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted in support of this supplement for pediatric patients, 6 to 11 years old, with severe eosinophilic asthma. Nonclinical studies were reviewed with the original BLA submission for adults and adolescents ≥12 years old.

The nonclinical program with mepolizumab was conducted in cynomolgus monkeys, which were determined to be the only pharmacologically relevant nonclinical test species. Mepolizumab was equipotent for inhibiting exogenous IL5-induced differentiation of eosinophils, obtained from the bone marrow of human volunteers or cynomolgus monkeys, with half maximal effective concentration (EC_{50}) values of 13.3pM. Further, the amino acid sequence of monkey IL5 differs from human IL5 by two conservative substitutions in a region not related to the presumed mepolizumab binding epitope on human IL5.

In a chronic 6-month toxicology study with cynomolgus monkeys that receive mepolizumab by the intravenous (IV) route at doses up to 100 mg/kg every 4 weeks or the subcutaneous (SC) route at a dose of 10 mg/kg every 4 weeks, eosinophil counts were decreased by up to 95% at all doses from days 29 (first time point) to the end of the study. Evaluation of bone marrow suggested a block of maturation and/or release of eosinophils from the bone marrow and not depletion by mepolizumab of eosinophil lineage cells. There were no adverse histopathological findings. Male and female fertility was unaffected based upon no adverse findings from histopathological examinations of reproductive organs. No adverse effect levels were identified as 100 mg/kg every 4 weeks by the IV route and 10 mg/kg every 4 weeks by the SC route provide adequate safety margins for the proposed clinical dose.

In reproductive toxicity studies, there were no adverse findings in a pre- and postnatal development study with monkeys that were treated with mepolizumab at IV doses up to 100 mg/kg every 4 weeks. Infants were evaluated for up to 9 months after birth.

There were no adverse findings in a fertility and embryofetal development study with mice that received an analogous antibody, which inhibits the activity of murine IL5.

Based upon the observed nonclinical pharmacology and toxicology profile of mepolizumab, a juvenile animal study is not required to support use in pediatric patients down to 6 years of age. The available nonclinical program provides adequate support for clinical use of mepolizumab in pediatric patients down to 6 years old. The no adverse effect levels in the 6-month monkey study provide adequate safety margins for the proposed clinical dose in pediatric subjects (safety margins for subjects ≥12 years with respect to reproductive and general toxicity were large [significantly greater than 1]).

6. Clinical Pharmacology

6.1. Executive Summary

Mepolizumab is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) approved for "add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype". The approved dose in patients 12 years and older is 100 mg administered subcutaneously (SC) once every 4 weeks (Q4W). The Applicant has submitted a prior approval supplement (sBLA-012) to expand the approved severe eosinophilic asthma indication to include patients aged 6 to 11 years. The Applicant proposes a dose of 40 mg SC Q4W in patients 6 to 11 years.

This efficacy supplement for mepolizumab in severe asthma with an eosinophilic phenotype in patients aged 6 to 11 years old is supported by demonstration of comparable systemic exposure compared to the approved 100 mg SC dose in adolescents and adults ≥12 years old. Trial 200363 was conducted to investigate the pharmacokinetics (PK), pharmacodynamics (PD), and long-term safety of mepolizumab administered SC to subjects with severe asthma with an eosinophilic phenotype aged 6 to 11 years. A population PK model was utilized to facilitate the systemic exposure comparison between adults and pediatrics for the proposed 40 mg SC Q4W dose.

6.2. Summary of Clinical Pharmacology Assessment

Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology study submitted in BLA 125526/S-012. This sBLA is approvable from a clinical pharmacology perspective.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology findings for mepolizumab in pediatrics in Trial 200363 that supports the extrapolation of established efficacy of mepolizumab in adults are summarized below:

1. The observed trough concentrations (C_{trough}) at Day 28 for subjects <40 kg who received 40 mg Q4W (6.28 µg/mL) and for subjects ≥40 kg who received 100 mg Q4W (10.50 µg/mL) in pediatric Trial 200363 were 1.39-fold and 2.32-fold higher, respectively, compared to the historical adult C_{trough} of 4.51 µg/mL.
2. Model derived mepolizumab exposure (area under the concentration-time curve; AUC_{0-inf}) for subjects <40 kg who received 40 mg Q4W (454 µg·day/mL) and for subjects ≥40 kg who received 100 mg Q4W (675 µg·day/mL) in pediatric Trial 200363 were 1.32-fold and 1.97-fold higher, respectively, compared to the historical adult exposure of 343 µg·day/mL. The model derived ratios were consistent with the ratios from the observed data.

3. Following SC administration of mepolizumab 40 mg (for those weighing <40 kg), and 100 mg (for those weighing ≥40 kg) Q4W, marked and similar reductions in blood eosinophil counts were observed at Week 4 (first postdose assessment). These reductions were sustained through to Week 12 (4 weeks after the last dose of mepolizumab).
4. Office of Study Integrity and Surveillance (OSIS) inspection was requested for Trial 200363 (analytical lab, validation report and analytical study report), and they recommended accepting the Applicant's data.
5. Based on the population pharmacokinetics analysis and simulation, the proposed fixed dose of 40 mg Q4W dose will result in a 20% lower mepolizumab exposure in subjects ≥40 kg compared to the target adult exposure. The slightly lower exposure is not expected to be clinically relevant as it will achieve a near 90% reduction in the blood eosinophil count based on the adult dose-response model from Trial 114092 in the original BLA.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The following dosing regimen of mepolizumab is recommended for patients 6 to 11 years:

- 40 mg administered subcutaneously once every 4 weeks

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Mepolizumab is a humanized monoclonal anti-IL5 antibody. IL5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. Mepolizumab was originally approved in November 2015 for add-on maintenance treatment for severe asthma, and with an eosinophilic phenotype in patients aged 12 years and older. The approved dosing regimen is 100 mg SC Q4W. The general pharmacology and PK of mepolizumab has been reviewed previously as part of the original BLA (BLA 125526 clinical pharmacology review by Dr. Yunzhao Ren, archived July 5, 2015).

To support the current supplement, the Applicant conducted Trial 200363 to characterize the PK and PD of mepolizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma. This study consisted of two phases:

- Part A (PK/PD phase): This phase assessed the PK and PD of either 40 or 100 mg of mepolizumab (depending on subject weight <40 kg or ≥40 kg, respectively), administered SC Q4W, for a total duration of 12 weeks.
- Part B (long-term safety/PD phase): This was a long-term safety/PD phase, in which extended treatment for a further 52 weeks was offered on an optional basis to those subjects eligible for continued treatment.

PK was only assessed in Part A of the study. Six blood samples per subject for the PK analysis were taken predose at Week 4 and Week 8, at Week 9 for an approximate peak plasma concentration, at Week 12 and finally during the Follow-up phase at Weeks 16 and 20. A PK sample was also taken at the Early Withdrawal Visit (when applicable). Of the 36 subjects who received mepolizumab SC, 26 subjects received 40 mg (weight <40 kg) and 10 subjects received 100 mg (weight ≥40 kg); all 36 subjects contributed a total of 202 blood samples to the analysis. No concentration data were excluded from the analysis.

Eleven of the 36 subjects who received mepolizumab were female. The median age was 8.5 years (range: 5 to 12 years). The median body weight at baseline was 27 kg (range: 20 to 37 kg), 50 kg (range: 41 to 61 kg) and 29 kg (range: 20 to 61 kg) in the mepolizumab 40 mg group (weight <40 kg), mepolizumab 100 mg group (weight ≥40 kg) and overall, respectively. The median baseline creatinine clearance was 114 mL/min (range: 85.7 to 135 mL/min) with all subjects having normal renal function.

In order to compare the observed PK data in Trial 200363 to that in adult patients receiving 100 mg Q4W, C_{trough} at Day 28 was used, as this was the only mutual sampling point in pediatric (Trial 200363) and adult (Study MEA115588) patients with severe asthma. The observed C_{trough} at Day 28 for subjects <40 kg who received 40 mg Q4W (6.28 µg/mL) and for subjects ≥40 kg who received 100 mg Q4W (10.50 µg/mL) in pediatric Trial 200363 were higher (1.39-fold and 2.32-fold for 40 mg Q4W and 100 mg Q4W, respectively) compared to the adult C_{trough} of 4.51 µg/mL in study MEA115588 (Table 2).

Table 2. Observed and Model-Derived Exposures in Adults and Pediatrics

	n	Body Weight (kg) Median (Range)	Observed C_{trough} at Day 28 (µg/mL) Median (range)	Model Derived $AUC_{0\text{-}inf}$ (µg·day/mL) Estimate (SE)
40 mg group in Trial 200363 (weight <40 kg)	26	27 (20-37)	6.28 (3.19, 9.96)	454.39 (15.89)
100 mg group in Trial 200363 (weight ≥40 kg)	10	50 (41-61)	10.50 (7.13, 15.81)	675.20 (35.90)
Study MEA115588 (Adult Phase 3 Study)	194	73 (45-140)	4.51 (0, 24.41)	343 (35.2)

Source: Table 14 and Table 2.1 in CSR 200363 for model derived values and observed values, respectively. Table 10.02 and Table 10.01 in CSR 115588 for model derived values and observed values, respectively
AUC = area under the curve; SE = standard error

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the patient population for which the indication is being sought?

Yes, the proposed 40 mg Q4W dose is reasonable from a clinical pharmacology perspective as the systemic exposure of mepolizumab achieved in pediatrics 6 to 11 years of age are generally comparable to the patients 12 years and older. In Trial 200363, 40 mg Q4W and 100 mg Q4W dose was tested in patients weighing <40 kg and ≥40 kg, respectively, resulting in a 1.3- and 2-fold higher exposure compared to adults, respectively. In order to address the high exposure for the 100 mg Q4W dose, a fixed dose of 40 mg Q4W was proposed in patients aged 6 to 11 years irrespective of the body weight. This dose will result in a marginal 20% lower exposure in pediatric patients weighing ≥40 kg compared to target adult exposure based on simulation from the population PK analysis.

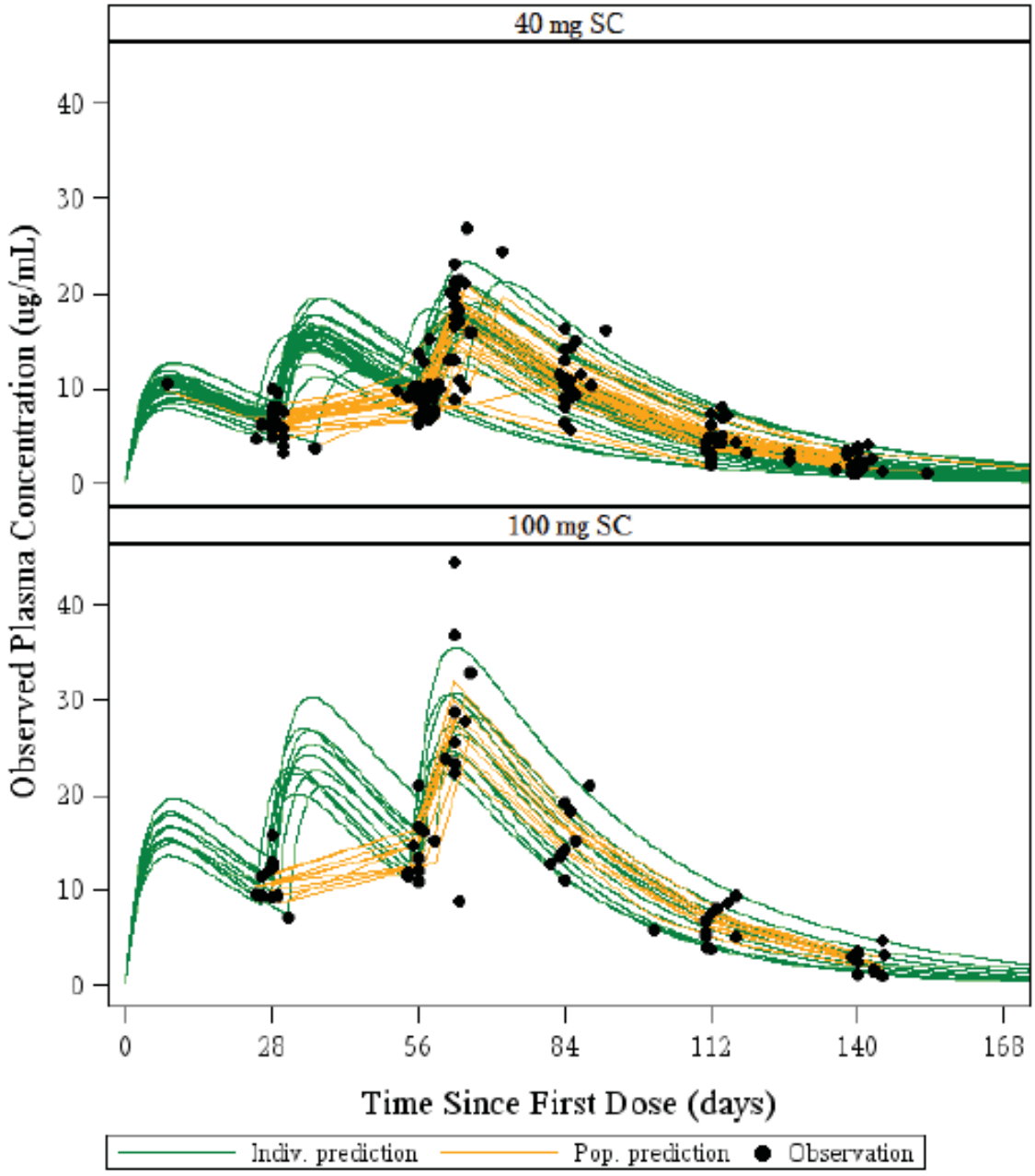
Based on the adult dose-response model from Study MEA114092 in the original BLA review, a 20% lower mepolizumab exposure still achieves a near 90% reduction of the blood eosinophil count. Thus, the slightly lower exposure for 40 mg Q4W in pediatric patients weighing ≥40 kg is not expected to lead a clinically relevant decrease in efficacy. Furthermore, there is limited safety data in pediatrics (n=14) to rule out potential safety concerns with the 2-fold higher mepolizumab exposure with 100 mg Q4W dose in patients weighing ≥40 kg.

What were the findings of the Population PK analysis?

An established population PK model, which is a two-compartment model with first order absorption and first order elimination, was used as the base model. All other parameters were fixed except for the absolute bioavailability; the allometric exponents for clearances and volumes were re-estimated. The estimate of SC absolute bioavailability was 105% (95% confidence interval (CI): 55 to 155%) and allometric exponents for clearances and volumes were 0.86 (95% CI: 0.29 to 1.43) and 0.66 (95% CI: 0.11 to 1.21), respectively. The final population PK model was able to capture the observed data in Trial 200363 (Figure 1).

Model derived mepolizumab exposure ($AUC_{0\text{-}inf}$) for subjects <40 kg who received 40 mg Q4W (454 µg·day/mL) and for subjects ≥40 kg who received 100 mg Q4W (675 µg·day/mL) in pediatric Trial 200363 were 1.32-fold and 1.97-fold higher, respectively, compared to the adult exposure of 343 µg·day/mL. The model derived ratios were consistent with the ratios from the observed data (Table 2).

Figure 1. Observed (Black Dots), Population Predicted (Yellow Lines) and Individual Predicted (Green Lines) Mepolizumab Concentration-Time Profiles by Treatment



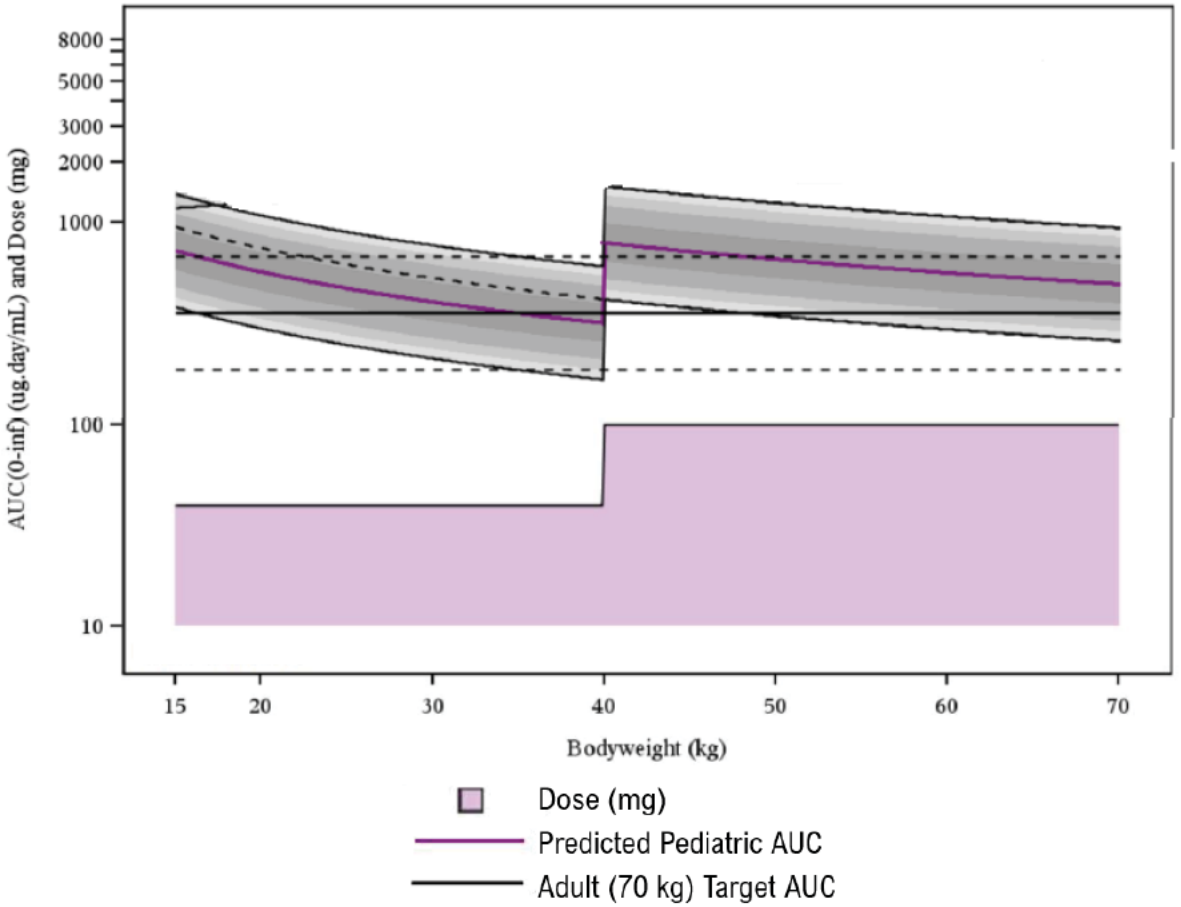
Source: Figure 2.1 in CSR 200363
SC = subcutaneously

In order to address the higher exposure in the dosing regimen tested in Trial 200363, which utilized a 40 kg body weight cut-off to differentiate between the 40 mg Q4W dose and the standard adult 100 mg Q4W dose, alternative dosing regimens were evaluated for the purpose of achieving comparable mepolizumab exposure in patients aged 6 to 11 years to adults. A fixed dosing regimen of 40 mg Q4W, regardless of body weight, was proposed by the Applicant and discussed in the Type C meeting dated March 1, 2018. This fixed dosing regimen provided a

modeled average exposure ($AUC_{0\text{-}inf}$) in 6- to 11-year-olds that was generally within the 95% prediction interval of the adult exposure (Figure 2 and Figure 3).

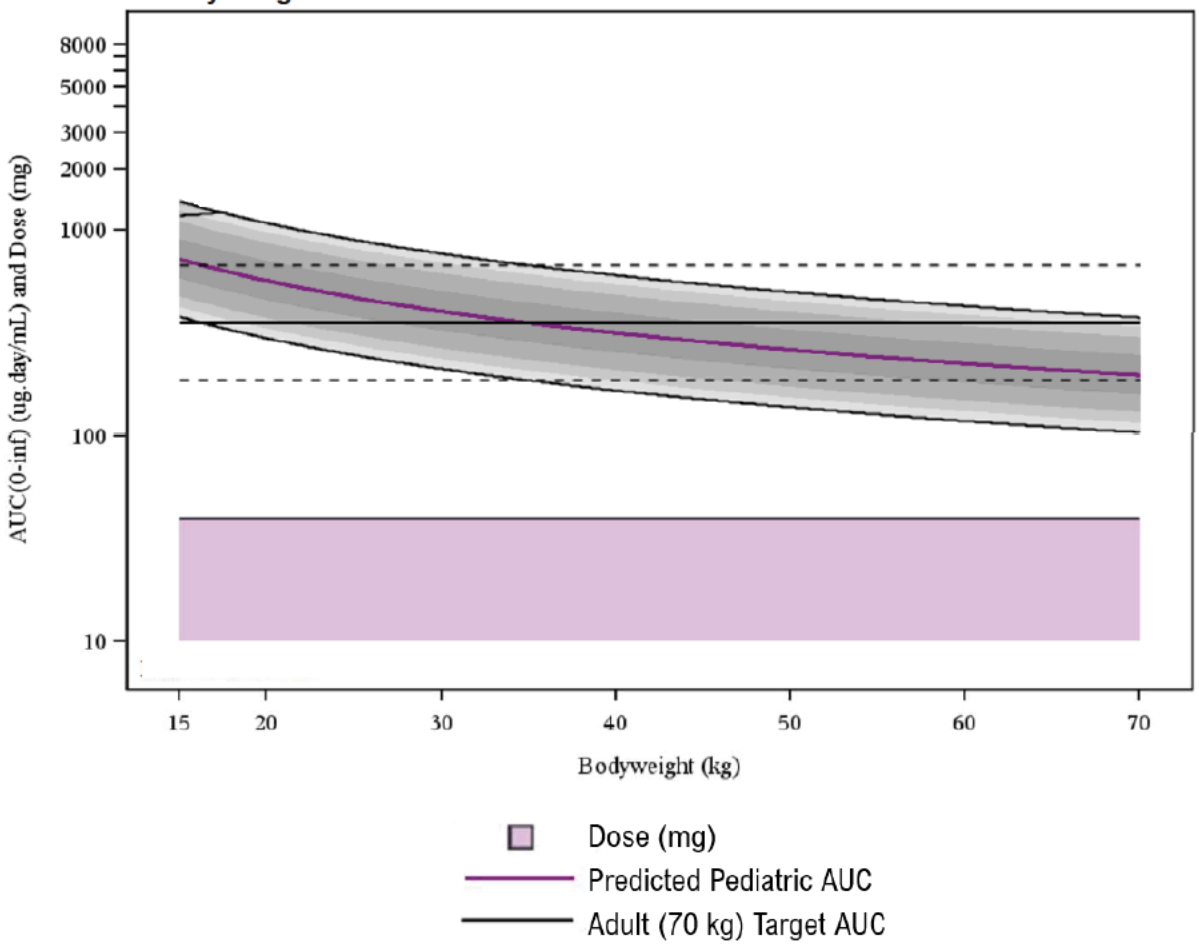
A 20% lower exposure is expected for the 40 mg Q4W dose in subjects ≥40 kg based on the simulation of the population PK analysis. This slightly lower exposure is not expected to be clinically relevant as it still achieves a near 90% reduction in the blood eosinophil count based on the Applicant's previous adult dose-response model in the original submission (data from study 114092).

Figure 2. Mepolizumab Exposure (Mean and 95% Prediction Interval) for the 40- and 100-mg Dose as a Function of Body Weight in Children 6 to 11 Years Old



Source: Adjusted from Figure 1 in Applicant's Meeting background materials (meeting date March 1, 2018)
AUC = area under the curve

Figure 3. Mepolizumab Exposure (Mean and 95% Prediction Interval) for the 40-mg Flat Dose as a Function of Body Weight in Children 6 to 11 Years Old



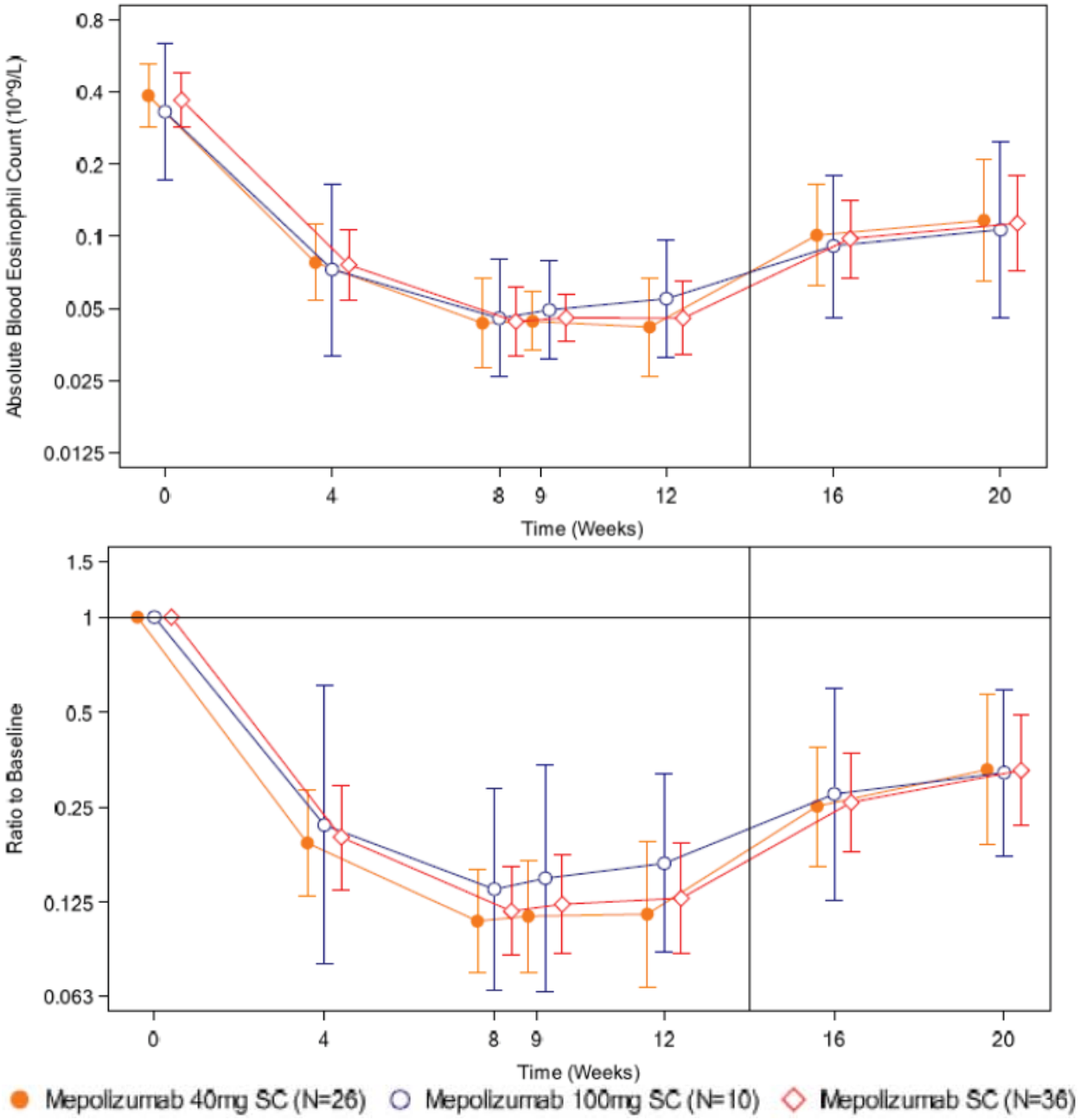
Source: Adjusted from Figure 2 in Applicant's Meeting background materials (meeting date March 1, 2018)
AUC = area under the curve

What are the pharmacodynamics characteristics of mepolizumab following subcutaneous administration in patients aged 6 to 11 years in Trial 200363 ?

Absolute blood eosinophils were measured as a PD endpoint in both Part A and B of Trial 200363.

In Part A, the geometric mean baseline absolute blood eosinophil counts were 386 and 331 cells/µL in the mepolizumab 40 mg (weight <40 kg) and 100 mg (weight ≥40 kg) treatment groups, respectively. Marked and similar reductions in blood eosinophil counts were observed in subjects in the mepolizumab 40 mg (weight <40 kg) and 100 mg (weight ≥40 kg) groups at Visit 3 (Week 4; first postdose assessment). These reductions were sustained through to Week 12 (4 weeks after the last dose of mepolizumab; Figure 4). At Week 12, the geometric mean ratio of blood eosinophil count to baseline was 0.115 in the mepolizumab 40 mg group (weight <40 kg) and 0.166 in the mepolizumab 100 mg group (weight ≥40 kg), indicating an 88.5% and 83.4% reduction, respectively.

Figure 4. Absolute (Top) and Ratio to Baseline (Bottom) Blood Eosinophil Count (Geometric Mean and 95% Confidence Intervals) Profiles in Part A of Trial 200363

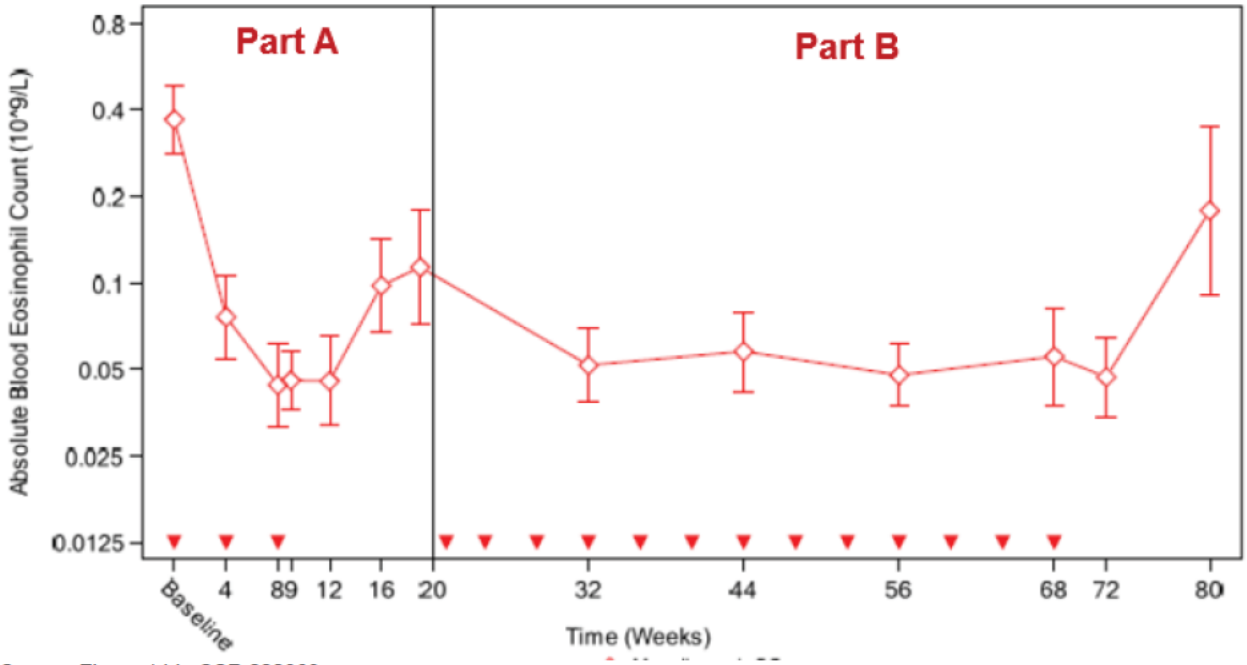


Source: Figure 2 and 3 in CSR 200363
SC = subcutaneously

In Part B, the geometric mean baseline absolute blood eosinophil counts were 306, 331, and 506 cells/µL in the mepolizumab 40 mg (weight <40 kg), 100 mg (weight ≥40 kg), and 40/100 mg (weight increase to ≥40 kg post-Visit 9) treatment groups, respectively. Marked and similar reductions in blood eosinophil counts were observed in subjects in all dose groups at Week 32 compared with baseline. These reductions were sustained through to Week 72 (4 weeks after the last dose of mepolizumab) (Figure 5).

At Week 72, the geometric mean ratio of blood eosinophil count to baseline was 0.148 in the mepolizumab 40 mg group (weight <40 kg), 0.134 in the mepolizumab 100 mg group (weight ≥40 kg), and 0.098 in the mepolizumab 40/100 mg group (weight increase to ≥40 kg post-Visit 9), indicating reduction from baseline of 85.2%, 86.6%, and 90.2%, respectively.

Figure 5. Absolute Blood Eosinophil Count (Geometric Mean and 95% Confidence Intervals) Profiles in Part A Through Part B of Trial 200363



Source: Figure 14 in CSR 200363

What is the incidence of the formation of ADA and the impact of immunogenicity on mepolizumab exposure?

In Trial 200363, the incidence of antidrug antibody (ADA) was assessed prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), and at Visit 8 (Week 20) and Early Withdrawal in Part A; prior to dosing at Visit 15 (Week 44), Visit 21 (Week 68) and, when applicable, at Follow-up Visit 23 (Week 80) and Early Withdrawal in Part B of the study.

ADAs to mepolizumab were reported in two (6%) subjects in Part A. The presence was transient in both subjects, with low titers; all samples were negative for neutralizing antibodies. There was no obvious difference in the PK or PD of mepolizumab in the two ADA positive subjects compared to ADA negative subjects by visual inspection. No ADAs were detected to mepolizumab in any subject in Part B of the study.

What are the findings from OSIS inspection?

DPARP requested an OSIS inspection for the bioanalytical site of Trial 200363 on January 11, 2019 (Reference ID: 4375076 in Document Archiving, Reporting, and Regulatory Tracking System; DARRTS).

OSIS recommends accepting the bioanalytical data from Trial 200363 ; refer to the memorandum by Dr. Li-Hong Yeh archived May 14, 2019 for details (Reference ID: 4432691 in DARRTS).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

Is the bioanalytical method properly validated to measure mepolizumab concentration in plasma samples?

The bioanalytical assay used for Trial 200363 (Method 111202M01, Version 05) updated an already validated method (Method 111202M01, Version 03, reviewed previously under BLA 125526 by Dr. Yunzhao Ren, achieved July 5, 2015), which was used to determine the plasma concentrations of mepolizumab for the phase 3 clinical studies in adults (Study 115588 and 115575) in the original submission. The changes between Version 05 and 03 are minor, as the assay procedure remains unchanged, and the same capture antibody (AdB16075) and detection antibody (A10648) were used. The bioanalytical assay for measuring mepolizumab is acceptable with reasonable accuracy and precision.

OCP Conclusions and Recommendations:

The Office of Clinical Pharmacology concludes that the mepolizumab exposure in patients aged 6 to 11 years upon subcutaneous administration of mepolizumab 40 mg Q4W supports the extrapolation of the established efficacy of mepolizumab in adult patients.

The OCP recommends that the clinical pharmacology study submitted to sBLA 125526/S-012 addresses the PMR requirements. This sBLA is approvable from a clinical pharmacology perspective.

7. Sources of Clinical Data and Review Strategy

7.1. Review Strategy

This supplement review contains one trial (200363) evaluating PK, PD, and safety endpoints. The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. Efficacy was evaluated in the original approval in November 2015 for ages 12 and older. Trial 200363 was not designed or powered to detect significant changes in the clinical assessments but the study did evaluate patient reported outcomes as key secondary endpoints and lung function and exacerbation rates as exploratory endpoints which are briefly discussed both in Section 7 and in the Supportive Efficacy Information Appendix (Section 14.3). Review and approval of this supplement was based on PK and PD endpoints (See Section 6) and safety evaluation (See Section 8.2). The safety review is divided into the study's two parts: Part A and Part B, with more emphasis placed on Part B as the purpose of Part B was specifically to evaluate long-term safety. The safety data for the two parts were not pooled and are reviewed individually.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial 200363

8.1.1.1. Administrative Information

- **Study title:** An open-label study to characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma.
- **Study dates:** Initiation date, August 25, 2016; Part A completion, December 7, 2016; Part B completion, January 31, 2018
- **Study sites:** Japan, Poland, United States, United Kingdom
- **Study report date:** July 16, 2018.

8.1.1.2. Objectives

Part A

Primary Objectives:

1. To characterize the PK of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

2. The characterize the PD of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

Secondary Objectives:

1. To compare the body weight-adjusted clearance between adults and subjects aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously.
2. To characterize asthma control following SC administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma.
3. To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

Part B

Primary Objective:

1. To assess the long-term safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

Secondary objective:

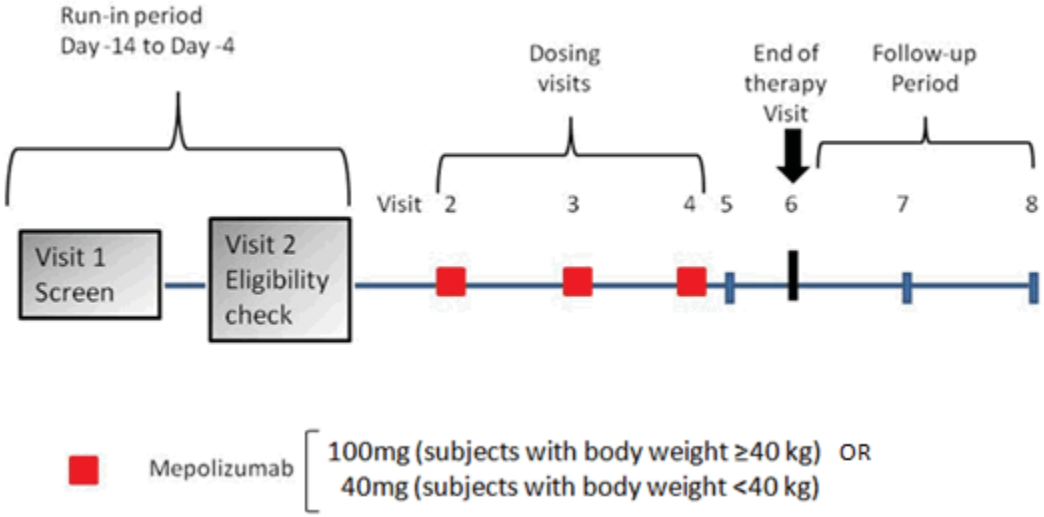
1. To characterize the long term durability of PD of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

8.1.1.3. Study Design and Conduct

8.1.1.3.1. Procedures

Trial 200363 was a multicenter, open-label trial involving 36 subjects from the ages of six to eleven years old. The study was divided into two parts: Part A (Figure 6) was a 12-week treatment period and 8-week follow-up phase assessing PK and safety while Part B was a 52-week long open extension study evaluating safety and PD.

Figure 6. Study Design: Pharmacokinetic/Pharmacodynamic Phase (Part A)



Source: Trial 200363, Protocol Amendment 5

8.1.1.3.2. Patient Population

The study enrolled children diagnosed with severe asthma per Global Initiative for Asthma guidelines for at least 12 months prior to the study, and who had a blood eosinophil count ≥300 cells/µL in the past 12 months or ≥150 cells/µL at Visit 1, and were on a daily inhaled corticosteroid (>200 µg fluticasone propionate or equivalent) in the 12 months prior (with or without maintenance oral corticosteroid and/or an additional controller within the last three months).

8.1.1.3.3. Treatment

Two SC doses were studied based on weight: Subjects weighing <40 kg were administered mepolizumab 40 mg while those ≥40 kg were administered mepolizumab 100 mg. The Applicant proposes the fixed 40-mg dose for patients 6-11 year of age regardless of weight based on the Division's March 2018 recommendation upon review of the Part A data that showed increased exposure of mepolizumab in children.

Eligible subjects were assigned the study treatment based on body weight at Visit 2 and this assigned dose remained the same irrespective of body weight changes during Part A treatment phase. Those subjects who were eligible for Part B were assigned study treatment based on their body weight at Visit 9. Subjects with body weight <40 kg at Visit 9 were weighed at each subsequent visit and their dose adjusted to 100 mg once their body weight reached ≥40 kg.

8.1.1.3.4. Study Endpoints

Part A

Primary endpoints:

1. PK endpoints: $AUC_{0\text{-}inf}$, C_{max}, $T_{1/2}$
2. Change from baseline in blood eosinophil count at Week 12

Secondary endpoints:

1. Body weight adjusted clearance estimates obtained in population PK methods
2. Patient Reported Outcomes:
    a. Change from Baseline in Asthma Control Questionnaire 7 (ACQ-7) measured at Week 12
    b. Change from Baseline in ACQ-7 measured at Weeks 4, 8, 16, and 20
    c. Change from Baseline in Childhood Asthma Control Test (C-ACT) measured at Week 12
    d. Change from Baseline in C-ACT measured at Weeks 4, 8, 16, and 20
3. Incidence of adverse events
4. Incidence of clinically significant changes in clinical laboratory parameters
5. Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies
6. Incidence of clinically significant changes in vital sign measurements

Exploratory endpoints:

1. Number of asthma exacerbations that occur while on treatment (Week 0 to Week 12)
2. Number of asthma exacerbations that occur on-treatment and post-treatment (Week 0 to Week 20)
3. Change from baseline in FEV_1 measured at Week 12

Part B

Primary endpoints:

1. Incidence of adverse events
2. Incidence of clinically significant changes in clinical laboratory parameters
3. Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies
4. Incidence of clinically significant changes in vital sign measurements.

Secondary endpoint:

1. Change from Week 0 in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72, and 80.

Exploratory endpoints:

1. Incidence of asthma exacerbations
2. Change from baseline in in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80.

8.1.1.3.5. Efficacy Parameters

ACQ-7/ACQ-IA

The ACQ-7 is a questionnaire designed to measure the adequacy of asthma control and change in asthma control. The questionnaire includes 7 items and requires a 1 week recall (for items on symptoms and rescue inhaler use). The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment) for six questions regarding symptoms and rescue use. The seventh component is the measured FEV1 percentage. The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5.

The questions include:

1. In general, during the past week, how much of the time did you wheeze?
2. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day?
3. In general, during the past week, how limited were you in your activities because of your asthma?
4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
5. In general, during the past week, how much of the time did you wheeze

6. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day?

The ACQ-IA (Interview Administered) has a multi-dimensional construct assessing symptoms (5 items administered by clinic staff to the child using the interviewer administer format), rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff. The ACQ-IA will be administered to subjects for whom an appropriate translation is available.

C-ACT

The Childhood Asthma Control Test (C-ACT) assesses asthma control in children 4-11 years of age. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 to be completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 to be completed by the caregiver. A total sum score based upon responses to all items is calculated to provide an overall measure of asthma control.

Questions include:

1. How is your asthma today?
2. How much of a problem is your asthma when you run, exercise, or play sports?
3. Do you cough because of your asthma?
4. Do you wake during the night because of your asthma?
5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

Asthma exacerbation

At each study visit the investigator will make an assessment of the occurrence of an asthma exacerbation. An exacerbation of asthma as defined as worsening of asthma which requires use of systemic corticosteroids and/or hospitalization and/or Emergency Department (ED) visits. For all subjects, intravenous or oral steroid (e.g., prednisone) for at least 3 days or a single intramuscular dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

8.1.1.3.6. Statistical Analysis Plan on Clinical Outcome Measures

The clinical development program of mepolizumab for severe eosinophilic asthma in children aged 6 to 11 consisted of a single uncontrolled open-label trial (200363). Trial 200363 was a PK/PD study conducted as part of an extrapolation strategy to support the use of mepolizumab in this age group and indication. The primary efficacy endpoints and a collection of secondary efficacy endpoints consisted of PK/PD endpoints; statistical analysis plan and analysis results regarding the PK/PD endpoints were reviewed under the Clinical Pharmacology Review in

Section 6 and will not be repeated here. This study also assessed clinical outcome measures, (ACQ-7 and C-ACT), however, these were not used as primary or key secondary endpoints.

With the small sample size and uncontrolled design, Trial 200363 provided limited clinical outcome measure data and was not designed to detect significant changes in the clinical assessments. Instead, the Applicant used summary statistics on clinical assessments through bootstrap resampling analyses and Bayesian robust mixture prior analyses results to justify the consistency in clinical outcomes between the pediatric population and the adult/adolescent population, supporting the extrapolation through PK/PD matching.

Specifically, the Applicant provided the following summaries, analyses, and justifications:

- Trial 200363 summary statistics for population baseline disease characteristics and clinical outcome results were viewed in the context of such statistics from the adult/adolescent study data that supported the initial approval of mepolizumab for the treatment of the same indication in patients 12 years and older
- Bootstrap resampling analyses were performed to demonstrate consistency for exacerbation
- Bayesian robust mixture prior analyses of controlled exacerbation data collected in adolescents in the adults/adolescents severe eosinophilic asthma clinical program were carried out to inform on the magnitude of response found in this limited uncontrolled trial in children aged 6 to 11 years

This section will describe aspects of the statistical analysis plan on sample size determination, analysis population, and summary statistics used for selected efficacy endpoints (clinical assessments, as opposed to PK/PD data). The Applicant's methodologies, analysis results, and interpretation with the bootstrap resampling analyses and Bayesian robust mixture prior analyses will be briefly summarized in Appendix 15.6.

Sample Size

The sample size was determined for Part A to meet PK/PD assessment requirements. Approximately 40 subjects with severe eosinophilic asthma, aged 6 to 11 years (inclusive), were screened to achieve approximately 28 eligible subjects entering the treatment phase. This sample size was intended to allow availability of 20 evaluable subjects, with a minimum of six subjects enrolled in the <40 kg body weight group. An evaluable subject was defined to be a subject who has received all three doses of mepolizumab and had all PK and PD assessments completed through to Week 12. Sample size was not determined for Part B. All subjects completing Part A were eligible for Part B.

Analysis Populations

Part A

Safety: All subjects receiving at least one dose of mepolizumab beginning at Visit 2 (Part A, first dose of mepolizumab, Week 0) were included in the analysis. The population was used to evaluate study population, safety, and immunogenicity.

Pharmacodynamic (Outcome Assessments) (PDo) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one Part A assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, FEV_1, IgE or IL5) were included in the analysis.

Part B

Safety: All subjects receiving at least one dose of mepolizumab beginning at Visit 9 (Part B, first dose of mepolizumab, Week 20) were included in the analysis. The population was used to evaluate study population, safety and immunogenicity.

Pharmacodynamic (Outcome Assessments) (PDo) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one Part B assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, or FEV_1) were included in the analysis.

Selected Efficacy Endpoints and Corresponding Summary Statistics

The following clinical outcome endpoints were preplanned secondary or exploratory efficacy endpoints for summary statistics reporting.

Secondary Endpoints

Asthma Control Questionnaire

- The ACQ-7 score (mean of seven items) and change from baseline in the ACQ-7 score were to be summarized by visit, mepolizumab dose, and mepolizumab overall for the PDo population.
- The ACQ-5 score (mean of five symptom items) and change from baseline in the ACQ-5 score were to be summarized by visit, mepolizumab dose, and mepolizumab overall for the PDo population.

Childhood Asthma Control Test (C-ACT)

- The C-ACT score (sum of seven items) and change from baseline in the C-ACT score were to be summarized by visit, mepolizumab dose, and mepolizumab overall for the PDo population.

Exploratory Endpoints

Asthma Exacerbations

- Number of asthma exacerbations that occurred while on treatment (Week 0 to Week 12) and number of asthma exacerbations that occurred on-treatment and post-treatment (Week 0 to Week 20) were to be summarized by mepolizumab dose group and mepolizumab overall.
- Number of asthma exacerbations that occurred during Part B (Week 20 to Week 72) was to be summarized by mepolizumab dose group and mepolizumab overall.

Forced expiratory volume in 1 second (FEV_1)

FEV_1 recorded at postdose visits and change from baseline were to be listed and summarized by mepolizumab dose group and mepolizumab overall for each visit.

8.1.1.3.7. Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practice is in the Clinical Study Report.

8.1.1.3.8. Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. The Applicant did report there was one investigator that was a current or former employee and received a payment of $201,705.80. He was the Principal Investigator for center (b) (6), which recruited (b) (6) subjects. As that accounts for (b) (6)% of the total enrollment, the Applicant conducted an impact analysis. The data collected in these (b) (6) subjects aligned with data collected across all sites and did not appear to impact the results of the study.

See Appendix 15.2 of this review for additional details.

8.1.1.3.9. Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

8.1.1.4. Study Results

8.1.1.4.1. Protocol Amendments

The original protocol was approved in December 2014. There were a total of five amendments. A major amendment was made in September 2015 in which the investigator extended mepolizumab treatment for 52 weeks to study long term safety effects as recommended by the Division. Minor administrative amendments were made before database lock and were determined to not affect the interpretation of the study results.

8.1.1.4.2. Protocol Deviations

In Part A, 19 subjects had at least one important protocol deviation. The most frequent deviation was a missed assessment or procedure and/or a visit or assessment occurring outside of the protocol-defined window. No subjects were excluded from any population as a result of a protocol deviation.

One subject in the mepolizumab 100 mg group had a protocol deviation of eligibility criteria not met. This subject failed the inclusion criteria of well-documented regular treatment with an inhaled corticosteroid therapy of >200 ug/day of fluticasone propionate in the 12 months prior to enrollment. The Investigator understood from the referring physician that the subject was treated with 500 ug/day of fluticasone propionate, however, after review of documents provided, the subject had only received 200 ug/day of fluticasone propionate for approximately 7 to 12 months prior. This participant was permitted to remain in the study.

Reviewer comment: As the use of 200 ug/day of ICS was at the cut-point of the inclusion criteria, this would not be expected to affect the results.

For Part B, 8 subjects had at least one protocol deviation. The most frequent protocol deviation was failure to report a severe adverse event (SAE), pregnancy, or liver function abnormality per protocol and/or missed assessment. No subjects were excluded based on these protocol deviations. One subject completed the study after only receiving 6 of the 13 required doses of mepolizumab.

8.1.1.4.3. Efficacy

8.1.1.4.3.1. Disposition

Of the 44 subjects enrolled, 36 subjects qualified and were enrolled to mepolizumab treatments, with 26 receiving the 40-mg dose (weight <40 kg) and 10 subjects received the 100-mg dose (weight ≥40 kg). Seven subjects of the 44 who were enrolled did not meet inclusion/exclusion criteria and one subject did not meet the continuation criteria.

A total of 32 subjects (89%) completed Part A of the trial (Table 3). Four subjects withdrew from the trial, all of whom were enrolled in the 40 mg group. One subject withdrew at the Investigator's discretion due to repeat asthma exacerbations. Another subject withdrew consent due to a combination of adverse events throughout the study. The third subject withdrew due to the subject's parent's distress in blood collection. The forth subject withdrew due to an adverse event of asthma exacerbation.

Table 3. Trial 200363, Part A Subject Disposition (Safety Population)

Disposition	Mepolizumab 40 mg SC (N=26)	Mepolizumab 100 mg SC (N=10)	Mepolizumab SC (N=36)
Study completion status			
Completed	22 (84.6%)	10 (100%)	32 (88.9%)
Withdrawn from study	4 (15.4%)	0	4 (11.1%)
Primary reason for withdrawal			
Adverse event	1 (3.8%)	0	1 (2.8%)
Physician decision	1 (3.8%)	0	1 (2.8%)
Withdrawal by subject	2 (7.7%)	0	2 (5.6%)

Source: Statistical Review
SC = subcutaneous

For Part B, subjects must have completed all study assessments and received all three doses in Part A to qualify to continue to Part B. Of the 32 subjects who completed Part A, 30 subjects continued onto Part B. Two subjects chose not to continue. Of the 30 subjects who continued onto Part B, 29 subjects completed Part B.

8.1.1.4.3.2. Demographics

The demographics are summarized in Table 4. Majority of the subjects were male (69%) and white (56%). The majority of the subjects were above 7 years old with approximately 17% in the 5 to 6 year age group. The mean age was 8.6 years old.

Table 4. Trial 200363, Part A Baseline Demographics

	Treatment Arm			
Characteristic	**Mepolizumab 40 mg (N=26)**	**Mepolizumab 100 mg (N=10)**	**N**	**% of Total**
Sex				
Male	20	5	25	69%
Female	6	5	11	31%
Race				
White	14	6	20	56%
Asian	7	1	8	22%
Black or African American	4	3	7	19%
Multiple	1	0	1	3%
Age range in years				
10-12	7	8	15	42%
7-9	13	2	15	42%
5-6	6	0	6	17%

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363

The subjects enrolled had an overall mean of 4.0 exacerbations requiring systemic corticosteroids in the 12 months prior to the study. Of these exacerbations, 44% required hospitalization. Six of the 25 subjects enrolled in the 40 mg arm did not have a blood eosinophil count of ≥150 cells/µL at Visit 1, indicating that they had a blood eosinophil count ≥300 prior to screening. All subjects in the mepolizumab 100 mg group had a blood eosinophil count of ≥150 cells/µL at Visit 1. Approximately 23% of the mepolizumab 40 mg group and 20% of the 100 mg were on regular maintenance oral corticosteroids. The above population characteristics is similar to that of the original adult and adolescent study.

8.1.1.4.3.3. Primary Endpoints

As the primary endpoint was PK, the results are given in the Clinical Pharmacology Section 6.

8.1.1.4.3.4. Secondary Endpoints: Patient Reported Outcomes

The PK and immunogenicity endpoint results are discussed in the Clinical Pharmacology Section 6. Safety endpoints are reviewed in Section 8.2.

Regarding the Patient Reported Outcomes, there was an overall improvement in the ACQ-7 responses. Data from the mepolizumab 40 mg SC group (weight <40 kg) showed a sustained trend towards ≥0.5 point reduction in ACQ-7 score over the treatment period (Week 0 to Week 12). There was also an overall increase in total C-ACT scores with a peak response at Week 8.

At Week 72, a ≥0.5 point reduction from baseline was observed in 55% of subjects overall in the ACQ-7 questionnaire.

Reviewer comment: As 0.5 is considered the minimal clinical importance difference for ACQ-7 these results are supportive of efficacy in children 6-11 years of age.

8.1.1.4.3.5. Exploratory Endpoint: Asthma Exacerbations

A summary of the on-treatment asthma exacerbations for Part A is shown in Table 5 and for Part B in Table 6. The annualized rate of exacerbation for Part B is also provided (Table 7).

Table 5. Summary of On-Treatment Asthma Exacerbations (PDo, Week 0 to Week 12)

	Mepolizumab 40 mg SC (N=26)	Mepolizumab 100 mg SC (N=10)	Mepolizumab SC (N=36)
By number of exacerbations			
0, n (%)	18 (69%)	8 (80%)	26 (72%)
1, n (%)	6 (23%)	1 (10%)	7 (19%)
2, n (%)	2 (8%)	1 (10%)	3 (8%)
By number of exacerbations requiring hospitalization			
0, n (%)	23 (89%)	10 (100%)	33 (92%)
1, n (%)	3 (12%)	0	3 (8%)
By number of exacerbations requiring hospitalization or emergency room visit			
0, n (%)	22 (85%)	10 (100%)	32 (89%)
1, n (%)	3 (12%)	0	3 (8%)
2, n (%)	1 (4%)	0	1 (3%)

Source: Statistical Reviewer
PDo = pharmacodynamic (outcome assessments) population; SC = subcutaneous

For the first 12-weeks of the trial (Part A), a total of 28% (10/36) of subjects experienced an asthma exacerbation. About 1/3 of the 10 subjects who had an exacerbation required hospitalization or an emergency room visit.

Table 6. Summary of On-Treatment Asthma Exacerbations During the 52-Week Treatment Period (PDo, Part B)

	Mepolizumab 40 mg SC (N=16)	Mepolizumab 100 mg SC (N=10)	Mepolizumab 40/100 mg SC (N=4)	Mepolizumab SC (N=30)
By number of exacerbations				
0, n (%)	8 (50%)	7 (70%)	1 (25%)	16 (53%)
1, n (%)	5 (31%)	0	0	5 (17%)
2, n (%)	3 (19%)	1 (10%)	1 (25%)	5 (17%)
3, n (%)	0	0	2 (50%)	2 (7%)
4, n (%)	0	1 (10%)	0	1 (3%)
6, n (%)	0	1 (10%)	0	1 (3%)
By number of exacerbations requiring hospitalization				
0, n (%)	14 (88%)	8 (80%)	3 (75%)	25 (83%)
1, n (%)	2 (13%)	1 (10%)	1 (25%)	4 (13%)
2, n (%)	0	1 (10%)	0	1 (3%)
By number of exacerbations requiring hospitalization or emergency room visit				
0, n (%)	14 (88%)	8 (80%)	3 (75%)	25 (83%)
1, n (%)	2 (13%)	0	1 (25%)	3 (10%)
2, n (%)	0	1 (10%)	0	1 (3%)
3, n (%)	0	1 (10%)	0	1 (3%)

Source: Statistical Reviewer
PDo = pharmacodynamic (outcome assessments) population; SC = subcutaneous

For the one-year portion of the study (Part B), about half of the subjects (14/30) had an exacerbation, with the majority of those (10/14) having 1 or 2 exacerbation over the 1-year period. Of the 14 subjects who had an exacerbation about 1/3 of those subjects (5/14) required

hospitalization or an emergency room visit. Overall, compared to the first 12-weeks, the number of subjects with exacerbation was higher which is expected given the longer duration; however the severity (requiring hospitalization or emergency room visit) appears consistent. When compared to baseline values, overall 80% of subjects had a ≥50% reduction in the rate of on-treatment exacerbations in Part B compared with the 12 months prior to screening (Table 7).

Table 7. Annualized Rate of Pre-Treatment and On-Treatment Exacerbations (PDo, Part B)

	Mepolizumab 40 mg SC (N=16)	Mepolizumab 100 mg SC (N=10)	Mepolizumab 40/100 mg SC (N=4)	Mepolizumab SC (N=30)
Pre-Treatment exacerbation				
Rate	2.9	3.7	5.0	3.5
95% CI	2.29, 3.51	1.64, 5.76	2.88, 7.12	2.68, 4.32
On- Treatment exacerbation				
Rate	0.77	1.20	1.98	1.09
95% CI	0.34, 1.73	0.49, 2.92	0.55, 7.17	0.64, 1.86
Pre-Treatment Exacerbations requiring hospitalization				
Rate	1.4	1.2	1.5	1.4
95% CI	0.25, 2.55	-0.39, 2.79	-0.83, 3.83	0.56, 2.24
On-Treatment exacerbations requiring hospitalization				
Rate	0.14	0.30	0.25	0.21
95% CI	0.03, 0.64	0.08, 1.13	0.03, 2.34	0.09, 0.52
On-Treatment exacerbations requiring hospitalization or emergency room visit				
Rate	0.17	0.50	0.25	0.30
95% CI	0.03, 1.00	0.11, 2.32	0.02, 4.10	0.11, 0.85

Source: Statistical Reviewer, Clinical Reviewer, and CSR
CI = confidence interval; PDo = pharmacodynamic (outcome assessments) population; SC = subcutaneous

Annualized rate of exacerbations by dose strength was calculated using a negative binomial model with logarithm of time on treatment as an offset variable. The annualized rates were used by the Applicant to show consistency with annualized rates observed in adults/adolescents trials. In the original severe eosinophilic asthma phase 3 clinical program, two placebo-controlled studies, MEA115588 and 200862, showed that mepolizumab reduced the rate of clinically significant exacerbations (CSE) by 47% and 58%, respectively, when compared with placebo. The annualized rate of exacerbation in the adult and adolescent studies ranged from 0.83 to 1.24 for the mepolizumab treatment groups. As Trial 200363 was not powered nor designed to assess an exacerbation endpoint, the sponsor used Bootstrap analysis to show consistency with incidence rates observed in adults/adolescents trials. The sponsor concludes that the reduction in clinically significant exacerbation rate in adults with severe eosinophilic asthma translates to the pediatric subpopulation with greater than 50% similarity, and that there is little reason to doubt that the magnitude of response observed in the pediatric subpopulation is not consistent with that in the much larger adult population, despite the small sample size. This was further supported by a Bayesian Dynamic Borrowing with a Mixture Prior approach which offers a numerical model to predict efficacy with increasing prior weights indicating greater confidence in the extrapolation strategy. See Section 15.6 for further description as to the extrapolation.

8.1.2. Assessment of Efficacy Across Trials

Efficacy in children 6 to 11 years of age was extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older. The extrapolation was supported by pharmacokinetic (PK) analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks and a similar pharmacodynamic response. Extrapolation of efficacy based on comparable systemic exposure is appropriate because of the similar clinical presentation of both adult and pediatric severe eosinophilic asthma, consistency in therapeutic approach, consistency of mepolizumab mechanism of action, and relevance of the clinical endpoints for both efficacy and safety.

Trial 200363 was not designed to assess efficacy given the small sample size, duration, and uncontrolled design. However, exploratory analysis did show efficacy results consistent with the adolescent and adult trials. There was a trend towards a ≥0.5 reduction from baseline in Asthma Control Questionnaire 7 (ACQ-7) score over the treatment period along with an increase in total Childhood Asthma Control Test (C-ACT) scores in all groups, suggesting an improvement in asthma control.

For the one-year portion of the study (Part B), about half of the subjects (14/30) had an exacerbation, with the majority of those (10/14) having 1 or 2 exacerbation over the 1-year period. Of the 14 subjects who had an exacerbation about 1/3 of those subjects (5/14) required hospitalization or an emergency room visit. When compared to baseline values, overall 80% of subjects had a ≥50% reduction in the rate of on-treatment exacerbations in the one year portion of the study (Part B) compared with the 12 months prior to screening. The annualized asthma exacerbation rate was 1.09. A Bootstrap analysis showed consistency of the annualized asthma exacerbation incidence rates observed in the treatment group of the 6-11 year old trial with adults/adolescents trials. This was further supported by a Bayesian Dynamic Borrowing with a Mixture Prior approach which offers a numerical model to predict efficacy with increasing prior weights indicating greater confidence in the extrapolation strategy. See Section 15.6 for further details on the Bootstrap analysis and the Bayesian Dynamic Borrowing with a Mixture Prior approach.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review is divided into the study's two parts: Part A and Part B, with more emphasis placed on Part B as the purpose of Part B was to evaluate long term safety. Part A consisted of a 12-week treatment period and an 8-week follow-up phase and Part B was a 52-week long open extension study. Adverse events were monitored during the entirety of the study. The safety data for the two parts were not pooled and will be reviewed individually.

8.2.2. Review of the Safety Database

Overall Exposure

Part A

Ninety-two percent of all subjects in Part A received all three treatments of mepolizumab with an average of 84 days on treatment. Three subjects, all from the 40-mg dose, withdrew from the study after two doses.

Part B

Ninety percent of all subjects in Part B received all 13 mepolizumab treatments. One subject withdrew from Part B after two doses due to lack of adherence/protocol deviation. Most subjects (90%) received all 13 treatments and spent an average of 355 days on treatment.

Adequacy of the safety database

Overall, the safety database is of sufficient size and duration to assess the safety of the proposed pediatric dose given the previous safety database for the approved adolescent and adult asthma indication.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this BLA were identified.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols. Adverse events (AEs) were captured from signing of informed consent through the final follow up visit. Treatment emergent adverse events were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using the Medical Dictionary for Regulatory Activities version 19.1.

The Applicant's coding of verbatim terms to preferred terms was appropriate. Adverse events of special interest included systemic reactions (nonallergic and allergic/hypersensitivity), local injection site reactions, cardiac disorders including serious cardiac, vascular thromboembolic and serious ischemic events, infections, and malignancies. The Applicant analyzed standardized Medical Dictionary for Regulatory Activities queries for anaphylaxis and hypersensitivity events, drug-related hepatic disorders, malignancy or unspecified tumors, and conjunctivitis.

Routine Clinical Tests

Safety assessments consisted of routine reporting of all adverse events, serious adverse events, relationship to the drug, concomitant medications, and pregnancies. Participants also underwent regular monitoring of bloodwork (hematology, chemistry, urine analysis), vital signs and physical exams. A 12-lead electrocardiogram was obtained at Visit 1, during Treatment Period of Part A, Exit Visit of Part A, and Exit Visit of Part B. Blood samples were also obtained regularly to assess for immunogenicity.

8.2.4. Safety Results

Deaths

There were no deaths in either Part A or Part B of the study.

Serious Adverse Events

Part A

A total of six subjects reported at least one serious adverse event. Five of the six subjects were in the 40 mg treatment arm. There were a total of twelve SAEs reported overall.

Table 8. Trial 200363, Part A Serious Adverse Events Per Treatment Arm

		Treatment Arm		
System Organ Class	Preferred Term	Mepolizumab 100 mg SC (N=10)	Mepolizumab 40 mg SC (N=26)	Total
Gastrointestinal disorders	Nausea	0	1	1
General disorders and administration site conditions	Chest pain	0	1	1
	Pain	0	1	1
Infections and infestations	Cellulitis	0	1	1
	Lower respiratory tract infection	1	1	2
Musculoskeletal and connective tissue disorders	Back pain	0	1	1
Nervous system disorders	Dizziness	0	1	1
	Headache	0	1	1
Respiratory, thoracic and mediastinal disorders	Asthma	0	3	3
Total		1	11	12

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363

Each of the SAEs occurred as singular events with the exception of lower respiratory tract infection and asthma. There was not dose-related SAEs. The asthma exacerbation events are expected in this population.

Part B

A total of seven subjects reported at least one SAE during Part B. Four subjects were in the 40 mg treatment arm, two in the 100 mg treatment arm, and one received both 40 and 100 mg due to change in weight. The majority of the SAEs were singular events with the exception of

two subjects. One subject reported two separate episodes of asthma exacerbation and one other subject reported two separate SAEs (asthma exacerbation and pneumonia) for the same event. Frequent asthma exacerbations along with concurrent pneumonia diagnoses are expected of this patient population. As a result, there were a total of nine SAEs reported. One anaphylaxis event occurred in a 7-year-old boy 277 days after his first mepolizumab injection and 3 days after his last injection. He had a known peanut allergy and accidentally ingested peanut which required hospitalization for treatment. Due to this known ingestion and timing of the event from his last mepolizumab injection, the episode of anaphylaxis does not appear to be treatment related. The types of SAEs seen were consistent with what was seen in the adult and adolescent studies.

Table 9. Trial 200363, Part B Serious Adverse Events Per Treatment Arm

		Treatment Arm			
System Organ Class	Preferred Term	Mepolizumab 100 mg SC (N=10)	Mepolizumab 40/100 mg SC (N=4)	Mepolizumab 40 mg SC N(=16)	Total
Immune system disorders	Anaphylactic shock	0	0	1	1
Infections and infestations	Pneumonia	1	0	0	1
Respiratory, thoracic and mediastinal disorders	Asthma	3	1	2	5
	Epistaxis	0	0	1	1
Total		4	1	4	9

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363
SC = subcutaneous

In the 120 Day Safety Update report from the Applicant, they report one SAE in Trial 201956, GSK's Long Term Access Program. An 11 year reported the SAE of adenoidal hypertrophy 38 days after the first dose of mepolizumab.

Dropouts and/or Discontinuations Due to Adverse Effects

Part A only had one adverse event that lead to withdrawal from the trial (Subject (b) (6)). Subject (b) (6) enrolled in the mepolizumab 40 mg arm and withdrew due to the adverse event of asthma. Of note, there was another subject, Subject (b) (6), who withdrew consent due to a combination of adverse events, but this was captured as "Withdrawal by subject." Subject (b) (6) reported various AEs (dictionary derived term: cough, wheezing, hypersensitivity reaction, lethargy, nausea, sore throat, pain, headache, dizziness, rash), with one SAE (dictionary derived term: rash). See also disposition in Section 8.1.1.4.3.1.

There were no dropouts or discontinuations due to AEs in Part B.

Treatment Emergent Adverse Events

Given the absence of a placebo group in Trial 200363, it is difficult to assess relatedness of events to medication use. Generally, events were mostly singular and balanced between treatment arms; therefore, a review of all AEs in Trial 200363 did not reveal any new safety concerns. Common AEs (occurring in ≥2 subjects in one or more treatment groups) reported are

summarized in Table 10 and Table 11. In both Part A and Part B, headache, asthma, nasopharyngitis are common AEs seen. However, in Part A, injection site reactions is a reported AE that is not seen in Part B. This is expected as injection site reactions tend to resolve after repeated exposure. In Part B, bronchitis is reported as a common AE which is expected given the nature of the primary disease and the longer duration of the study. Overall, the safety profile for pediatric patients is similar to that observed in patients aged 12 years and older.

Table 10. Trial 200363, Part A Subjects With Common Adverse Events (n ≥2)

	Treatment Arm		
Preferred Term	**Mepolizumab 40 mg SC (N=26)**	**Mepolizumab 100 mg SC (N=10)**	**Total Subjects (N=36)**
Headache	3 (12%)	2 (20%)	5 (14%)
(Injection site reaction	5 (19%)	0 (0%)	5 (14%)
Asthma	4 (15%)	0 (0%)	4 (11%)
Nasopharyngitis	3 (12%)	1 (10%)	4 (11%)
Nausea	3 (12%)	0 (0%)	3 (8%)
Upper respiratory tract infection	2 (8%)	1 (10%)	3 (8%)
Wheezing	2 (8%)	1 (10%)	3 (8%)
Constipation	2 (8%)	0 (0%)	2 (6%)
Dizziness	2 (8%)	0 (0%)	2 (6%)
Lower respiratory tract infection	1 (4%)	1 (10%)	2 (6%)
Oropharyngeal pain	2 (8%)	0 (0%)	2 (6%)
Pain	2 (8%)	0 (0%)	2 (6%)
Pharyngeal erythema	1 (4%)	1 (10%)	2 (6%)
Rash	2 (8%)	0 (0%)	2 (6%)
Sinusitis	1 (4%)	1 (10%)	2 (6%)
Viral upper respiratory tract infection	2 (8%)	0 (0%)	2 (6%)
Vomiting	1 (4%)	1 (10%)	2 (6%)

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363
SC = subcutaneous

Table 11. Trial 200363, Part B Subjects With Common Adverse Events (n ≥2)

	Treatment Arm			
Preferred Term	**Mepolizumab 40 mg SC (N=16)**	**Mepolizumab 100 mg SC (N=10)**	**Mepolizumab 40/100 mg SC (N=4)**	**Total Subjects (N=30)**
Bronchitis	5 (31%)	3 (30%)	1 (25%)	9 (30%)
(30.(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 (0%)	1 (25%)	4 (13%)
Abdominal pain upper	2 (13%)	1 (10%)	0 (0%)	3 (10%)
Cough	1 (6%)	2 (20%)	0 (0%)	3 (10%)
Eczema	2 (13%)	1 (10%)	0 (0%)	3 (10%)
Epistaxis	3 (19%)	0 (0%)	0 (0%)	3 (10%)
Pharyngitis	3 (19%)	0 (0%)	0 (0%)	3 (10%)
Viral upper respiratory tract infection	2 (13%)	0 (0%)	1 (25%)	3 (10%)
Aggression	2 (13%)	0 (0%)	0 (0%)	2 (7%)

	Treatment Arm			
Preferred Term	Mepolizumab 40 mg SC (N=16)	Mepolizumab 100 mg SC (N=10)	Mepolizumab 40/100 mg SC (N=4)	Total Subjects (N=30)
Back pain	2 (13%)	0 (0%)	0 (0%)	2 (7%)
Conjunctivitis	1 (6%)	1 (10%)	0 (0%)	2 (7%)
Constipation	1 (6%)	0 (0%)	1 (25%)	2 (7%)
Dermatitis atopic	1 (6%)	1 (10%)	0 (0%)	2 (7%)
Diarrhea	2 (13%)	0 (0%)	0 (0%)	2 (7%)
Ear infection	0 (0%)	1 (10%)	1 (25%)	2 (7%)
Gastroenteritis	2 (13%)	0 (0%)	0 (0%)	2 (7%)
Impetigo	1 (6%)	1 (10%)	0 (0%)	2 (7%)
Lower respiratory tract infection	1 (6%)	1 (10%)	0 (0%)	2 (7%)
Pyrexia	1 (6%)	1 (10%)	0 (0%)	2 (7%)
Rash	2 (13%)	0 (0%)	0 (0%)	2 (7%)
Rhinitis	0 (0%)	1 (10%)	1 (25%)	2 (7%)

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363
SC = subcutaneous

Laboratory Findings

Laboratory assessments (hematology, chemistry, and urinalysis) were conducted periodically during the study. All chemistry results were compared with baseline. The majority of subjects had values for clinical chemistry within normal range.

Chemistry:

There were no clinically relevant changes from baseline in any clinical chemistry parameter in Part A of this study. One subject in the 100 mg SC group had an AE of hyperglycemia that occurred 19 days after the first dose. It was categorized as mild and nonserious. In Part B, two subjects reported AEs related to chemistry changes. One subject had an AE of hypoglycemia 85 days after the first dose of mepolizumab in Part B where the onset date was the same date as a treatment visit. The event resolved after 9 days without a mepolizumab dose change or interruption. All other glucose values for this subject in both Part A and Part B were normal. The other subject had an event of hyperglycemia 249 days after the first dose of mepolizumab in Part B and 29 days after the most recent dose. The event also resolved without any dose change or interruption in treatment.

Part A had no abnormal liver function test. One subject in Part B had an elevated bilirubin. No liver stopping criteria were met in Part A or Part B of the study.

Hematology:

With the exception of the decline in eosinophils, which is expected based on mepolizumab's mechanism of action, there were no clinically relevant changes. For changes in eosinophils, see Clinical Pharmacology Questions Section 6.3.2. Part A did have 11 subjects who had low value of neutrophils, with the lowest value of 0.57 x 10^9/L at Week 20. One subject (Subject (b) (6)) had a nonserious AE of neutrophil count decrease. This subject had a neutrophil count below the lower limit of normal at every study visit in Part A and Part B including the screening visit. One

subject had low values for platelets at week 9 and 12. The above laboratory changes had no clinical relevance.

Vital Signs

Routine vital signs such as sitting pulse rate and blood pressure were performed periodically during the study. The mean changes from baseline in all parameters were small and there were no treatment effect detected.

Electrocardiograms

Twelve-lead electrocardiograms were performed periodically during the study. Five subjects (19%) in the mepolizumab 40 mg group and four subjects (40%) in the 100 mg group had baseline electrocardiograms classified as abnormal. At any visit post baseline, there were seven subjects (27%) in the 40 mg group and four subjects (40%) in 100 mg group that were classified as abnormal. The abnormalities reported were intraventricular conduction deficit or prolonged QT.

Immunogenicity

No subjects reported positive ADA results at baseline. There were two subjects who had transient positive responses for binding ADAs with low titers in Part A. They became negative at subsequent visits. There were no positive ADA responses in Part B.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest included systemic (allergic and nonallergic) reactions, local injection site reactions, cardiac disorders including serious cardiac, vascular, thromboembolic and serious ischemic events, infections and malignancies.

Part A

In Part A, there was one reported nonallergic systemic reaction in an 11-year-old who experienced pruritus less than 24 hours following first injection of mepolizumab. It was not considered serious and was mild in intensity. The event lasted 57 days and resolved without mepolizumab interruption or dose change.

There were five subjects who reported at least one injection site reaction (seven events total). All events were nonserious and mild intensity, described as mild erythema, swelling, itching, pain, and rash. All resolved without a mepolizumab interruption or dose change.

There were 18 subjects who had an on-treatment infection adverse event. Three of these were considered serious (one cellulitis and two lower respiratory tract infection). There were no opportunistic infections. There were no on treatment cardiovascular events. A summary of the above adverse events of special interest can be found in Table 12.

Table 12. Trial 200363, Part A Subjects With Adverse Events of Special Interest

		Treatment Arm		
Adverse Event SOC	**Preferred Term**	**Mepolizumab 100 mg SC (N=10)**	**Mepolizumab 40 mg SC (N=26)**	**Total (N=36)**
Immune system disorders	Hypersensitivity	0 (0%)	1 (4%)	1 (3%)
General disorder and administration site conditions	Injection site reaction	0 (0%)	5 (19%)	5 (14%)
Infections and infestations*	All	4 (40%)	14 (54%)	18 (50%)
	(Viral) respiratory tract infection (upper and lower); croup infection	2 (20%)	7 (27%)	9 (25%)
(25	(Naso)pharyngitis	1 (10%)	4 (15%)	5 (14%)
	(Acute) sinusitis	1 (10%)	2 (8%)	3 (8%)
	Acute otitis media	0 (0%)	1 (4%)	1 (3%)
	Bronchitis	0 (0%)	1 (4%)	1 (3%)
	Cellulitis	0 (0%)	1 (4%)	1 (3%)
	Bronchitis	0 (0%)	1 (4%)	1 (3%)
	Gastroenteritis	0 (0%)	1 (4%)	1 (3%)
	Eczema infection	0 (0%)	1 (4%)	1 (3%)
	Oral herpes	1 (10%)	0 (0%)	1 (3%)
	Pneumonia	0 (0%)	1 (4%)	1 (3%)
	Tinea infection	0 (0%)	1 (4%)	1 (3%)
	Rhinitis	1 (10%)	0 (0%)	1 (3%)
	Wound infection	1 (10%)	0 (0%)	1 (3%)
Cardiac disorders		0 (0%)	0 (0%)	0 (0%)
Neoplasms		0 (0%)	0 (0%)	0 (0%)

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363
* Each subject could have reported multiple preferred terms.
SC = subcutaneous; SOC = system organ class

Part B

In Part B, there was one subject who experienced an anaphylaxis event after consumption of peanut in a known peanut allergic subject. Due to this known ingestion and timing of the event from his last mepolizumab injection, the episode of anaphylaxis does not appear to be treatment related. There was also another subject who experienced an allergic generalized rash that occurred 339 days after the first dose of mepolizumab and 3 days after his final dose. This event was not considered serious.

There was a total of 22 subjects with infections, one characterized as serious and one as opportunistic (Table 13). Twenty two subjects had an infection while on treatment. The most common infections reported were bronchitis, upper respiratory infection, nasopharyngitis, viral gastroenteritis, influenza, and viral pharyngitis. One subject had a serious infection (pneumonia) 53 days after the first dose of mepolizumab. One 10-year-old reported an opportunistic infection due to an outbreak of oral herpes 183 days after the first dose of mepolizumab. The same subject had another outbreak of oral herpes 351 days after first mepolizumab treatment. There were no local injection site reactions, cardiac events, or malignancies. Overall, the infection adverse events did not identify any new safety concerns.

Table 13. Trial 200363, Part B Number Subjects With Adverse Events of Special Interest

		Treatment Arm			
Adverse Event SOC	**Preferred Term**	**Mepolizumab 100 mg SC (N=10)**	**Mepolizumab 40 mg SC (N=16)**	**Mepolizumab 100/40 (N=4)**	**Total (N=30)**
Immune system disorders	Hypersensitivity	1 (10%)	1 (6%)	0 (0%)	2 (7%)
General disorder and administration site conditions	Injection site reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infections and Infestations*	All	7 (70%)	11 (69%)	4 (100%)	22 (73%)
	Bronchitis	3 (30%)	5 (31%)	1 (25%)	9 (30%)
	(Viral) Upper respiratory tract infection	2 (20%)	4 (25%)	2 (50%)	8 (27%)
	Nasopharyngitis	1 (10%)	3 (19%)	2 (50%)	6 (20%)
	(Viral) Gastroenteritis	0 (0%)	4 (25%)	0 (0%)	4 (13%)
	Influenza	0 (0%)	3 (19%)	1 (25%)	4 (13%)
	(Viral) Pharyngitis	0 (0%)	3 (19%)	1 (25%)	4 (13%
	Conjunctivitis	1 (10%)	1 (6%)	0 (0%)	2 (7%)
	Ear Infection	1 (10%)	0 (0%)	1 (25%)	2 (7%)
	Empyema	0 (0%)	0 (0%)	1 (25%)	1 (3%)
	(Bacterial) pneumonia	1(10%)	0 (0%)	1 (25%)	2 (7%)
	Impetigo	1 (10%)	1 (6%)	0 (0%)	2 (7%)
	Lower respiratory tract infection	1 (10%)	1 (6%)	0 (0%)	2 (7%)
	Oral herpes	1 (10%)	0 (0%)	0 (0%)	1 (3%)
	Croup infection	0 (0%)	1 (6%)	0 (0%)	1 (3%)
	Hordeolum	1 (10%)	0 (0%)	0 (0%)	1 (3%)
	Paronychia	0 (0%)	1 (6%)	0 (0%)	1 (3%)
	Tinea infection	1 (10%)	0 (0%)	0 (0%)	1 (3%)
	Tracheitis	0 (0%)	1 (6%)	0 (0%)	1 (3%)
Cardiac disorders		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neoplasms		0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer generated table in JMP using dataset without screen failures, Trial CSR 200363
* Each subject could have reported multiple preferred terms.
SC = subcutaneous; SOC = system organ class

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

Not applicable

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

Not applicable

Pediatrics and Assessment of Effects on Growth

Not applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The current prescribing information for mepolizumab include postmarketing events of hypersensitivity reactions, including anaphylaxis. This is a known safety concern with biologics and no events were seen in the pediatric study.

Expectations on Safety in the Postmarket Setting

Not applicable.

8.2.11. Integrated Assessment of Safety

There were no new safety concerns identified in Trial 200363 that alter the risk-benefit profile of mepolizumab for the population 6 to 11 years of age. The frequency and type of AEs were consistent with previous studies in adults and adolescents. Most of the AEs experienced were mild or moderate in severity. Headache, bronchitis, and injection site reaction were the three most common AE.

8.3. Statistical Issues

Not applicable

8.4. Conclusions and Recommendations

The recommended regulatory action is approval of mepolizumab for the add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype, ≥6 year of age. Given the similar clinical presentation of both adult and pediatric severe eosinophilic asthma, consistency in the therapeutic approach, consistency of the mepolizumab mechanism of action, and relevance of the clinical endpoints, efficacy in children 6 to 11 years of age was extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older based on comparable systemic exposure for 40 mg administered subcutaneously every 4 weeks to the approved 100 mg SC dose, and a similar pharmacodynamic response. Long-term safety in patients 6 to 11 years of age was evaluated in

part B of the trial; the safety profile demonstrated in Trial 200363 is similar to the established safety profile in adolescents and adults. Mepolizumab is the first anti-human interleukin 5 (anti-IL5) proposed for patients less than 12 years of age and the first biologic approved for children less than 12 years of age with severe asthma with an eosinophilic phenotype. The overall risk-benefit is favorable for the approval of mepolizumab down to age 6 years of age, as add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype.

9. Advisory Committee Meeting and Other External Consultations

As mepolizumab is approved for the same indication in adolescents and adults and there were no safety or efficacy concerns identified for this pediatric program, no advisory committee meeting was required.

10. Pediatrics

The Applicant submitted data from Trial 200363 to fulfill the requirements of two Pediatric Research Equity Act (PREA) Post-Marketing Requirements (PMRs) (2979-1 and PMR 2979-2) that were issued for children 6 to 11 years of age. See Postmarketing Requirements and Commitments for further details. The requirement of studies in ages 0 to 5 years were waived because necessary studies are impossible or highly impracticable as severe asthma with eosinophilic phenotype is unlikely to exist in sufficient numbers to allow for a study to be conducted.

On August 7, 2019, the Pediatric Review Committee (PeRC) reviewed Trial 200363 and agreed that this clinical trial fulfilled the outstanding PMRs (2979-1 and PMR 2979-2). Approval of the pediatric indication (extending age of use down to 6 years of age) was also endorsed.

Trial 200363 also fulfills the PREA PMRs 3620-3 and 3620-4 for BLA 761122 for the Liquid Formulation for subcutaneous injection via autoinjector or safety syringe device.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant provided an amended label for NUCALA. These labels incorporate the pediatric information that pertains to children ages 6 to 11 years in Sections 2 DOSAGE AND ADMINISTRATION, 5 WARNINGS AND PRECAUTIONS, 6 ADVERSE REACTIONS, 8 USE IN SPECIFIC POPULATIONS, and 12 CLINICAL PHARMACOLOGY.

Recommendations from labeling consultants in DMEPA, DMPP, OPDP, Patient Labeling Team were incorporated into the final label. Table 14 reflects the labeling changes received on August 9, 2019.

As mentioned in the Product Information, in addition the efficacy supplement (S-012) submitted to BLA 125526, GSK also submitted a prior approval labeling supplement (S-002) to BLA 761122 (for the liquid formulation for subcutaneous injection via an autoinjector or safety syringe device) to provide labeling revisions to the prescribing information, patient information and the Instructions For Use to align the labels for both BLA 125526 and BLA 761122. BLA 761122/S-002 also included minor administrative changes to the Instructions For Use label. Approval of these supplements will result in a single United States Product Insert (USPI) for all approved indications, formulations and presentations.

Table 14. Mepolizumab Prescribing Information

Section	Proposed Labeling	Approved Labeling
Section 2.1, 2.3 Administration Information	The Applicant provided dosage information and administration instructions for the 6-11 years old pediatric dose.	Agreed with the addition.
Section 6.1 Adverse Events: Clinical Trials Experience in Severe Asthma	A statement was provided to state no additional adverse reactions were identified to those reported in the adolescent and adult severe asthma trials.	Agreed with the addition.
Section 6.3 Adverse Events: Immunogenicity	Immunogenicity data from the pediatric trial was provided.	Agreed with the addition
Section 8.4: USE IN SPECIFIC POPULATIONS: Pediatric Use	A summary of the pediatric trial was provided. (b) (4)	The summary was modified to explain how efficacy was determined in the pediatric population. (b) (4) were remove (b) (4)
Section 12.2 and 12.3: CLINICAL PHARMACOLOGY: Pharmacodynamics and Pharmacokinetics	A summary of the pharmacokinetic and pharmacodynamic findings from the pediatric trial was provided.	The summary was modified (b) (4) to avoid confusion.

12. Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of mepolizumab for 6- to 11-year-olds, there are no additional risk management strategies required.

13. Postmarketing Requirements and Commitment

Data submitted for Trial 200363 fulfills PREA PMRs 2979-1 and 2979-2 under BLA 125526. All PREA PMRs associated with BLA 125526 have been fulfilled. The PMRs from the November 4, 2015 approval are outlined below:

2979-1 Conduct a 12 week, randomized, open-label, pharmacokinetic and pharmacodynamics study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part A of Study 200363).

2979-2 Conduct a 12 month long-term safety and pharmacodynamics extension study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part B of Study 200363).

As mepolizumab is also approved under BLA 761122 for the Liquid Formulation for Subcutaneous Injection via Autoinjector and Safety Syringe Device an additional prior approval supplement (S-003) was submitted to BLA 761122 for Trial 200363 to fulfill the PMRs 3620-3 and 3620-4 under BLA 761122. All PREA PMRs associated with BLA 761122 have been fulfilled; however a post-marketing commitment (PMC) remains open for BLA 761122. The PMRs from the June 6, 2019 approval are outlined below.

3620-3 Conduct a 12-week, randomized, open-label, pharmacokinetic and pharmacodynamics study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part A of Study 200363).

3620-4 Conduct a 12-month long-term safety and pharmacodynamics extension study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part B of Study 200363).

14. Division Director (Clinical) Comments

Mepolizumab is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) approved for "add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype". The approved dose in patients 12 years and older is 100 mg administered subcutaneously (SC) once every 4 weeks (Q4W). The Applicant submitted a prior approval supplement to expand the approved indication to include patients aged 6 to 11 years. The Applicant proposes a dose of 40 mg administered subcutaneously (SC) every 4 weeks (Q4W) in patients 6 to 11 years. The 40 mg dose is available as a lyophilized powder in a single-dose vial for reconstitution administered by a healthcare provider. The recently approved prefilled safety syringe device and autoinjector will not be used for patients 6 to 11 years of age.In this efficacy supplement, the sponsor submitted the results for Trial 200363, an open label study to characterize the pharmacokinetics, pharmacodynamics, and long-term safety in patients 6 to 11 years of age. The study consisted of 2 parts: 1) Part A assessed the PK and PD of either 40 or 100 mg of mepolizumab (depending on subject weight <40 kg or ≥40 kg, respectively), administered SC Q4W, for a total duration of 12 weeks; 2) Part B assessed the long-term safety and PD, in which patients were treated for 52 weeks.

In Part A of Trial 200363, 40 mg SC Q4W and 100 mg SC Q4W doses were tested in patients weighing <40 kg and ≥40 kg, respectively, resulting in a 1.3- and 2-fold higher exposure compared to adults, respectively. In order to address the high exposure for the 100 mg SC Q4W dose, a fixed dose of 40 mg SC Q4W was proposed in patients aged 6 to 11 years, irrespective of the body weight. While simulation from population PK analysis predicts 20% lower exposure in 6 to 11 year old patients weighing ≥40 kg, data from the adult-dose response model in the original BLA review demonstrates that the predicted exposure will still achieve a near 90% reduction in blood eosinophils. Given that there is limited safety data in pediatric patients to rule out a potential safety concern with a 2-fold higher mepolizumab exposure with the 100 mg SC Q4W dose, and similar pharmacodynamic response with the marginally lower systemic exposure, selection of 40 mg SC Q4W as the dose in patients 6 to 11 years of age is appropriate.

Because of the comparable systemic exposures and because the disease process in the older population is the same as that in the 6 to 11 year old population, efficacy in the proposed age group was extrapolated from the ≥12-year-old age group where efficacy had been demonstrated in clinical trials. No new safety signals were identified in Part B (52 week) of the trial. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments and the recommendation of approval. The Agency and the Applicant have also agreed upon final labeling language. The action for this application will be **Approval.** This efficacy supplement fulfills the PREA PMRs for both this BLA and BLA 761122. During this review, the sponsor submitted labeling supplements to align the labels for both BLA 125526 and BLA 761122 (autoinjector and prefilled syringe presentations), as well as to update the Instructions for Use. Approval of these supplements will result in a single USPI for all approved indications, formulations and presentations.

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15. Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 200363

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 73		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: $201,705.80 Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Supportive Efficacy Information

Mepolizumab is a humanized monoclonal antibody targeted against human interleukin 5 (IL5) that was approved in the United States in November 2015 as an add-on maintenance treatment for patients with severe asthma aged 12 years and older (adults and adolescents) with an eosinophilic phenotype. The current supplemental BLA consists of data supporting the use of mepolizumab in the treatment of children aged 6 to 11 years with severe eosinophilic asthma and seeks FDA approval for the extension of the indication to include the pediatric population.

Due to the low prevalence of severe eosinophilic asthma in children 6 to 11 years old, recruiting patients for a conventional clinical trial is challenging. Therefore, the mepolizumab pediatric asthma clinical development program consisted of a single open-label, uncontrolled clinical trial (Trial 200363) conducted in children aged 6 to 11 years that investigated mepolizumab pharmacokinetics (PK), pharmacodynamics (PD), and long-term safety. To support approval efficacy and safety observed in open-label Trial 200363 were compared to those of the adult/adolescent program that were the basis of the initial approval. Comparability in baseline disease characteristics was demonstrated through these comparisons. To support pediatric use of mepolizumab in the asthma indication through a partial extrapolation approach the Applicant conducted Bayesian dynamic borrowing analyses to provide evidence of consistency in efficacy response between adults (≥18 years old) and adolescents (12 to 17 years old) in the severe eosinophilic asthma indication. In addition, to compare the pediatric subpopulation response to mepolizumab with simulated equivalent trials in adult subjects, the Applicant also performed bootstrap resample analysis.

The Applicant's Bayesian Extrapolation of Mepolizumab Efficacy in Adults to Adolescents from Severe Eosinophilic Asthma Studies

This section briefly describes the Applicant's statistical approach of Bayesian robust mixture prior analyses, supported by a summary of the study data and key findings.

In the original severe eosinophilic asthma phase 3 clinical program, two placebo-controlled studies, MEA115588 and 200862, showed that mepolizumab reduced the rate of clinically significant exacerbations (CSE) by 47% and 58%, respectively, when compared with placebo. A total of 34 adolescent subjects were randomized across both studies (Table 15). A Bayesian statistical approach was used to borrow information from adult clinical trial data to provide inferences on a pediatric population based on limited adolescent data collected within the original adult/adolescent program. Specifically, the aim of the Bayesian analysis is to investigate whether the efficacy results observed in two placebo-controlled studies, MEA115588 and 200862, for adolescent subjects are consistent with those of adults.

Table 15. Severe Eosinophilic Asthma Studies Included Within Analyses

Study	Route	Treatment Duration	Treatment Arms	Total No. Subjects	No. Subjects 12-17 Years Old (%)	No Subjects ≥18 years old (%)	CSE Rate Ratio (vs. Placebo) (95% CI)
MEA115588	IV and SC	Q4W, 32 Weeks	Mepolizumab 100 mg SC Mepolizumab 75 mg IV Placebo	576	25 (4)	551 (96)	0.53 (0.36, 0.65)
200862	SC	Q4W, 24 Weeks	Mepolizumab 100 mg SC Placebo	551	9 (2)	542 (98)	0.42 (0.31, 0.56)

CSE = clinically significant exacerbations; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous

Each study was first analyzed for adults and adolescents on CSE separately, point estimates and squared standard error of the log-rate ratio from a negative binomial regression of the observed exacerbation counts. Analysis used individual patient-level data and was performed using two approaches: an interaction model (primary analysis) including a categorical covariate for age group and the interaction of age group with treatment group, with additional adjustment for baseline covariates; and a separate model (sensitivity analysis) estimating the rate ratio for mepolizumab relative to placebo separately with a separate negative binomial regression model for each combination for study and age subgroup. Results from the above approaches are summarized in Table 16. An inverse variance weighted fixed-effect meta-analysis approach was used to combine the results from the two studies. These results will be used as feeds for the Bayesian analysis. In the description below, the combined rate ratios in natural log scale (Adolescents: rate ratio [RR] =-0.5102, standard error [SE] =0.6377 ; Adults: RR =-0.7691, SE =0.0986) from the interaction model approach will be used as an example.

Table 16. Study MEA115588 and Study 200862: Estimated Exacerbation Rate, Rate Ratio and 95% CI by Age Group

Robust Mixture Prior and Likelihood Scenario	Age group	Treatment Group	Number of subjects	Number of exacerbations	Total follow-up years	Exacerbation rate	Rate ratio	95% CI	Normal Distribution of Rate Ratio	
									Natural log scale	
									Estimate	Standard Error
Interaction Model (MEA115588)	Adolescents (12-17 years old)	Placebo	9	6	5.7	0.95	0.67	(0.17, 2.68)	-0.3945	0.7033
		Mepo	16	6	9.94	0.64				
	Adults (>=18 years old)	Placebo	182	210	110.16	1.8	0.50	(0.39, 0.64)	-0.6941	0.1303
		Mepo	369	227	223.02	0.9				
	Weak Prior								0	3.0577
Interaction Model (MEA115588 + 200862)	Adolescents (12-17 years old)	Placebo	12	7	7.11	0.94	0.60	(0.17, 2.10)	-0.5102	0.6377
		Mepo	22	7	12.76	0.56				
	Adults (>=18 years old)	Placebo	456	389	233.14	1.52	0.46	(0.38, 0.56)	-0.7691	0.0986
		Mepo	637	305	347.42	0.71				
	Weak Prior								0	3.2602
Separate Models (MEA115588)	Adolescents (12-17 years old)	Placebo	9	6	5.7	1.08	0.56	(0.09, 3.45)	-0.5886	0.9322
		Mepo	16	6	9.94	0.6				
	Adults (>=18 years old)	Placebo	182	210	110.16	1.91	0.54	(0.41, 0.70)	-0.6251	0.1356
		Mepo	369	227	223.02	1.02				
	Weak Prior								0	3.1831
Separate Models (MEA115588 + 200862)	Adolescents (12-17 years old)	Placebo	12	7	7.11	0.95	0.54	(0.12, 2.47)	-0.62	0.7783
		Mepo	22	7	12.76	0.51				
	Adults (>=18 years old)	Placebo	456	389	233.14	1.71	0.49	(0.40, 0.60)	-0.7152	0.1036
		Mepo	637	305	347.42	0.84				
	Weak Prior								0	3.4264

Source: The Applicant
CI = confidence interval

The Bayesian mixture prior approach uses the observed efficacy response for the adult subjects to form a prior distribution for the efficacy response in adolescents. By varying the weight, the robust mixture prior approach allows for dynamic borrowing of prior information. The mixture prior was constructed as a weighted average of the informative prior and weak priors: the prior weight, w, assigned to the informative component represents the prior degree of confidence in the extrapolation strategy; the weak prior distribution is centered on a mean of zero and with variance scaled to represent information equivalent to one subject:

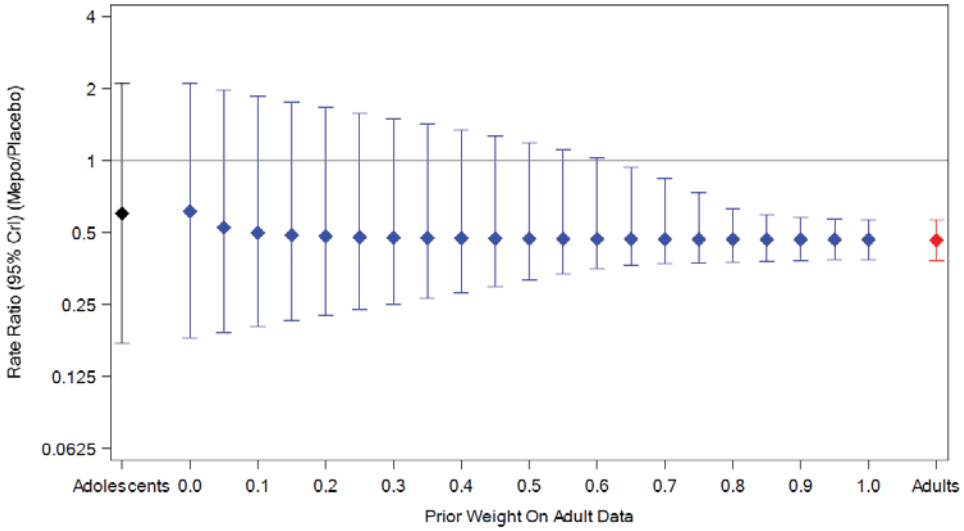
$$Robust\ mixture = w\ \times Normal\ (m_{adult}, v_{adult}) + (1 - w) \times Normal\ (mean_{weak}, v_{weak})$$

From MEA115588+200862: m_{adult} = -0.7691, v_{adult} =0.0986^2, m_{weak} =0, v_{weak} =3.2602^2.

Following standard conjugate Bayesian theory, the robust mixture prior was updated with the adolescent data to obtain a posterior mixture distribution for the adolescent treatment effect in log-rate ratio. A normal approximation was assumed for the sampling distribution of the observed log rate ratio in the adolescent subjects, y_{adol}, with variance v_{adol}, where y_{adol}= -0.5102 and v_{adol} =0.6377^2 were the point estimate and squared standard error of the log-rate ratio. This sampling distribution for the observed data were combined with the robust mixture prior using standard conjugate Bayesian theory to obtain the posterior means and variances of each component, and the posterior weight. Figure 7 presents the posterior medians and 95% credible intervals for the estimated exacerbation rate ratio of mepolizumab versus placebo in adolescents as a function of the prior weight given to the adult component in the robust mixture prior: the tipping point occurs at a prior weight between 0.6 and 0.65. For prior weights

of 0.65 or higher the upper limit of the posterior 95% credible interval for the rate ratio is below one, indicating a statistically significant treatment benefit of mepolizumab in adolescents. This suggests that if we are willing to assume prior odds of at least 2 to 1 in favor of the adolescent treatment effect being similar to the adult treatment effect, then we can conclude that there is evidence of a reduction in exacerbations in adolescents.

Figure 7. Posterior Median and 95% Credible Interval for the Rate Ratio of Exacerbation in Adolescents Robust Mixture Prior and Likelihood Derived From MEA115588+200862



Source: The Applicant
Crl = credible interval

FDA Reviewer Comment:

While the appropriateness of an extrapolation approach primarily depends on similarity of disease presentation, therapeutic approach, and adult to pediatric PK/PD predictability, the Applicant's Bayesian Dynamic Borrowing with a Mixture Prior approach offers a numerical model to predict efficacy with increasing prior weights indicating greater confidence in the extrapolation strategy. Based on these analyses, when we assume a weight (applicability coefficient) of about 0.65 on the informative adult prior, the posterior 95% credible interval for adolescent efficacy excludes 1.

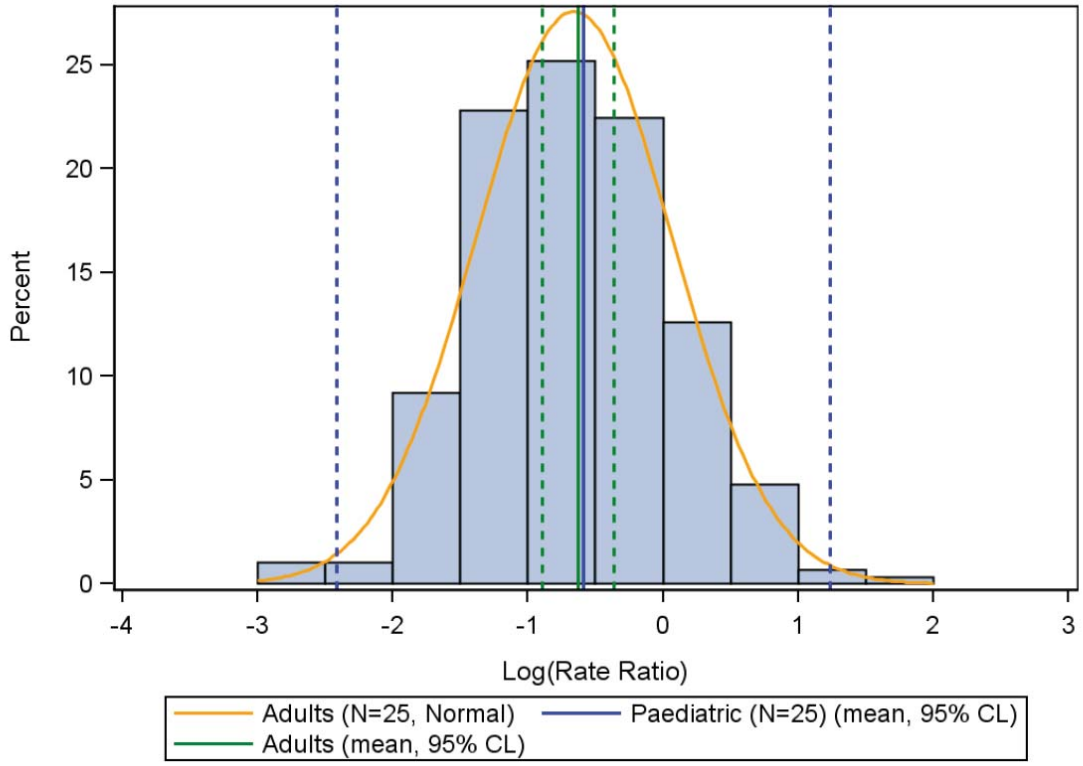
The Applicant's Bootstrap Resampling Approach

Severe asthma data from study MEA115588 were analyzed using a negative binomial generalized linear model with an interaction term for adolescents versus adults. Three thousand covariate-matched, adolescent-equivalent sized adult trials were sampled with replacement from the adult population and analyzed using the same model. The effects of various covariates were tested by sampling, and finally the degree of overlap between probability density functions for estimated treatment effects compared by age group.

After adjusting for covariates, the mean reduction in exacerbation rate compared with placebo is approximately 50% for adults and pediatric subjects, although the confidence limits for the latter are wide due to the small sample size (N=25) (Figure 8). A bootstrap distribution of 3000

matched adult samples (considered simulated "trials") of similar size to the pediatric subpopulation has the same mean response (-0.659 versus -0.589), and similar "trial"-to-"trial" variability (0.723 versus 0.932) as that of the pediatric population in study MEA115588. The Z-score for the pediatric efficacy estimate compared with adults is 0.097. There is a 62% overlap in response between the pediatric and adult populations. The probability that the ratio of pediatric to adult treatment responses falls within the equivalence bounds 50 to 200% is 44%. By comparison, the same probability for a similar-sized trial in adults, compared with the full adult population is 50%. The Applicant concludes that the reduction in clinically significant exacerbation rate in adults with severe eosinophilic asthma translates to the pediatric subpopulation with greater than 50% similarity, and that there is little reason to doubt that the magnitude of response observed in the pediatric subpopulation is not consistent with that in the much larger adult population, despite the small sample size.

Figure 8. Bootstrap Resampled Treatment Effects



Source: The Applicant
CL = confidence level

FDA Review Comment:

The Applicant's Bootstrap Resample Approach offers another measure of consistency (Z-score) in treatment effect between the adolescent population and the adult population. The Z-score for the pediatric efficacy estimate compared with adults is 0.097 and is considered by this review as a persuasive value to support consistency.

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