CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125526Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 14, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125526
Applicant Name:	GlaxoSmithKline
Date of Submission:	November 4, 2014
PDUFA Goal Date:	November 4, 2015
Proprietary Name:	Nucala
Established Name:	Mepolizumab
Dosage form:	Lyophilized powder for subcutaneous injection, 100 mcg of mepolizumab per single use vial
Strength:	Upon reconstitution with sterile water for injection, each single-use vial delivers 100 mg/mL mepolizumab in 1 mL
Proposed Indications:	Severe asthma
Action:	Recommend Approval

1. Introduction

GlaxoSmithKline (GSK) submitted this Biologics Licensing Application (BLA) for mepolizumab as an add-on treatment for a subgroup of patients, ages 12 years and older, with severe asthma, namely patients with severe asthma with eosinophilic phenotype. The proposed dose of mepolizumab is 100 mg administered subcutaneously (SC) every 4 weeks. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for use in patients with persistent asthma. These include inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are the most effective long-term therapy for all severity of persistent asthma, and are commonly used as the first drug when a maintenance treatment is necessary. When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is often added, preferably for a limited time period with the intent of discontinuing the LABA once asthma control is achieved and maintained. Since some patients with persistent asthma use both an ICS and a LABA, these two drugs have been combined together and marketed as inhaled combination products. There are multiple such combination products in the market in the United States for patients with asthma. These include Advair Diskus and Advair HFA Inhalation Aerosol (combination of fluticasone propionate and salmeterol xinafoate), Symbicort (combination of budesonide and

formoterol fumarate), Dulera (combination of mometasone furoate and formoterol fumarate), and Breo Ellipta (combination of fluticasone furoate and vilanterol).

The majority of patients with persistent asthma can be adequately controlled by following step-wise treatment recommendations noted above and described in US and global asthma treatment guidelines.[1, 2] However, some patients are not controlled despite step-wise treatments, e.g., high dose ICS plus additional controller medications, such as a LABA. These patients often have asthma exacerbations requiring hospital or emergency department (ED) care, and may require treatment with high dose oral corticosteroid (OCS). An American Thoracic Society (ATS) and European Respiratory Society (ERS) Task Force report from 2014 identified these patients as "severe asthma" defined as "asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy." [3] An ATS Workshop report from 2000 identified patients with similar characteristics as "refractory asthma." [4] Regular or periodic use of oral corticosteroids (OCS) may become necessary in patients with "severe asthma" or "refractory asthma" due to frequent exacerbations. Due to undesired effects of OCS, the aim of treatment is to utilize the lowest effect dose or avoid use of OCS when possible. The alternate therapeutic options for these patients are limited. For patients with allergic asthma, Xolair (anti-IgE antibody) is an option. GSK developed mepolizumab as an add-on treatment for a subgroup of these patients with severe asthma, namely patients with severe asthma with an eosinophilic phenotype.

One challenge in the review of this application is the use of the qualifier "eosinophilic" to describe a phenotype of severe asthma. Eosinophilic asthma is not described as a phenotype in US and global asthma treatment guidelines. The asthma literature has often used the term "eosinophilic" to describe an asthma phenotype, which has been variably defined with different cut-off numbers for eosinophil counts in blood, sputum, BAL fluid, and other markers such as exhaled nitric oxide. A consensus has not been developed in the scientific academic community to uniformly identify and define this phenotype in a clinically useful way. In this BLA submission, GSK cites publications, including those studies conducted with mepolizumab, to indicate that severe eosinophilic asthma can be characterized by blood eosinophil thresholds (count>150 cells/μL at a time point, or >300 cells/μL in the previous 12 months) despite high dose ICS treatment in a poorly-controlled exacerbating asthma phenotype. GSK states, citing some literature, that eosinophilic asthma can be associated with increased severity, atopy, late-onset disease, and steroid insensitivity.

---

[1] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. At: http://www nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines

[2] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/

[3] Task Force Report, ERS/ATS Guidelines on Severe Asthma. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. 2014. Eur Respir J 2014: 43:343-373.

[4] Proceedings of the ATS Workshop on Refractory Asthma. 2000. Am J Respir Crit Care Med 2000; 162:2341-2351.

Regulatory interaction between the Agency and GSK:

The Division and GSK had typical milestone meetings regarding mepolizumab for asthma as follows: Pre-IND in October 1996, Advice meeting in February 2006, Type B meeting in April 2009, End of Phase II meeting in May 2012, and Pre-BLA meeting in January 2014. Areas of discussion that were left as contingent to review of the data were acceptability of dose ranging in the event of safety findings of concern, bridging strategy from IV to SC route of administration, defining the asthma phenotype for labeling, and the relevance of the OCS reduction study for product labeling.

3. Chemistry, Manufacturing, and Controls

Mepolizumab is a humanized IgG1κ monoclonal antibody that binds to human interleukin-5 (IL-5), a cytokine responsible for regulation of blood and tissue eosinophils. Mepolizumab is produced by standard recombinant DNA technology in CHO cells. The commercial mepolizumab for injection will be supplied as a sterile preservative-free lyophilized powder in single-use glass vials for reconstitution with sterile water. Upon reconstitution, each single-use vials will deliver 100 mg of mepolizumab in 1 mL, along with 160 mg sucrose/mL, 7.14 mg sodium phosphate dibasic heptahydrate/mL, and 0.67 mg/mL polysorbate 80, with a pH of 7.0.

During mepolizumab clinical development, there were some changes in the final product, but qualitative composition and dosage form of the drug product were maintained across all strengths of the product used in clinical studies. During nonclinical studies and early clinical studies (including study 06, Table 1), the drug product was supplied as a 50 mg/vial presentation. In 2008, the drug product was replaced by a 250 mg/vial presentation, incorporating minor changes in quantitative formulation and manufacturing process (used in studies 97, 88, and 75, Table 1). The proposed commercial 100 mg/vial presentation was developed later and was introduced in open-label extension studies after conduct of the controlled portion of the pivotal efficacy and safety studies. The same drug substance composition was used to manufacture the 250 mg/vial and 100 mg/vial drug product, hence the drug product composition was the same for these two strengths. The comparability of the two strengths of the product was further supported by release and analytical characterization testing.

Mepolizumab drug substance will be manufactured at the GSK facility in Conshohocken, PA, USA, and the drug product will be manufactured at the GSK facility in Parma, Italy. At this time, the FDA's Office of Compliance has deemed that the drug product manufacturing facility in Parma, Italy is not acceptable. The reason for the not acceptable decision was based on finding during May 2015 inspection where the inspectors noted some GMP issues and improper documentation (altering a cleaning log) at the (b) (4), which is a dedicated facility for some (b) (4). GSK provided a detailed response in June 2015 where they have outlined a series of corrective steps to address the findings of the FDA inspection, including investigation of the improper documentation described in the FDA inspection report. It is noteworthy that mepolizumab drug product is manufactured in a different

building at the GSK's Parma site, and the mepolizumab [redacted] (b) (4) [redacted]. It does not appear that mepolizumab manufacturing is directly related to the FDA inspection findings at the [redacted] (b) (4). From the clinical perspective, I would recommend exercise of regulatory discretion for approval of mepolizumab given that there are no other outstanding issues for this BLA, and mepolizumab is first in a class product for the treatment of a limited subset of severe asthma patients with significant morbidity and with unmet medical need.

4. Nonclinical Pharmacology and Toxicology

GSK submitted results from a full preclinical program to the Agency. 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 IL-5-induced differentiation of eosinophils, obtained from the bone marrow of human volunteers or Cynomolgus monkeys, with EC_{50} values of 13.3 pM. Further, the amino acid sequence of monkey IL-5 differs from human IL-5 by two conservative substitutions in a region not related to the presumed mepolizumab binding epitope on human IL-5. In a chronic 6-month toxicology study with Cynomolgus monkeys that received mepolizumab by the IV route at doses up to 100 mg/kg q4 weeks or the SC route at a dose of 10 mg/kg q4 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 histopathological examinations of reproductive organs. In reproductive toxicity studies, there were no adverse findings in a pre- and post-natal development study with monkeys that were treated with mepolizumab at IV doses up to 100 mg/kg q4 weeks or a fertility and embryofetal development study with mice that received a surrogate anti-IL-5 antibody. Given the absence of pre-neoplastic or neoplastic lesions in the 6-month toxicology study with monkeys and that rodents were not pharmacologically relevant species, a carcinogenicity study with mepolizumab was not required; concurrence was obtained from the Executive Carcinogenicity Assessment Committee.

5. Clinical Pharmacology and Biopharmaceutics

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess pharmacokinetics and pharmacodynamics.

The pharmacokinetics of mepolizumab is consistent with other IgG1 monoclonal antibodies targeting soluble ligands. The pharmacokinetics is linear, dose-proportional, and time-dependent after both IV and SC administration. The absolute bioavailability of mepolizumab after SC dosing is approximately 80%, and the terminal-phase elimination half-life is about 20 days. Mepolizumab is degraded by widely distributed proteolytic enzymes, which are not restricted to hepatic tissues. Hepatic function does not therefore

influence the elimination of mepolizumab. Mepolizumab has a molecular weight of 149 kDaltons, precluding elimination by glomerular filtration. For these reasons no specific hepatic or renal impairment studies were necessary. Drug-drug interaction potential for mepolizumab is low considering its proteolytic elimination pathway and also because IL-5 does not effect hepatocyte function.

Mepolizumab exerts its activity by binding to human IL-5, preventing IL-5 from binding to the alpha chain of IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting signaling. Neutralization of IL-5 leads to reduction in the production rate and survival of eosinophils. Mepolizumab treatment produces a dose-dependent reduction in blood eosinophil count. Dose-response is unchanged by administration route, after adjusting for bioavailability.

6. Clinical Microbiology

GSK proposed acceptable testing regimen involving the bulk drug product and the product packaged in the commercial presentation.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1, with studies listed chronologically by the month and year of study conduct. Selected characteristics of the patients enrolled in these studies are shown in Table 2. Pediatric patients had disease severity based on exacerbation history and eosinophil counts similar to the overall patients, but pediatric patients had higher FEV_1 values and less severe obstructive pattern based on FEV_1/FVC ratio, compared to the overall patients (Table 2).

The target patients enrolled in the mepolizumab studies evolved over the course of clinical development (Table 1 and Table 2). Study 06 (12 week study in 362 patients), conducted in 1999 in moderate asthma patients with airflow as the targeted benefit, failed to show efficacy.[5] There were no large asthma clinical studies conducted with mepolizumab for about a decade after this failed study. Two relatively small investigator-supported proof-of-concept studies published in 2009 suggested that mepolizumab might provide benefit in asthma exacerbations in a sub-set of patients with severe asthma with an eosinophil phenotype. In one study (52 week study in 61 patients), exacerbation benefit with mepolizumab was demonstrated in patients with severe refractory asthma with sputum eosinophil $\geq$ 3% who had two or more exacerbations requiring OCS in the prior year that occurred while patients were receiving high-dose ICS.[6] In another study (16 week study in 20 patients), OCS dose reduction with

[5] Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176: 1062-1071.
[6] Halder P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Eng J Med 2009; 360:973-984.

mepolizumab was demonstrated in OCS-dependent asthma with sputum eosinophilia.[7] Informed by these two studies, GSK conducted further studies in patients with severe asthma with an eosinophilic phenotype with asthma exacerbation as the primary target for benefit (Table 1, Studies 97, 88, and 75). While the two investigator-supported studies informed the design of subsequent GSK studies, these two studies are not part of GSK's pivotal BLA studies and are not discussed further in this review.

Study 97 was conducted in a severe asthma patient population enriched for airway eosinophilic inflammation that was defined using multiple markers. Subsequently, Study 88 was conducted also in severe asthma patients enriched for airway eosinophilic inflammation, but used only blood eosinophil count for enrichment. Studies 97 and 88 were designed to assess the benefit of mepolizumab on asthma exacerbation. Study 75, conducted at around the same time as Study 88, employed similar patient enrollment criteria. Study 75 was designed to assess oral corticosteroid reduction in response to mepolizumab treatment. All patients in these studies were receiving standard-of-care treatment optimized to asthma severity; either mepolizumab or placebo was added on to the standard-of-care.

All eosinophil counts were measured by (b) (4) using the Beckman Coulter LH750 analyzer. GSK states that eosinophil count using Beckman Coulter LH750 has comparable performance across several other available counting platforms.

Table 1. Relevant controlled clinical studies with mepolizumab in moderate and severe asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
Moderate Asthma – Bronchodilator (lung function) study					
06 [02/99 to 09/99]	- 18 to 55 yr - FEV_1 50-80%, on moderate-dose ICS, [no blood or sputum eosinophil threshold, no history of exacerbation] - Parallel arm, DB - 12 weeks	Mepo 250 mg IV Mepo 750 mg IV Placebo	120 116 126	1^o: Domiciliary AM PEFR at wk 12 2^o: ΔFEV_1 trough baseline to wk 12	US, UK, France, Germany, Netherlands (58% US)
Severe "Eosinophilic" Asthma – Dose Ranging PK-PD study					
92 [02/11 to 03/12]	- 18 to 65 yr - FEV_1 50-80%, and blood eosinophil $\geq$ 300µL in past year or $\geq$200µL at screening - Parallel arm, open label - 12 weeks	Mepo 12.5 mg SC Mepo 125 mg SC Mepo 250 mg SC Mepo 75 mg IV	21 15 23 11	Blood eosinophil count	US, Germany, Estonia, France (7% US)
Severe "Eosinophilic" Asthma – Dose Ranging Exacerbation study					
97 [11/09 to	- 12 to 65 yr - FEV_1 <80%, on high-dose ICS + another controller,	Mepo 75 mg IV Mepo 250 mg IV Mepo 750 mg IV	153 152 156	1^o: Rate of asthma exacerbation ** 2^o: ΔFEV_1 trough	US, Canada, Australia, EU countries, Russia,

[7] Nair P, Pizzichini M, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Eng J Med 2009; 360: 985-993.

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
12/11]	blood eosinophil ≥ 300μL or sputum eosinophil ≥ 3% or eNO ≥50 ppb or loss of asthma control with ≤ 25% steroid reduction - Parallel arm, DB - 52 weeks	Placebo	155	baseline to wk 52	Ukraine, Argentina, Chile (13% US)
Severe "Eosinophilic" Asthma – Exacerbation study					
88 [10/12 to 01/14]	- ≥12 yr - FEV_1 <80%, on high-dose ICS + another controller , and ≥2 exacerbation in past year, and blood eosinophil ≥ 300μL in past year or ≥150μL at baseline - Parallel arm, DB - 32 weeks	Mepo 100 mg SC Mepo 75 mg IV Placebo	194 191 191	1^o: Rate of asthma exacerbation ** 2^o: ΔFEV_1 trough baseline to wk 32	US, Canada, Mexico, Australia, EU countries, Russia, Ukraine, Argentina, Chile, Japan, S Korea (12% US)
Severe "Eosinophilic" Asthma – Oral corticosteroid (OCS) reduction study					
75 [10/12 to 12/13]	- ≥12 yr - FEV_1 <80%, on OCS or high-dose ICS, and blood eosinophil ≥ 300μL in past year or ≥ 150μL at baseline - Parallel arm, DB, DD - 24 weeks	Mepo 100 mg SC Placebo	69 66	1^o: Percent reduction in OCS during wk 20-24 from baseline while maintaining asthma control 2^o: ΔFEV_1 trough baseline to wk 32	US, Canada, Mexico, EU countries (5% US)

* Study ID shown (top to bottom) as GSK's study number, and [month/year study started-completed]
† DB = double blind, DD = double dummy
‡ Mepo = Mepolizumab
§ Intent to treat (ITT)
¶ FEV_1 for study 06 wase analyzed using Analysis of Covariance (ANCOVA) model. Exacerbation rates in studies 97 and 88 were analyzed using a generalized linear model with negative binomial distribution. Reduction of OCS dose in study 75 was analyzed using a proportional odds model.
// EU countries included UK, France, Germany, Italy, Spain, Netherlands, Belgium, Poland, Romania, Czech Republic
** Asthma exacerbation defined as worsening of asthma that in the investigator opinion required oral/systemic corticosteroid (for patients on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required), and/or hospitalization and/or ED visit. Investigators were instructed to take the following into account when making the exacerbation assessment: decrease in morning peak flow, increase in the use of rescue medication, increase in the frequency of nocturnal wakening due to asthma symptoms requiring rescue medication use.

Table 2. Selected characteristics for patients in the relevant controlled clinical studies

	Study 06	**Study 97**	**Study 88**	**Study 75**
All Patients : Adults + Pediatrics				
Demographics				
Age, mean in years	36	49	50	50
Asthma duration, mean in years	NA	19	20	19
Percentage patients never smoked	70	78	72	61
Pulmonary function test				
Prebronchodialtor FEV_1, mean % predicted	68	58	61	59
Post-broncodilator FEV_1/FVC ratio, mean	NA	0.67	0.66	0.66
Reversibility, mean % ΔFEV_1 post SABA	25	28	27	26
Eosinophil				
Baseline mean blood eosinophil count in μL, Arth mean	366	384	443	381

	Study 06	Study 97	Study 88	Study 75
Exacerbation history				
Mean number of exacerbations in previous year	NA	3.6	3.6	3.1
Percentage patients with ≥2 exacerbation in previous year	NA	>99	>99	67
Percentage patients with ≥3 exacerbation in previous year	NA	54	57	50
Background treatments for asthma				
Medium dose inhaled corticosteroids (ICS)	Yes	No	No	No
High dose inhaled corticosteroids (ICS)	No	Yes	Yes	Yes
Non-ICS controller drug	No	Yes	Yes	Yes
Oral corticosteroids (OCS)	No	Yes & No	Yes & No	Yes
Patients : Pediatrics (12 to 17 yrs) only [Study 88 has 25 patients; other 3 studies together had 2 patients and all in study 75]				
Demographics				
Age, mean in years	-	-	15	-
Asthma duration, mean in years	-	-	10	-
Percentage patients never smoked	-	-	96	-
Pulmonary function test				
Prebronchodialtor FEV_1, mean % predicted	-	-	82	-
Post-broncodilator FEV_1/FVC ratio, mean	-	-	0.84	-
Reversibility, mean % ΔFEV_1 post SABA	-	-	26	-
Eosinophil				
Baseline mean blood eosinophil count in μL, Arth mean	-		243	
Exacerbation history	-			
Mean number of exacerbations in previous year	-	-	3.7	
Percentage patients with ≥2 exacerbation in previous year	-	-	>100	
Percentage patients with ≥3 exacerbation in previous year	-	-	48	
Background treatments for asthma				
Medium dose inhaled corticosteroids (ICS)	-	-	No	
High dose inhaled corticosteroids (ICS)	-	-	Yes	
Non-ICS controller drug	-	-	Yes	
Oral corticosteroids (OCS)	-	-	Yes & No	
NA = Information not collected				

b. Design and conduct of the studies

Moderate asthma, lung function Study 06:

Study 06 was conducted in patients with moderate asthma who were receiving medium dose of ICS, without a history of frequent exacerbation; patients were not required to have elevated blood or sputum eosinophil levels. Some relevant study design and study conduct characteristics are shown in Table 1.

Severe asthma, exacerbation Studies 97 and 88:

Studies 97 and 88 were conducted in patients with severe asthma with a clearly documented record of high-dose ICS use in the 12 months prior to screening, and with an eosinophil phenotype. The criteria used to identify the eosinophil phenotype differed between the two studies. Study 97 used one or more criteria to identify eosinophil phenotype (described in Table 1). Exploratory analyses of eosinophil phenotype enrollment criteria as well as other patient and disease characteristics suggested that peripheral blood eosinophil threshold (≥300 cells/μL in past year or ≥150 cells/μL at baseline) and number of asthma exacerbations in the prior year predicted exacerbation benefit in response to mepolizumab treatment. The identified peripheral blood eosinophil

threshold (≥300 cells/μL in past year or ≥150 cells/μL at baseline) was then required for enrollment of patients in Study 88, and Study 75 (OCS reduction study) (Table 1). Some relevant study design and study conduct characteristics are shown in Table 1. Asthma exacerbation was defined using accepted criteria (Table 1 footnote).

Severe asthma, OCS reduction Study 75:

Study 75 was conducted in patients with severe asthma with the same peripheral blood eosinophil criteria used in Study 88, and with a documented requirement for regular treatment with systemic corticosteroids (5 to 35 mg prednisone or equivalent) in addition to high-dose ICS use in the 6 months prior to screening. The intended study population was patients who were likely to experience a loss of asthma control if OCS treatment was reduced or stopped. Some relevant study design and conduct characteristics are shown in Table 1. In the early part of the study (Weeks 3 to 10), the OCS dose was titrated to the lowest dose possible while maintaining asthma control. During the latter part of the study, the OCS dose was reduced by a specified titration schedule while assessing asthma control. Asthma control was assessed by: morning peak flow, asthma-related nighttime awakenings, rescue medication use, and ACQ score.

c. Efficacy findings and conclusions

The submitted data from the clinical program are adequate to support efficacy of mepolizumab at a dose of 100 mg SC every 4 weeks for patients with severe asthma in a specified target population. GSK states that based on mepolizumab's mechanism of action and the demonstrated reduction of blood eosinophils, it is reasonable to consider that mepolizumab will be a therapeutic intervention in asthma patients with eosinophilic inflammation. Based on efficacy data acquired throughout their development program, GSK indicated the following target population for mepolizumab: (a) patients who continue to experience exacerbations despite standard of care treatment optimized to asthma severity (i.e., high-dose ICS plus an additional controller with or without continuous OCS use); and, (b) an eosinophilic phenotype with defined blood eosinophil levels (≥300 cells/μL in past year or ≥150 cells/μL at baseline). GSK has also concluded that patients who do not meet the target population criteria described above are unlikely to benefit from treatment with mepolizumab.

GSK's proposed target population for mepolizumab based on exacerbation history is similar to "refractory asthma" as defined at the ATS report from 2000 and "severe asthma" defined at the ATS-ERS report from 2014 (discussed in Section 2 above). GSK further proposes to add eosinophil threshold to the exacerbation history to further characterize the patients most likely to benefit from mepolizumab treatment. GSK's general conclusions regarding the target population for mepolizumab based on exacerbation history and eosinophil threshold are conceptually reasonable; however, the proposed labeling language will need to be modified. The exacerbation data that support these conclusions are reviewed later in this section.

Dose and dosing schedule:

The proposed dose of mepolizumab 100 mg SC every 4 weeks is supported by the submitted data. This dose corresponds to the lowest IV dose (75 mg) tested that provided meaningful reduction of exacerbations (discussed further below in this section). This dose also provides 90% of the maximum achievable reduction in blood eosinophil count. The 4-week dosing interval is supported by the 20-day half-life of mepolizumab, providing approximately two-fold drug accumulation at steady-state along with maintaining consistent effect.

SC and IV dosing:

The relevant clinical studies used both SC and IV dosing, necessitating linking the two routes of administration. Study 92 was specifically conducted to provide this link (Table 1). In Study 92, a dose-dependent decrease in blood eosinophil counts was seen with similar reduction for 125 mg SC and 75 mg IV (Figure 1). This data, along with model-estimated inhibition of blood eosinophil count supported evaluating both 100 mg SC and 75 mg IV in Study 88. In Study 88, similar treatment effects on exacerbation (discussed further below) and similar decreases in blood eosinophil level (Figure 1) were seen for both these doses.

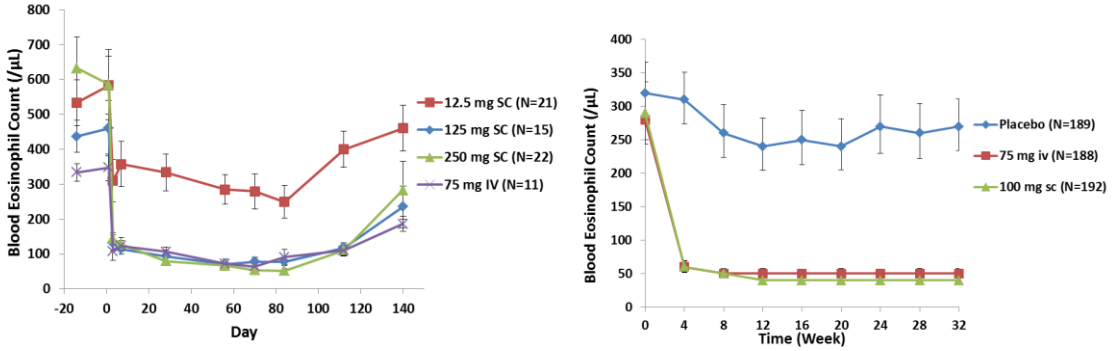

Figure 1. Mean (SE) blood eosinophil counts over time, Study 92 (left panel), Study 88 (right panel)

Bronchodilator (lung function) effects:

Spirometry was conducted in Studies 06, 97, 88, and 75 as an efficacy measure (Table 1). Trough FEV_1 was the measure of interest, which assesses sustained effect over time on lung function. Trough FEV_1 results for all four studies are shown in Table 3, and the time profile curves over study duration are shown from Study 97 (Figure 2) and Study 88 (Figure 3). Study 06 (in a sample of moderate asthma patients not enriched for eosinophilic phenotype), which studied bronchodilation as the primary efficacy measure, did not show benefit with mepolizumab (Table 3). Studies 97 and 88 (exacerbation studies in a sample of severe asthma patients enriched for potential markers of eosinophilic phenotype) and 75 (OCS reduction study in a sample of severe asthma patients enriched for potential markers of eosinophilic phenotype) showed numerical

improvement in trough FEV_1 with mepolizumab over placebo (Table 3, Figure 2, Figure 3), but the differences were not consistently statistically significant. Lack of robust FEV_1 benefit is not surprising given the mechanism of action of mepolizumab.

Table 3. Change from pre-dose trough FEV_1 in various studies, shown as mean (95% CI)

		At Week 12	At Week 24	At Week 52
Study 06	Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo	89 (11, 167) 84 (6, 162) 133 (58, 208)	- -	- -
Study 97	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo			121 (47, 195) 140 (66, 213) 115 (43, 188) 60 (-14, 133)
Study 88	Mepolizumab 100 mg SC Mepolizumab 75 mg IV Placebo		184 (123, 244) 186 (125, 248) 86 (25, 147)	
Study 75	Mepolizumab 100 mg SC Placebo		110 (01, 221) -4 (-118, 110)	

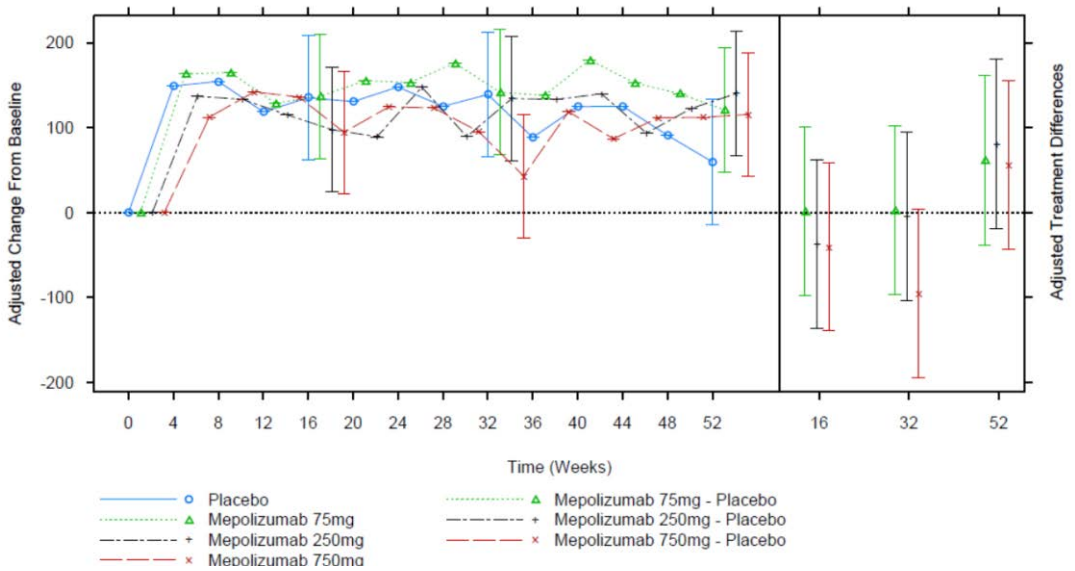

Figure 2. Change from baseline in trough FEV_1 in mL, Study 97

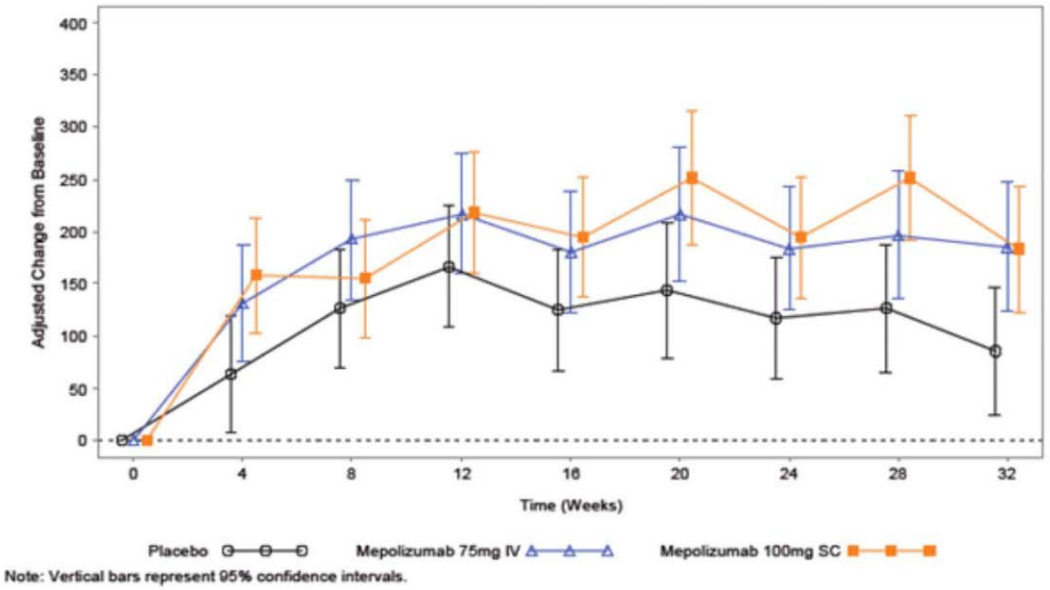

Figure 3. Change from baseline in trough FEV_1, Study 88

Exacerbation effects:

Statistically significant reduction in asthma exacerbation rate was seen in both exacerbation studies for all mepolizumab doses with no significant benefit of doses higher than the 75 mg IV dose, and no significant difference between the mepolizumab 75 mg IV dose and 100 mg SC dose (Table 4). Kaplan-Meier analysis of time-to-first exacerbation also showed beneficial response for mepolizumab-treated groups compared to placebo (Study 88 results shown in Figure 4).

While the overall rates of exacerbations requiring ED visits or hospitalizations were low across treatment groups (approximately 1 in every 5 to 10 exacerbations required ED visits or hospitalizations), these more severe exacerbations also occurred less frequently in the mepolizumab treatment groups compared to placebo group, with rate-ratio generally in the same range as that for total exacerbations (Table 5).

Table 4. Asthma exacerbation rate (all exacerbations) from Studies 97 and 88

Study	Treatment	n	Annual rate of asthma exacerbation	Difference to placebo	Rate Ratio (95% CI), p-value
97	Mepolizumab 75 mg IV	153	1.24	-1.16	0.52 (0.39, 0.69), <0.001
	Mepolizumab 250 mg IV	152	1.46	-0.94	0.61 (0.46, 0.81), <0.001
	Mepolizumab 750 mg IV	156	1.15	-1.24	0.48 (0.36, 0.64), <0.001
	Placebo	155	2.40		
88	Mepolizumab 100 mg SC	191	0.83	-0.92	0.47 (0.35, 0.64), <0.001
	Mepolizumab 75 mg IV	194	0.93	-0.81	0.53 (0.40, 0.72), <0.001
	Placebo	191	1.74		

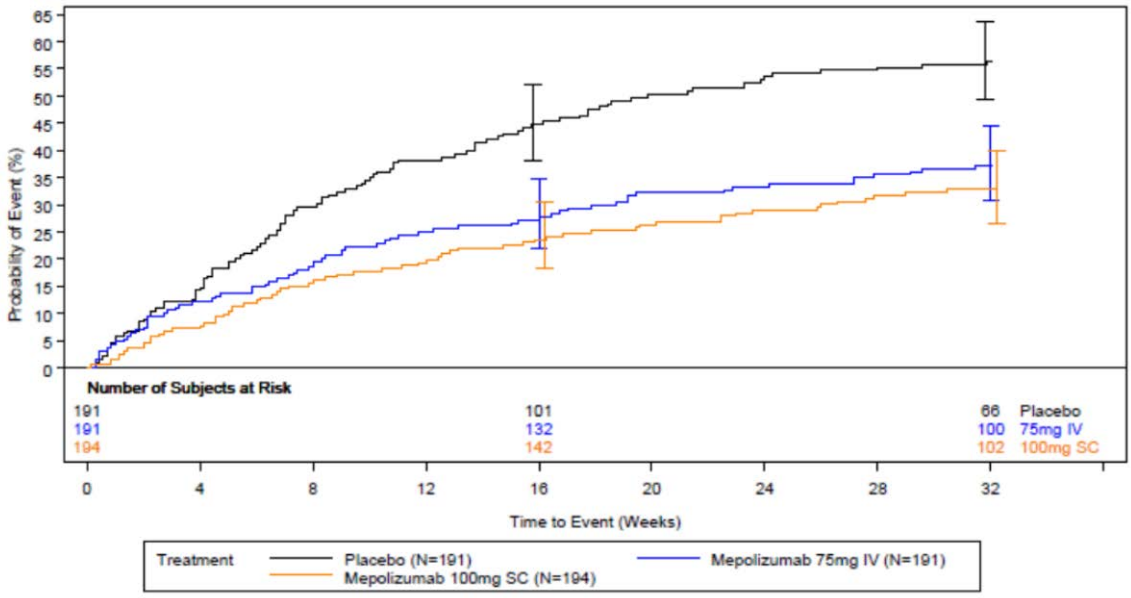

Figure 4. Kaplan-Meier cumulative incidence curve for time to first asthma exacerbation, study 88

Table 5. Asthma exacerbation rate for exacerbations requiring ED visits or hospitalization from Studies 97 and 88

Study	Treatment	n	Annual rate of asthma exacerbation requiring ED visit or hospitalization	Rate Ratio (95% CI) of asthma exacerbation requiring ED visit or hospitalization
97	Mepolizumab 75 mg IV	153	0.17	0.40 (0.19, 0.81)
	Mepolizumab 250 mg IV	152	0.25	0.58 (0.30, 1.12)
	Mepolizumab 750 mg IV	156	0.22	0.52 (0.27, 1.02)
	Placebo	155	0.43	
88	Mepolizumab 100 mg SC	191	0.14	0.68 (0.33, 1.41)
	Mepolizumab 75 mg IV	194	0.08	0.39 (0.18, 0.83)
	Placebo	191	0.20	

The benefit of mepolizumab on asthma exacerbations was demonstrated in Studies 97 and 88, in which patients were selected based on a previous history of exacerbation and presence of an eosinophilic phenotype. Study 97 used one or more criteria to identify eosinophil phenotype (described in Table 1). An exploratory analysis of the various criteria indicated that number of asthma exacerbations in the prior year, and peripheral blood eosinophil threshold (≥300 cells/μL in past year or ≥150 cells/μL at baseline) predicted exacerbation benefit response to mepolizumab. In Study 88, the peripheral blood eosinophil threshold (≥300 cells/μL in past year or ≥150 cells/μL at baseline) was prospectively used to screen patients for enrollment, and this study also showed benefit for exacerbation in this patient population. In Study 75 (OCS reduction study described later in this section), the same blood eosinophil threshold was prospectively used to screen patients for enrollment, and showed benefit. Taken together, the exacerbation and OCS reduction data support GSK's conclusions regarding the target population for

mepolizumab based on exacerbation history and eosinophil phenotype. Potentially, a dedicated study to show lack of exacerbation benefit in patients selected with history of exacerbation, but with blood eosinophil counts below the threshold, might help to solidify the role of the eosinophil threshold with respect to who is most likely to benefit and not benefit from mepolizumab treatment. Such a study is arguably not necessary because the specific mechanism of action of mepolizumab selectively targets eosinophils. As discussed below, exploratory analyses using existing data from the exacerbation Studies 97 and 88 already show decrement of exacerbation benefit with decreasing blood eosinophil count.

The effect of blood eosinophil count at screening and baseline was used for exploratory analyses by the FDA statistical team to further understand the relationship of exacerbation benefit and blood eosinophil count. The exacerbation benefit of mepolizumab appears to be directly related to blood eosinophil counts with increase in exacerbation benefit with increase in blood eosinophil count (Figure 5). This conclusion is consistent with that of GSK regarding the relationship between dichotomized peripheral blood eosinophil threshold (≥150 cells/μL at baseline or ≥ 300 cells/μL in the past year) and exacerbation effect; however, these analyses also suggest that a strict threshold above which treatment benefit will be received and below which it will not, may be oversimplified. Rather, the FDA analyses suggest that the treatment effect varies in accordance with the continuous measurement of blood eosinophil with a gradual increase in treatment effect with higher blood eosinophil count. Statistical testing for the continuous measure of screening blood eosinophil count and treatment effect interaction showed significance for screening blood eosinophil count for Study 97 (nominal p-value 0.04) and Study 88 (nominal p-value 0.03). One limitation of these analyses is that there were few patients with low eosinophil count as defined by the enrollment criteria in these two studies (Table 1), so that the observed effect of mepolizumab on exacerbation in this population is unknown. Judging from the observed decrement of exacerbation benefit with decreasing blood eosinophil count through, one may conjecture that benefit to patients with eosinophil levels lower than what was required for entry to this study is unlikely. The visual display of the data in Figure 5 shows that the relationship between screening blood eosinophil count and asthma exacerbation rate was less prominent in Study 97 than Study 88. This is possibly because Study 97 allowed patients to be enrolled by various eosinophil related enrichment criteria (blood eosinophil ≥ 300 cells/μL or sputum eosinophil ≥ 3% or eNO ≥50 ppb or loss of asthma control with ≤ 25% steroid reduction), whereas Study 88 allowed patients to be enrolled only by blood eosinophil criteria (blood eosinophil ≥150 cells/μL at baseline or ≥ 300 cells/μL in the past year).

Results from Study 88 suggest that of the two blood eosinophil counts, baseline count obtained proximal to start of mepolizumab treatment is more predictive than the count in the past year. In Study 88, patients in the category of screening blood eosinophil count 150 cells/μL or less had virtually no exacerbation benefit, whereas other groups with counts higher than 150 cells/μL had exacerbation benefit (Figure 5 right panel). Patients in Study 88 with screening blood eosinophil count 150 cells/μL or less could only be entered in the study if their blood eosinophil count was ≥ 300 cells/μL in the past year.

The data suggests that screening eosinophil count of ≥150 cells/μL immediately prior to initiation of mepolizumab is a predictive marker of exacerbation benefit with mepolizumab. These data are suggestive, but not sufficiently definitive to include labeling language for threshold eosinophil count for the indication and usage section or as a limitation of use for eosinophil count below a threshold. The indication and usage section can use the general term "blood eosinophilia" or "eosinophilic phenotype" with or without describing other clinical characteristics of patients, to define the target patient population for mepolizumab. The clinical trials section of the labeling can describe the characteristics of the patients studied in the program, including eosinophil counts used for enrollment. The term "blood eosinophilia" is generally understood and used in the context of asthma and is mentioned in generally accepted asthma treatment guidelines, such as the current updated versions of GINA Guideline and the NAEPP ERP 3.

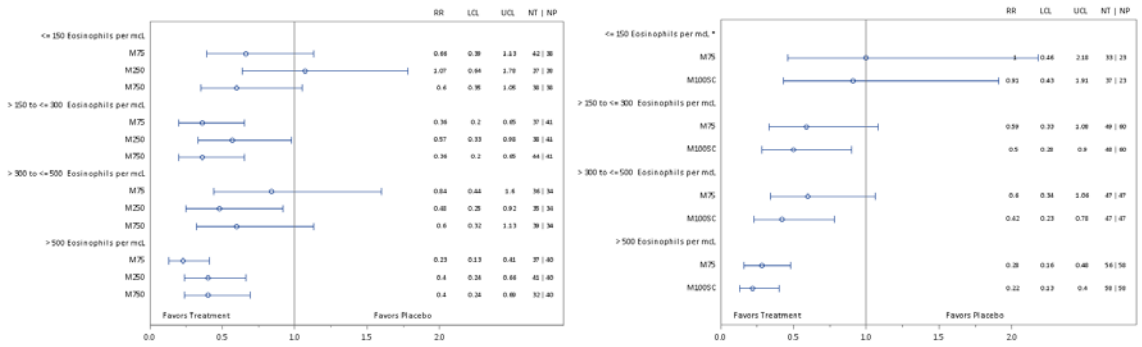

Figure 5. Ratio of the risk of exacerbation in the treatment and placebo groups by baseline eosinophil count, Study 97 (left panel), Study 88 (right panel)

Oral corticosteroid reduction:

Oral corticosteroid (OCS) reduction is an indirect way of assessing exacerbation, in addition to being a relevant stand-alone measure of efficacy. In Study 75, mepolizumab treatment resulted in significant reduction in OCS use (Table 6).

Table 6. Oral corticosteroid reduction shown as frequency (percent), Study 75

	Placebo (n=66)	Mepolizumab (n=69)
Categorized OCS % reduction from baseline to weeks 20-24		
90% to 100%	7 (11%)	16 (23%)
75% to <90%	5 (8%)	12 (17%)
50% to <75%	10 (15%)	9 (13%)
>0% to <50%	7 (11%)	7 (10%)
No decrease in OCS, lack of control, withdrawal from treatment	37 (56%)	25 (36%)
Odds ratio (95% CI), p-value		2.39 (1.25, 4.56), 0.008

St Georges Respiratory Questionnaire (SGRQ):

SGRQ is designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease.[8] SGRQ is designed to measure health impairment in patients with asthma and COPD.[9]

SGRQ was assessed in Studies 88 and 75, but not in Study 97. In both studies, mepolizumab treatment groups achieved improvements in mean SGRQ scores measured as change from baseline to measurement endpoint of week 32 or 24, and the difference between mepolizumab treatment arms and placebo were statistically significantly different (Table 7). Of note, in Study 88, the placebo group also experienced improvement from baseline, which may reflect the beneficial effect of close monitoring of patients with monthly follow-up for injections. In Study 88, the proportions of subjects with benefits in SGRQ larger than the Minimal Clinical Important Difference or MCID of 4 were statistically significantly greater in mepolizumab treatment arms than placebo. Results in Study 75 were numerically consistent with Study 88, but did not reach statistical significance (Table 8).

Table 7. Mean SGRQ scores from Studies 88 (baseline to week 32) and 75 (baseline to week 24)

Study	Treatment	n	Baseline	Week 32 or 24	Δ baseline to week 32 or 24	Difference from placebo (95% CI)
88	Mepolizumab 100 mg SC	194	47.7	31.4	-16	-7.0 (-10.2, -3.8)
	Mepolizumab 75 mg IV	191	45.0	30.2	-15	-6.4 (-9.7, -3.2)
	Placebo	191	47.2	37.9	-9	
75	Mepolizumab 100 mg SC	69	50.1	40.6	-9	-5.8 (-10.6, -1.0)
	Placebo	66	44.5	42.1	-2	

Table 8. SGRQ responder analysis (threshold of 4 points or more) from Studies 88 (baseline to week 32) and 75 (baseline to week 24)

Study	Treatment	n	% with improvement of ≥ 4	Odds ratio to placebo (95% CI)
88	Mepolizumab 100 mg SC	194	137 (71%)	2.07 (1.33, 3.22)
	Mepolizumab 75 mg IV	191	130 (68%)	1.95 (1.26, 3.02)
	Placebo	191	105 (55%)	-
75	Mepolizumab 100 mg SC	69	40 (58%)	1.92 (0.95, 3.82)
	Placebo	66	27 (41%)	

Asthma Control Questionnaire (ACQ):

ACQ and AQLQ are commonly used measurements tools for asthma with defined measurement properties,[10] and listed in common asthma treatment guidelines,[11, 12] and elsewhere.[13]

[8] St. George's Respiratory Questionnaire (SGRQ), at ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php
[9] St George's Respiratory Questionnaire Manual, at: http://www.healthstatus.sgul.ac.uk/SGRQ_download/SGRQ%20Manual%20June%202009.pdf

ACQ is a questionnaire to measure the adequacy of asthma control and change in asthma control that occur either spontaneously or as a result of treatment. There are 7 items in ACQ: 5 items of self-administered questions (breathlessness, nocturnal waking due to asthma, asthma symptoms upon waking, activity limitation, and wheeze), 1 item of self-administered rescue bronchodilator use, and 1 item of FEV_1 completed by clinic staff. The 7 item complete ACQ is commonly used. There are shortened versions of ACQ, including a 5 item version that do not use rescue bronchodilator use and FEV_1. The shortened versions have good measurement qualities but not quite as good as those of the complete ACQ versions. A change in score of 0.5 on the 7-point scale is the smallest difference that is considered clinically important, which is the minimal important difference for ACQ. An ACQ score ≥1.0 indicates that asthma is not well controlled.

ACQ was assessed in Studies 97, 88 and 75 (ACQ-6 in Study 97, and ACQ-5 in Studies 88 and 75). ACQ-6 did not use FEV_1 and ACQ-5 did not use rescue bronchodilator use and FEV_1. In some studies, mepolizumab treatment groups achieved improvements in ACQ-5 scores measured as mean change from baseline to measurement endpoints of weeks 52, 32, or 24, and the difference between mepolizumab treatment arms and placebo were statistically significantly different for some measures (Table 8). The proportion of patients with benefits ACQ-5 larger than the Minimal Clinical Important Difference or MCID of 0.5 were statistically significantly higher for mepolizumab than placebo groups in one case (Table 10).

Table 9. Mean ACQ-5 score from Studies 97 (baseline to week 52), 88 (baseline to week 32) and 75 (baseline to week 24)

Study	Treatment	N*	Baseline	Week 52, 32, 24	Δ baseline to week 52, 32, 24	Difference from placebo (95% CI)
ACQ-5, includes 5 items – excludes bronchodilator use and FEV_1 from ACQ-7 or complete ACQ						
97	Mepolizumab 75 mg IV	153	2.27	1.53	-0.74	-0.15 (-0.39, 0.10)
	Mepolizumab 250 mg IV	152	2.40	1.49	-0.91	-0.28 (-0.53, -0.04)
	Mepolizumab 750 IV	156	2.28	1.45	-0.83	-0.22 (-0.46, 0.02)
	Placebo	155	2.58	1.80	-0.78	
88	Mepolizumab 100 mg SC	194	2.18	1.25	-0.93	-0.44 (-0.63, -0.25)
	Mepolizumab 75 mg IV	191	2.12	1.21	-0.91	-0.42 (-0.61, -0.03)
	Placebo	191	2.28	1.72	-0.55	
75	Mepolizumab 100 mg SC	69	2.17	1.48	-0.69	-0.52 (-0.87, -0.17)
	Placebo	66	1.99	1.97	-0.02	
*Represents the number of subjects with both baseline and visit information. There were approximately 15-20% patients across various treatment arms who had baseline information, but no visit information.						

[10] Measurement of Health-Related Quality of Life & Asthma Control. At: https://qoltech.co.uk/index htm
[11] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. At: http://www nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
[12] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/
[13] ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php

Table 10. ACQ-5 responder analysis (threshold of 0.5 points or more) Mean ACQ-5 score from Studies 97 (baseline to week 52), 88 (baseline to week 32) and 75 (baseline to week 24)

Study	Treatment	N*	% with improvement of ≥ 0.5	Odds ratio to placebo (95% CI)
ACQ-5, includes 5 items – excludes bronchodilator use and FEV_1 from ACQ-7 or complete ACQ				
97	Mepolizumab 75 mg IV	153	72 (47%)	1.05 (0.65, 1.69)
	Mepolizumab 250 mg IV	152	76 (50%)	1.05 (0.65, 1.70)
	Mepolizumab 750 IV	156	74 (47%)	1.06 (0.66, 1.71)
	Placebo	155	77 (50%)	-
88	Mepolizumab 100 mg SC	194	111 (57%)	1.81 (1.17, 2.80)
	Mepolizumab 75 mg IV	191	91 (48%)	1.34 (0.87, 2.08)
	Placebo	191	85 (455)	-
75	Mepolizumab 100 mg SC	69	29 (42%)	1.71 (0.77, 3.83)
	Placebo	66	19 (29%)	
*Represents the number of subjects with both baseline and visit information. There were approximately 15-20% patients across various treatment arms who had baseline information, but no visit information.				

Subgroup population analysis:

Efficacy data were analyzed based on various subgroups, such as gender, age, ethnicity, and geographical regions. In general, exacerbation benefit numerically trended in favor of mepolizumab for these subgroups, but the confidence intervals for some subgroups were large because of small numbers, particularly for the pediatric age group and those of African ethnicity. There were 29 patients in the 12 to 17 year age group, which is rather small, but adequate to conclude efficacy for this age group. The number of patients of African ethnicity was 40 (approximately 3% of total) for Studies 97 and 88, and there were none in Study 75. The efficacy for patients of African ethnicity can be supported based on this small number, when taking into consideration that the morbidity and mortality from asthma is thought to be higher in this ethnic subgroup.

8. Safety

a. Safety database

The safety assessment of mepolizumab for asthma is based on the studies shown in Tables 1, and the ongoing safety extension Studies 61 and 66, where patients from exacerbation Studies 97 and 88 and OCS reduction Study 75 were enrolled. Study 61 enrolled 651 patients and Study 66 enrolled 347 patients, and all patients were treated with mepolizumab 100 mg SC for a duration ranging from 1 year to approximately 3.5 years. The safety database is reasonable.

b. Safety findings and conclusion

The submitted data support the safety of mepolizumab for treatment of severe asthma.

GSK conducted a comprehensive safety analysis of the available data. Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs[14]),

[14] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience

common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. Given the nature of the product, adverse events of interest were allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity.

Deaths, SAEs, dropouts and discontinuations:

Death was rare in the clinical program. A total of 6 deaths were reported in the severe asthma program, occurring evenly between mepolizumab and placebo treatment groups, and none reported to be related to the study drug by the investigators. Causes of deaths during controlled period of the studies included accident (placebo), gastrointestinal hemorrhage (placebo), suicide (mepolizumab 750 mg IV), pancreatitis (mepolizumab 250 mg IV), asthma exacerbation (mepolizumab 250 mg IV), and during open-label extension period included respiratory arrest (mepolizumab 100 mg SC).

Serious adverse events (SAEs) occurred with comparable frequencies between mepolizumab and placebo treatment groups. The majority of the events were related to asthma exacerbation.

Dropouts and discontinuations were low (approximately 1 to 3% in various treatment groups) in the controlled clinical studies. Common adverse events leading to withdrawal were asthma worsening, fatigue, and headache (<1% for each).

Common adverse events:

Common adverse events seen were typical of asthma programs. Adverse event profiles were generally similar across treatment groups, except injection site reaction (3% in placebo, 3% in mepolizumab 75 mg IV, and 8% in mepolizumab 100 mg SC). Common adverse reactions seen in the asthma clinical program that occurred with higher frequency in mepolizumab 100 mg SC compared to placebo (difference of about 1 to 3%) included (reported in decreasing frequency): headache, back pain, fatigue, pain in extremity, injection site reaction, urinary tract infection, lower respiratory tract infection, pharyngitis, upper abdominal pain, nasal congestion, and pyrexia. Headache and back pain were reported by approximately 15-20% patients, and other events were reported by approximately 2-6% of patients.

Laboratory findings and ECGs:

No clinically meaningful effects on hematologic or chemistry parameters were noted in the clinical program, other than the expected decrease in blood eosinophil counts. Assessments of ECGs did not reveal a safety signal.

(defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Adverse events of interest:

Allergic reactions including anaphylaxis are a risk with biologics. Potential anaphylaxis events were prospectively assessed by investigators using accepted criteria.[15] There was no report of anaphylaxis in the clinical program. Allergic reactions (not anaphylaxis) were reported by ≤2% of patients with rates similar across mepolizumab and placebo treatment groups. There was one report of Type IV delayed hypersensitivity with onset 3 days after administration of month 9 dose of mepolizumab 100 mg SC, which required hospital ICU care, and resolved.

Local injection site reactions were reported for more patients treated with mepolizumab 100 mg SC (21 patients, 8%) compared with mepolizumab 75 mg IV (11 patients, 3%) and placebo (14 patients, 3%). Most of these reactions were mild to moderate in intensity and resolved within a few days.

Cardiac events were of interest because in Study 97 (exacerbation study) a numerical imbalance in the number of serious cardiac events was observed for mepolizumab (7 patients) compared to placebo (1 patient). All of these patients, with the exception of one, had cardiovascular (CV) risk factors at baseline. Because of this observation, extensive CV monitoring was employed in subsequent controlled Studies 88, 75, and open-label extension Studies 61 and 66, which included adjudication of pre-specified CV events and all-cause death by independent committees. The finding seen in Study 97 was not seen in subsequent studies 88, 75, 61, and 66. Cardiac events were infrequent in these studies (3% in both mepolizumab and placebo groups), and serious CV thrombotic and ischemic events were reported with similar frequencies across all treatment groups (<1% to 3%).

Infections, including serious infections and opportunistic infections, were reported with similar frequencies in mepolizumab and placebo groups (57% and 58%, respectively). However, two serious adverse reactions of herpes zoster occurred in patients treated with mepolizumab 100 mg SC compared to none in placebo. IL-5 blockage has a possible risk of impaired clearance of helminthic infection. All mepolizumab clinical studies excluded patients with known or risk of parasitic infection. This potential safety risk of mepolizumab can be addressed as a post-marketing study.

Malignancy is a risk for mepolizumab, but likely of a lower magnitude because IL-5 blocking is unlikely to induce general immunosuppression and alter host defense substantially. In the controlled severe asthma studies, a total of 17 neoplasms (benign and malignant) were reported with similar frequencies across treatment groups (0% to 2%). Malignancies were reported with similar frequency across treatment groups in controlled asthma studies (3 in placebo and 2 in mepolizumab). The malignancies reported were those that are common, such as basal cell carcinoma, prostate cancer, squamous cell carcinoma, and uterine cancer. There were no reports of lymphoma or lymphoproliferative cancers that suggest general immunosuppression.

[15] Sampson HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-397.

Immunogenicity is a potential for all therapeutic proteins that can result in ADA response with risk of loss of efficacy and risk of allergic and immunologic events. Immunogenicity with mepolizumab was not of major concern. In the controlled severe asthma studies, 6% (15 out of 263) patients treated with mepolizumab 100 mcg SC and 2% (13 out of 652) patients treated with mepolizumab had anti-mepolizumab antibodies. The antibodies were of low titer and mostly transient with 50% of these patients with only one positive result. There was no correlation between antibody titer to change in blood eosinophil level and PK of mepolizumab, and no signals of allergic reactions or serum-sickness-like reactions associated with anti-mepolizumab antibody status.

c. REMS/RiskMAP

GSK submitted a risk management plan that included routine surveillance and a pregnancy registry (b) (4). No REMS is proposed and none will be required.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on June 11, 2015, to discuss this application. Issues for discussion were the target patient population likely to benefit with mepolizumab, role of blood eosinophil count in identifying target patient population, adequacy of data in patients 12 to 17 years of age, and adequacy of data in various ethnic subgroups, particularly patients of African descent. The voting questions were broken down by age – adults 18 years of age and older, and pediatrics 12 to 17 years – because of the limited database in patients 12 to 17 years of age. In general the advisory committee members were of the opinion that the submitted data are adequate to support approval in adults, but not in patients 12 to 17 years of age (voting by committee members are shown in Table 10). The committee, although voted negatively for the adolescents, recognized that some adolescents will likely benefit from mepolizumab and would prefer that they should have access to the product. The committee members were supportive of the narrow target population identified by previous history of asthma exacerbation, and of the eosinophil phenotype. The committee members were of the opinion that threshold levels of blood eosinophil count at baseline (≥150 cells/μL) were more predictive than historical count (≥300 cells/μL in past year).

Table 11. AC voting on efficacy, safety, approvability, and large safety outcome trial

	Adults 18 years and older			**Pediatric 12 to 17 years**		
	Yes	No	Abstain	Yes	No	Abstain
Efficacy	14	0	0	5	9	0
Safety	13	1	0	2	12	0
Approval	14	0	0	4	10	0

10. Pediatric

The Pediatric Study Plan (PSP) is a waiver for assessment in children under 6 years of age because the disease (severe asthma with increased eosinophilic airway inflammation) is unlikely to exist in sufficient numbers to allow for a study to be conducted), a deferral for children 6 to 11 years of age, and inclusion of children 12 to 17 years of age in the adult development program. The severe subset of asthma patients targeted for treatment with mepolizumab is limited. The prevalence of severe asthma (based on treatment with high dose ICS + one additional controller) in the pediatric population is very low and prevalence varies in the reported literature. A prevalence of 1.9% was reported for children ages less than 14 years of age from a UK General Practice Research database.[16] This prevalence of severe asthma is without accounting for a subset of patients with increased airway eosinophilic inflammation which represents an even smaller number of patients. A waiver for patients less than 6 years of age and deferral for studies with mepolizumab for asthma for patients <12 years of age are reasonable. For patients 6 to 11 years of age, the pediatric program will include assessment of safety, assessment of PK, and assessment of PD parameters, such as reduction of blood eosinophil counts in response to mepolizumab. These plans were discussed at Pediatric Review Committee (PeRC) meetings in 2014. PeRC agreed with the pediatric plans outlined above.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two clinic representative sites from the exacerbation studies. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Four investigators had significant financial interest in GSK. The number of subjects enrolled in the investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proprietary name Nucala was reviewed by DMEPA and found to be acceptable.

[16] Prescribing patterns of asthma controller therapy for children in UK primary care: a cross-sectional observational study: *BMC Pulmonary Medicine 201; 10:29R*

b. Physician Labeling

GSK submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers.

One of the labeling discussion both internally within the review team and with GSK was how best to describe the eosinophil phenotype in the labeling. As discussion in Section 7 above, the submitted data are not definitive to include a labeling language for threshold eosinophil count for the indication and usage section or as a limitation of use for eosinophil count below a threshold. The Indication and Usage section may use the general term "blood eosinophilia" or "eosinophilic phenotype" with or without describing other clinical characteristics of patients, to define the target patient population for mepolizumab. The Clinical Trials section of the labeling will describe the characteristics of the patients studied in the program, including eosinophil counts used for enrollment.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DMEPA, and OBP and found to be acceptable.

d. Patient Labeling and Medication Guide

Mepolizumab will have patient counseling information. There will not be a Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of mepolizumab at a dose of 100 mg SC every 4 weeks for patients 12 years of age and older with severe asthma.

The intended use that will be reflected in the Indication section of labeling will capture the concept that mepolizumab treatment is an add-on for patients 12 years of age and older with severe asthma, (b) (4)

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of mepolizumab at a dose of 100 mg SC every 4 weeks for patients 12 years of age and older with severe asthma (b) (4) Based on sequential conduct of studies with change of endpoint from lung function to exacerbation (described in sections 2 and 7 above), GSK has identified a reasonable target population: patients who continue to experience exacerbations despite standard of care treatment optimized to asthma severity (i.e., high-dose ICS plus an additional controller with or

without continuous OCS use), and eosinophilic phenotype with blood eosinophilia. In this target population, consistent benefit in asthma exacerbation was shown. The submitted safety data, as discussed in section 8 above, did not raise any substantial safety concerns.

c. Post-marketing Risk Management Activities

No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

The required post-marketing studies will be the PREA required studies that are addressed by GSK in their PSP. GSK has also proposed a voluntary pregnancy registry for mepolizumab. (b) (4) . There will also be a product quality related post-marketing commitment study to qualify the bioburden test at the (b) (4) in the product manufacturing process and to implement a bioburden limit.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
10/14/2015