CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125526Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 23, 2015
From	Lydia I. Gilbert-McClain, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	125-526
Applicant	GlaxoSmithKline
Date of Submission	Nov 4, 2014
PDUFA Goal Date	November 4, 2015
Proprietary Name / Established (USAN) names	Nucala /Mepolizumab
Dosage forms / Strength	Lyophilized powder for reconstitution
Proposed Indication(s)	NUCALA ® is indicated for add-on maintenance treatment of severe eosinophilic asthma, as identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months, in patients aged 12 years and older. NUCALA has been shown to reduce exacerbations of asthma in patents with an exacerbation history
Recommended Action:	Approval (with revised indication statement from that proposed by applicant in original submission)

1. Introduction

GlaxoSmithKline (GSK) submitted a Biologics Licensing Application (BLA) on November 4, 2014 for mepolizumab for injection under section 351(a) of the Public Health Service Act for the treatment of patients with severe "eosinophilic" asthma. The proposed indication statement reads: "add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/µL in the past 12 months. Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history." The proposed dose is 100 mg by subcutaneous administration by a healthcare professional once every 4 weeks. As a new BLA this application is being reviewed under the PDUFA V "Program" and has a 12-month PDUFA clock. This review provides a summary of the overall application and my recommendation for the regulatory action.

2. Background

Mepolizumab is a monoclonal antibody (IgG1, Kappa) that binds to human interleukin 5 (IL-5), a soluble cytokine that is key to the regulation of blood and tissue eosinophils. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma and several

monoclonal antibodies blocking this pathway are in development as potential therapeutic targets for a subset of severe asthma patients with characteristics of increased eosinophilic airway inflammation[1]. Mepolizumab is not currently marketed in the United States or any other country in the world. If approved for the treatment of asthma, mepolizumab will be the first monoclonal antibody to IL-5 to be approved in the United States for any indication.

Asthma is a heterogeneous chronic inflammatory disease of the airways affecting more than 22 million persons in the United States. Asthma remains the most common chronic disease of childhood and can have significant impact at the individual and societal level. In spite of the therapeutic advances in the management and treatment of asthma, challenges remain in the management of asthma.[2]

There are several classes of products available for use in patients with persistent asthma. These include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and the monoclonal antibody to IgE known as omalizumab. While several products are approved for long-term maintenance treatment of asthma, there are no therapies approved specifically for a subset of patients with severe asthma and elevated blood eosinophil levels. With the appreciation that asthma is a chronic inflammatory disorder, inhaled corticosteroids are the cornerstone of maintenance therapy for patients with persistent asthma. However, spite of available therapies, there are patients who remain poorly controlled on maximum therapy (including oral corticosteroids) and there are patients with severe persistent asthma who are resistant to corticosteroids.[3] The subset of severe uncontrolled asthma represents less than 5% of the overall asthma population[4] and within the severe asthma population; patients with increased eosinophilic airway inflammation represent the subgroup that is the target for treatment with mepolizumab.

There is ongoing research in the area of severe persistent asthma to better understand the heterogeneity that exists in this subgroup and some results from this ongoing research and updated guidelines on severe asthma have been described in the literature.[5,6] Patients with severe persistent asthma are at risk for more frequent asthma exacerbations and hospitalizations due to asthma and therefore development of therapies to control asthma in this subpopulation is an important therapeutic step in improving asthma outcomes.

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[1] Jared Darveaux and William W. Busse. Biologics in Asthma – The next step toward personalized treatment. J *Allergy clin Immunol Pract March/April 2015 152 - 160*

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

[3] Donald Y.M. Leung, and Stanley J. Szefler. Diagnosis and management of steroid-resistant asthma. *Clin Chest Med. 1997 Sep; 18 (3): 611-625*

[4]

[5] Moore WC., Meyers DA., Wenzel SE., et.al Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir and Crit Care Med Vol 181: pp 313-323, 2010*

[6] Kian Fan Chung, Wenzel SE., Brozek JL., Bush A., et.al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Task Force Report ERS/ATS Guidelines on Severe Asthma. At: https://www.thoracic.org/statements/resources/allergy-asthma/Severe-Asthma-CPG-ERJ.pdf

In early clinical studies in mild asthmatics, mepolizumab was shown to decrease eosinophils in blood, bone marrow, and bronchial mucosa.[7] However, the first study conducted in patients with moderate persistent asthma did not show a benefit in lung function, and exacerbation data was not prospectively captured. There was a lapse of approximately 10 years from the time the initial study was completed to the start of the development program for severe asthma. The clinical studies to support this BLA were conducted in patients with severe persistent asthma and increased eosinophilic airway inflammation after results from 2 individual investigator proof-of-concept studies in a more severe population suggested that there was potential benefit of mepolizumab in this severe asthma population.

3. CMC/Device

Drug Substance/Drug Product

Mepolizumab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells and has a molecular weight of approximately 149 kDa. (b) (4) .

Nucala® (mepolizumab) for Injection is supplied as a sterile, preservative-free lyophilized powder for reconstitution and subcutaneous (SC) injection. The product is stored in 10-mL Type 1 clear glass vials, sealed with gray (b) (4) rubber (b) (4) stoppers and aluminum overseals with red flip-off caps. Upon reconstitution with 1.2 mL Sterile Water for Injection, each single-use vial delivers 100 mg of mepolizumab in a 1 mL withdrawable volume. The drug product formulation includes 160 mg sucrose/mL, 7.14 mg sodium phosphate dibasic heptahydrate/mL, and 0.67 mg/mL polysorbate 80 and has a pH of 7.0.

Three mepolizumab drug product presentations were used during the clinical development program. The mepolizumab product (pilot formulation containing 50 mg/vial) that was used in the early phase 1 and 2 studies (clinical trial 006, and several clinical pharmacology studies [01, 17, 18, 35, 36]) contained different excipient quantities and had differing manufacturing processes from the subsequent formulations. This pilot formulation was not used in subsequent studies and no bridging studies were conducted with the pilot product and subsequent formulations.

The mepolizumab product MDP1 containing 250 mg/vial was used in the subsequent pivotal clinical pharmacology studies (study 092 [PK/PD study in asthma patients]; study 05[PK study in healthy volunteers]), the clinical dose-ranging and confirmatory efficacy studies, and for the initiation of the open label safety extension studies. The MDP1 product is the same formulation as the product proposed for marketing (MDP2) but with a concentration of 100 mg/vial. GSK performed adequate CMC bridging data to support the marketing of the 100 mg/vial mepolizumab product. Regarding quality microbiology, GSK has adequate control strategies in place with bioburden and endotoxin testing as part of the in-process and release specifications. There are 2 potency assays which are acceptable for release and stability of the

[7] Study SB-240563/036 "A Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of 750 mg SB-240563 (Anti-IL-5) on Clinical Features, Cutaneous Late-Phase Reactions and Bronchial, Nasal, Skin, Bone Marrow and Blood Eosinophils in Male and Female Patients with Atopic Asthma" -GSK BLA 125-526 sequence 0000 November 4, 2014.

drug substance and drug product. The surface plasmon resonance (SPR) assay is used for the drug substance release and stability, and the IL-5 neutralization assay is used for the drug product release and stability. The process for the MDP2 product is considered representative of the commercial process and long term stability data from MDP1 lots support a commercial expiration dating period of (b) (4) months for the drug substance when stored at (b) (4). The shelf life for the drug product is 24 months at $\leq 25^0$C. Please refer to Dr. Marjorie Shapiro's executive summary review for further details.

Facilities/Inspections
The drug substance manufacturing location is GlaxoSmithKline LLC, Conshohocken, PA and the drug product manufacturing location is in GlaxoSmithKline Manufacturing S.P.A., Parma, Italy. At this time the compliance checks for all facilities listed, except the mepolizumab drug product manufacturing facility in Parma, Italy, are acceptable. The inspection of the manufacturing facility in Italy was conducted from May 19 to May 27, 2015. A substantial 483 was issued for the manufacturing facility in Italy. The major observations were made in the (b) (4) which is dedicated to (b) (4). Improper documentation (altering of a cleaning log) was observed in the facility as well as some GMP issues which led the inspectors to issue the 483. Of note, mepolizumab is not manufactured in the (b) (4) and the issues listed in the 483 are not identified as directly related to mepolizumab. GSK provided a detailed response (132 pages) to the 483 on June 17, 2015. In the response to the 483, GSK outlined a series of steps they were undertaking to address the findings of the inspection report including launching a comprehensive investigation of the circumstances surrounding the improper documentation incident described in the inspection report. In their response GSK indicated that they intend to perform a review of validation documentation, including manufacturing and testing documentation associated with mepolizumab even though mepolizumab is not manufactured in the (b) (4). The Establishment Inspection Report (EIR) notes that the mepolizumab bulk drug substance (b) (4) (EIR report page 27).

At present a "withhold" recommendation is being considered for the mepolizumab BLA because of the inspection findings. However, as of this writing, compliance has not issued a Warning Letter to GSK. From a clinical perspective I would advocate for the exercise of regulatory discretion regarding this recommendation given that there are no other outstanding approval issues from other disciplines for the BLA. Mepolizumab is indicated for a subset of the asthma population with significant morbidity and there is an unmet medical need for effective therapies in severe asthma. From the EIR it does not appear that the manufacture of mepolizumab is directly affected by these inspection findings. A Center Director briefing is scheduled for October 14, 2015 to discuss the implication of a "withhold" recommendation from Compliance and a possible regulatory path forward.

4. Nonclinical Pharmacology/Toxicology

The nonclinical program for mepolizumab was conducted in Cynomolgus monkeys which were determined to be the only pharmacologically relevant nonclinical test species. The overall nonclinical pharmacology/toxicology program is adequate to support approval of the

application from the nonclinical perspective. The pharmacology of mepolizumab was evaluated both *in vitro* and *in vivo*. Mepolizumab inhibited binding of IL-5 to its receptor *in vitro* with an IC_{50} value < 1.0 nM and the binding affinity of mepolizumab for human IL-5 ranged from 110 to 258 pM. Mepolizumab also inhibited exogenous IL-5 induced differentiation of eosinophils obtained from the bone marrow of healthy volunteers and Cynomolgus monkeys. Mepolizumab decreased peripheral eosinophil counts in Cynomolgus monkeys and reduced pulmonary eosinophilia in response to A. *Suum* challenge in an acute model of asthma.

In a 6-month chronic toxicology study, Cynomolgus monkeys that received mepolizumab IV or SC had decreased eosinophil counts by up to 95% at all doses tested from days 29 to the end of the study. Evaluation of bone marrow suggested a block of maturation and /or release of eosinophils from the bone marrow. There were no adverse histopathological findings. There were no pre-neoplastic or neoplastic lesions in the 6-month toxicology study with monkeys. Since the rodent was not a pharmacologically relevant species a carcinogenicity study with mepolizumab was not required. Male and female fertility was unaffected and there were no adverse findings in a pre- and post-natal development study with monkeys treated with mepolizumab IV. In addition, 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 IL-5. The pharmacology/toxicology team recommends approval of mepolizumab from a nonclinical perspective and I concur with their recommendation. Refer to Dr. Timothy Robison's pharmacology and toxicology review for additional details.

5. Clinical Pharmacology/Biopharmaceutics

Mechanism of Action

Mepolizumab is a humanized anti-IL 5 monoclonal antibody that binds to soluble IL-5 and blocks IL-5 binding to the IL-5α chain of the IL-5 receptor on eosinophils and other cells expressing the IL-5 receptor. IL-5 is a soluble dimer and is not expressed on cell surfaces. IL-5 cannot bind to both mepolizumab and its receptor at the same time because once IL-5 is bound to either mepolizumab or the IL-5 receptor, steric hindrance prevents binding of the other.

Asthma is a chronic lung disease that involves inflammation of the airways. Microscopically, asthma is characterized by the presence of increased numbers of inflammatory cells including eosinophils, neutrophils, lymphocytes and plasma cells. Activated T-lymphocytes direct the release of inflammatory mediators from eosinophils, mast cells, and lymphocytes. In addition, the Th2-subset of activated T-lymphocytes produces IL-4, IL-5, and IL-13 and in conjunction with IL-13 signals the switch from IgM to IgE antibodies. The cross-linkage of two IgE molecules by allergen causes mast cells to degranulate leading to the release of histamine, leukotrienes, and other mediators that perpetuate the airway inflammation. IL-5 activates the recruitment and activation of eosinophils and activated mast cells and eosinophils also generate their cytokines that help to perpetuate the inflammation[8]. The pathogenesis of asthma is complex, and although blocking IL-5 results in reduced eosinophils in the peripheral blood

[8] Fireman, Philip. Understanding asthma pathophysiology. *Allergy asthma Proc. 2003 Mar-Apr; 24 (2): 79-83*

and (to some extent) in tissues, a direct correlation with the reduction of eosinophil levels to clinical efficacy has not been established.[9]

Pharmacokinetics

Mepolizumab showed linear and dose-proportional PK with a mean elimination half-life of 20 to 36 days in healthy volunteers. In asthma patients the mean elimination half-life was 3 to 4 weeks. The observed terminal half –life ($t_{1/2}$) supports the proposed dosing interval of once every 4 weeks. The pharmacokinetics of mepolizumab was not significantly impacted by race, ethnicity, age, or gender.

Absorption, Distribution, Metabolism, Elimination

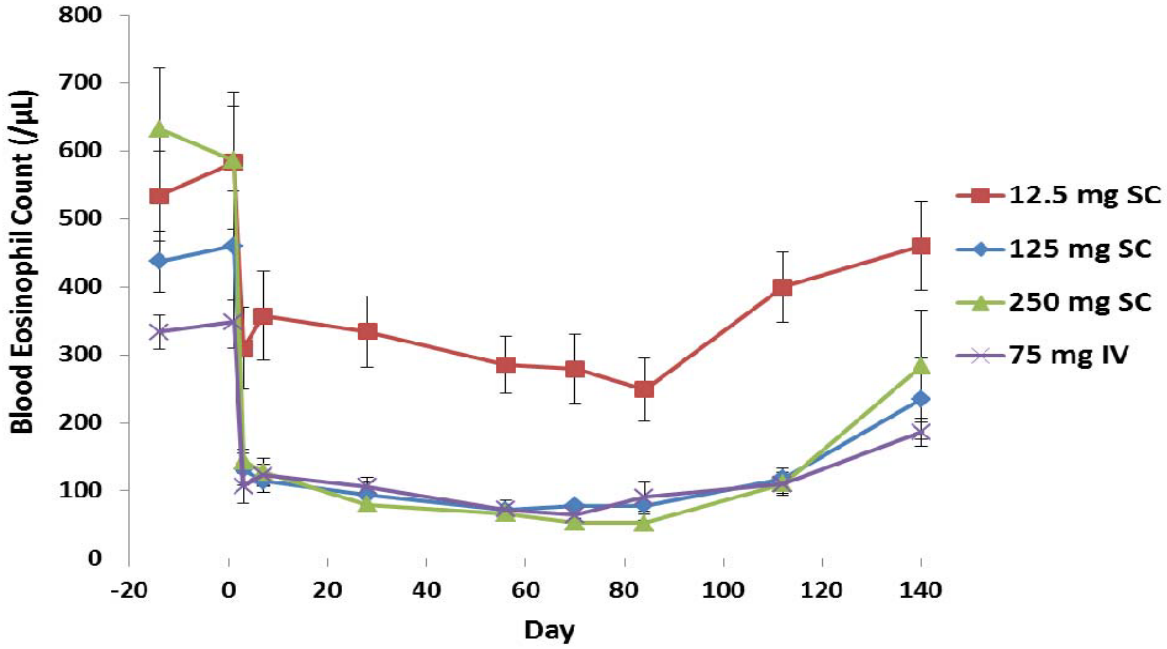
The absolute bioavailability of mepolizumab 100 mg via SC administration to the upper arm is estimated to be 80% by ANOVA analysis. As a monoclonal antibody catabolized by ubiquitous proteolytic enzymes, mepolizumab does not undergo target-mediated degradation. The clearance of mepolizumab is non-specific and the large molecular weight (149.2 kDa) precludes elimination by the kidney.

Dose selection

The pharmacodynamic response (blood eosinophil count) of mepolizumab played a role in guiding dose selection for the phase 3 clinical studies. GSK used modeling to predict the subcutaneous dose that would provide 50% and 90% of maximal reduction of blood eosinophils at Day 84 (study 92) along with clinical efficacy data from clinical trial 97 to determine dose selection for the confirmatory efficacy studies. Study 92 was a multi-center, open-label study to determine the pharmacokinetics and pharmacodynamics of mepolizumab administered intravenously or subcutaneously to adult asthmatic subjects (age 18 – 65 years). Subjects had to be on stable asthma medications at least 12 weeks prior to screening and have blood eosinophil counts ≥ 200 cells/μL within 12 months of screening. Mepolizumab was dosed once every 4 weeks for a total of 3 doses at a dose of 12.5 (n = 21), 125 (n =15), or 250 mg SC (n =23), or 75 mg IV (n =11). The results of the study showed that reduction of blood eosinophils was in the same range for the mepolizumab 125 and 250 SC doses and the 75 mg IV dose while less reduction was observed with the mepolizumab 12.5 mg SC dose (see Figure 1 copied from Dr. Yunzhao Ren's Clinical Pharmacology review).

[9] Leckie MJ et.al Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper responsiveness, and the late asthmatic response. *Lancet 2000; 356: 2144-8*

Figure 1: Arithmetic mean (±SE) absolute blood eosinophil counts profile following three doses of mepolizumab in study 92



Both linear and non-linear (I_{max}) dose-response models were fitted to the blood eosinophil data and based on these models the estimated IC_{50} dose was 11 mg SC (95% CI: 5.19,16.85) and the estimated IC_{90} dose was 99 mg SC (95% CI: 47,152). In order to include the 75 mg IV dose in the modeling (observed geometric mean reduction from baseline for the 75 mg IV dose = 78%) this dose was considered to equate to 100 mg SC assuming that the absolute bioavailability of the SC route was 75%.

Immunogenicity

Plasma samples for immunogenicity assessments were collected in the PK/PD study 92 and all three randomized controlled trials. Overall, 6% (15/260) of subjects in the confirmatory efficacy trials (Trial 88 and 75) treated with mepolizumab 100 mg SC developed anti-mepolizumab antibodies and 1 subject developed neutralizing antibodies. There was no evidence of a correlation between anti-mepolizumab antibody titers and the PD effect of mepolizumab.

Serum IL-5 levels

Consistent with the mechanism of action of mepolizumab, serum total IL-5 levels increased from baseline in almost all subjects following treatment with mepolizumab in study 92. While there was no clear dose-response relationship for serum IL-5 concentrations, IL-5 levels peaked around 2 weeks with an approximately 10 – 27-fold increase from the baseline levels.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The table below outlines the dose-ranging and pivotal efficacy [and safety] studies that were conducted in the severe asthma population.

Table 1. Controlled Efficacy and Safety studies in the Severe Asthma Population

ID Trial period (yr.) (Total enrolled)	Number of U.S. subjects (% of study population)	Study Characteristics -Subject age -Subject characteristics -Study design, objective -Study duration	Treatment groups (N§)	Primary efficacy endpoint
Dose-ranging/Efficacy Study				
MEA112997* 11 2009 -12/2011 616)	78 (13%)	-12 to 65 yr. -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC -52 weeks	Mepo 75 mg IV (n =153) Mepo 250 mg IV (n=152) Mepo 750 mg IV (n=156) Placebo (n =155)	§§Rate of asthma exacerbations
Confirmatory Efficacy Studies				
MEA115588 10 2012 -01/2014 576)	67 (12%)	-At least 12 yr. and minimum weight of 45 kg -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC, DD -32 weeks	Mepo 75 mg IV (n = 191) Mepo 100 mg SC (n = 194) Placebo (n = 191)	§§Rate of asthma exacerbations
115575 10 2012 -12/2013 135)	7 (5%)	-At least 12 yr. and minimum weight of 45 kg -Severe refractory asthma with markers of eosinophilic inflammation** -Randomized, DB, PC - 24 weeks	Mepo 100 mg SC (n = 69) Placebo SC (n = 66)	Percent reduction of OCS dose during weeks 20 - 24

Study ID shown as GSK study number. Studies are identified by the last 2 numbers (underlined) in this memo.
Trial Period= month/year study started to month/year study completed
DB = double-blind, DD = double-dummy, PC = placebo-controlled
Mepo = mepolizumab
*Study **97** is also an efficacy study
**Markers of eosinophilic inflammation defined as follows:
For study **97:** blood eosinophils ≥ 300/µL **or** sputum eosinophils ≥3% **or** exhaled nitric oxide ≥ 50 ppb **or** deterioration of asthma control following a ≤25% reduction in regular maintenance dose of ICS in the previous 12 months.
For study **88** and **75**: Blood eosinophil count of ≥300µ/L that is related to asthma in the past 12 months or ≥ 150/µL at Visit 1 (study 88) or between Visit 1 and Visit 3 (study 75).
§ N = Intent-to-treat; §§ GSK used "frequency" but "rate" is more appropriate term from statistical standpoint

Not shown in Table 1, is study 006 a 12-week lung function study conducted in 1999 in patients with moderate persistent asthma to evaluate the effect of mepolizumab (intravenous administration) on lung function improvement (FEV_1, PEF). The effect of mepolizumab on

lung function was not significant and the original drug development program was halted. Subsequently, two proof-of-concept individual investigator-led studies[10][11] were conducted that showed benefit of mepolizumab in a more severe asthma population with characteristics of increased eosinophilic airway inflammation. One study evaluated the benefit of mepolizumab on exacerbations in a severe asthma population with increased eosinophilic airway inflammation (n = 61; duration 52 weeks), and the other evaluated the benefit of mepolizumab in reducing oral corticosteroids in severe asthma patients on long term maintenance oral corticosteroid therapy (n = 20; duration 16 weeks). Following these results, GSK designed the development program for mepolizumab targeted to a subset of the severe asthma population with increased eosinophilic airway inflammation.

Dose Selection

As with all asthma development programs, dose and dosing regimen are important considerations. GSK explored both the intravenous (IV) and subcutaneous (SC) routes of administration in the earlier development of mepolizumab. For the selection of the dose and route of administration for the severe asthma program, GSK conducted one dose ranging study (study 97) in patients with severe refractory asthma that explored multiple doses using the IV route of administration and one pharmcodynamic study which was used to bridge the IV and SC routes of administration using a pharmacodynamic endpoint (reduction in blood eosinophil levels). The dose-ranging study 97 also served as an efficacy study.

Studies 97 and 92 provided evidence to support the selection of the 100 mg SC dose of mepolizumab for further evaluation in pivotal efficacy studies. In study 97, subjects received mepolizumab 75, 250, or 750 mg IV or placebo, once every four weeks over a 52-week treatment period. Additional details about this study will be discussed below with the discussion of the pivotal efficacy studies. In study 92, subjects received 12.5, 125, or 250 mg of mepolizumab SC, or 75 mg IV once every 4 weeks for a total of 3 doses. Results of study 97 showed that treatment with all 3 doses of mepolizumab resulted in a statistically significant reduction in exacerbation frequency compared to placebo and there was no significant treatment difference among the three doses. In study 92, a dose-dependent decrease in blood eosinophil levels was observed in all treatment groups by the third day post-treatment with similar reductions seen for the 125 mg SC and the 75 mg IV dose. These data, along with model-estimated inhibition of blood eosinophils, provided the rationale for evaluating both the 100 mg SC and the 75 mg IV mepolizumab doses in the pivotal phase 3 exacerbation study (Study 88). Importantly, similar treatment effects for both doses were seen in Study 88 providing evidence that the data from the 75 mg IV dose can be applied to the 100 mg SC dose. The clinical data from studies 97, and 88 support the conclusion that mepolizumab 75 mg IV and 100 mg SC would provide similar efficacy. The proposed dose for marketing is 100 mg SC.

[10] Haldar, et.al. N Engl J Med 2009; 360:973 -84. Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

[11] Nair, Et. al. *N Engl J Med 2009, 360: 985 – 93* Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Mepolizumab Dose-ranging and Confirmatory Clinical Trials

Characteristics of Enrolled Subjects

Selected demographic and baseline characteristics of the subjects enrolled in the dose-ranging/ efficacy and confirmatory clinical trials are shown in Table 2. The inclusion criteria are consistent with criteria that would characterize patients as having severe asthma by the most recent severe asthma guidelines.[12] In two of the trials (97 and 88) subjects were specifically required to meet criteria defined in the 2000 ATS workshop on refractory asthma.[13]

****Table 2: Baseline Characteristics and Demographics of the Subjects in the Pivotal Efficacy Clinical Studies and the Dose-Ranging/Efficacy Study**

Parameter	**Study 97 N = 616**	**Study 88 N = 576**	**Study 75 N = 135**
Mean age (yrs.) (range)	49 (15-74)	50 (12-82)	50 (16-74)
12-17 yrs. N	1	25	2
Female (%)	63	57	55
Males (%)	37	43	45
White n (%)	554 (90)	450 (78)	128 (95)
Black n (%)	23 (4)	16 (3)	0
Asian n (%)	35 (6)	106 (18)	3 (2)
Other n (%)	4 (<1)	4 (<1)	4 (3)
BMI ((mean) (range))	28.5 (17-52)	27.77 (16.1 -49.7)	28.6 (19.7 -52.1)
Smoking history (% never smoked)	78	72	82
Duration of asthma (yrs.) mean, median	19 (14.3)	20 (17.0)	19 (16.0)
Mean # exacerbations in prior yr. (%)	3.6	3.6	3.1
Pre-bronchodilator FEV1/FVC ((mean) (SD))	0.63 (0.14)	0.64 (0.13)	0.62 (0.12)
§ Reversibility at screening, ((mean) (SD))	25 (21.8)	28 (22.6)	24 (18.9)
ΩBaseline eosinophil count µL (SD)	384 (368)	445 (429)	377 (339)
ΩSource: Stats reviewer programs exacerbation forest plots subgr s 97 20150406.sas, exac forest plots subgr s88 20150417.sas, ocs subgr s75201503			
**Source: GSK submission: Study 97 CSR Tables 8, 5.15, 518; Study 88 CSR Tables 6, 7,8,9 and Study 75 CSR Table 9, 10, 12, 13			

A higher percentage of females were in the development program and the mean age of the study population was 49 years. There were only 28 adolescent patients and the majority (n = 25) were enrolled in the confirmatory exacerbation trial 88. Race representation was similar to what is typically seen with other asthma development programs with the majority of subjects being white and minorities making up less than 10% of the overall population. The overall percentage of subjects of African descent was ~ 3%. Although the number of adolescent subjects was low, the asthma characteristics of these subjects (shown in Table 3) are similar to

[12] Kian Fan Chung, Wenzel SE., Brozek JL, Bush A., et. al. International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma. Task Force Report ERS/ATS Guidelines on Severe Asthma. At: https://www.thoracic.org/statements/resources/allergy-asthma/Severe-Asthma-CPG-ERJ

[13] American Thoracic Society: Proceedings of the ATS Workshop on Refractory Asthma: Current Understanding, Recommendations and Unanswered Questions. *Am J Respir Crit Care Med Vol 162 pp 2341-2351, 2000*

that of the overall population except for the degree of lung function impairment which was more severe in the overall population (predominately adults) given the longer duration of asthma (20 years for adults vs. 9.6 years for adolescents).

Table 3: Baseline and Demographic Characteristics of Adolescents and Total Population in Trial 88

	Adolescents (12 – 17 years) N = 25	**Total Population N = 576**
Female	13 (52)	328 (57)
Caucasian	19 (76)	450 (78)
African Heritage	2 (8)	16 (3)
Duration of asthma	9.6	20
FEV1 at baseline (% predicted)	2.54 (82)	1.82 (61)
% reversibility	26	27
Pre SABA FEV_1/FVC	0.79	0.64
Post SABA FEV_1/FVC	0.84	0.66
Geometric mean eosinophil count at baseline cells/mc L	243 (20-910)	290 (0 -3600)
Exacerbation history (mean)	3.7	3.6

Source: GSK response to Information Request

Eosinophilic Airway Inflammation Enrichment Criteria

In addition to the clinical and demographic inclusion criteria, GSK used criteria deemed to be indicative of eosinophilic inflammation to select subjects for inclusion in the controlled clinical studies (see Table 1). Four criteria were used for this purpose in the dose-ranging/exacerbation trial (study 97), and two criteria were used in studies 88 and 75. Subjects in study 97 were required to meet at least one of these 4 criteria within 12 months of screening:

- Blood eosinophils ≥ 300 cells/μL
- Sputum eosinophils ≥3%
- Exhaled nitric oxide (FeNO) ≥ 50 ppb
- Deterioration of asthma control following a ≤25% reduction in regular maintenance dose of ICS

GSK conducted an exploratory multivariate modeling analysis of baseline variables from study 97 to investigate which baseline variables would predict the overall number of exacerbations and differential efficacy of mepolizumab. Baseline covariates considered for inclusion were not limited to the eosinophilic inflammation enrichment criteria but also included region, gender, age, weight, number of exacerbations in the year before the study (i.e. two, three, or more than three), use of maintenance oral corticosteroids, percentage of predicted FEV_1, airway reversibility, blood eosinophil count, and IgE concentration. GSK states that based on these exploratory analyses they determined that the blood eosinophil biomarker thresholds of a peripheral blood eosinophil count of ≥ 300 cells/μL in the 12 months prior to screening or a peripheral blood eosinophil count of ≥ 150 cells/μL at screening predicted response to mepolizumab[14]. GSK used these two eosinophil values in the inclusion criteria in the two confirmatory trials 88 and 75. Based on FDA analyses, the statistical reviewer concluded that

[14] GSK BLA submission. Clinical Overview Module 2 pages 19 -20

there is support for a baseline cutoff of ≥ 150 cells/μL at baseline as predictive of a significant effect of mepolizumab on exacerbations but there is no statistical evidence to support the historical threshold of peripheral blood eosinophil count of ≥ 300 cells/μL in the 12 months prior to screening (See Dr. Robert Abugov's Statistical Review Section 4.2.2, pages 36 – 39). I concur with the statistical team's assessment.

Study Design

All studies were randomized, placebo-controlled, parallel group studies. Study 88 included a double-dummy design to maintain the blind as this study evaluated both the IV and SC routes of administration. Subjects in study 97 and 88 were required to be on background maintenance therapy with high dose ICS for the prior 12 months (with or without oral corticosteroids [OCS]) plus an additional controller (LABA, leukotriene inhibitor, or theophylline). Subjects in study 75 were required to be on regular treatment with maintenance systemic corticosteroids (5 to 35 mg/day of prednisone or equivalent) and high-dose ICS in the 6 months prior to screening in addition to being on an additional controller medication. Subjects enrolled in study 97 and 88 were required to have a history of two (2) or more Exacerbations in the prior year, whereas, subjects in study 75 were not required to have a history of exacerbations. This is a reasonable exception as all subjects in study 75 were on continuous OCS.

The primary efficacy endpoint in studies 97 and 88 was the rate of asthma exacerbations. Asthma exacerbation was defined using criteria consistent with the ATS/ERS definition for asthma exacerbation.[15] Study 97 and 88 differed in the duration of treatment. Subjects were treated once every 4 weeks through week 48 for a treatment duration of 52 weeks in study 97, whereas, subjects were treated once every 4 weeks with the last dose given at week 28 for a total of 32 weeks of treatment in study 88. The primary efficacy endpoint for study 75 was the percent reduction of OCS dose at week 24 compared to the baseline dose. Study 75 had a 24-week treatment period and was designed with four (4) study periods: i) an initial oral corticosteroid optimization period of 3-10 weeks duration where subjects' oral corticosteroid dose was titrated in a scheduled manner to ensure that subjects entered the double-blind treatment period on the lowest OCS dose that controlled their symptoms; ii) an induction phase of 4 weeks duration where subjects received their first dose of blinded investigational treatment and their OCS dose was maintained; iii) the OCS reduction phase (weeks 4 to 20) when the OCS dose was reduced every 4 weeks as long as asthma control was maintained; iv) the maintenance phase (weeks 20 – 24) where no further reductions in OCS dose were made.

Secondary efficacy endpoints in study 97 and 88 include time to first exacerbation, rate of exacerbations requiring hospitalizations, lung function (mean change in FEV_1 from baseline over the treatment period), assessment of asthma control using the Asthma control questionnaire (ACQ – the ACQ-6 was used in study 97, and ACQ-5 in study 88), the St. George's Respiratory questionnaire (SGRQ) [in study 88], and blood and sputum [sputum in study 97 only] eosinophil levels. Secondary efficacy endpoints evaluated in study 75 include

[15]Helen K. Reddel, et.al An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am J Respir Crit Care Med Vol 180. pp 59-99, 2009*

various measures of OCS reduction during weeks 20-24 while maintaining asthma control (i.e. proportion of subjects who achieve: i) a 50% or greater reduction in their daily OCS dose; ii) total reduction in their OCS dose; iii) reduction of OCS dose to ≤ 5 mg), rate of asthma exacerbations, asthma exacerbations requiring hospitalizations, health-related quality of life using the SGRQ, the ACQ-5, and lung function (mean change from baseline in FEV_1 at week 24).

Efficacy Results

Exacerbations

Exacerbation results for studies 97 and 88 are shown in Table 3.

Table 3: Rate of Exacerbations in Studies 97 and 88

Study	Treatment in mg	N	Annual rate of asthma exacerbation	Difference to placebo	Rate Ratio* (95% CI)
97	Mepolizumab 75 mg IV	153	1.24	-1.16	0.52 (0.39, 0.69)
	Mepolizumab 250 mg IV	152	1.46	-0.94	0.61 (0.46, 0.81)
	Mepolizumab 750 mg IV	156	1.15	-1.24	0.48 (0.36, 0.64)
	Placebo	155	2.40	---	
88	Mepolizumab 75 mg IV	191	0.93	-0.81	0.53 (0.40, 0.72)
	Mepolizumab 100 mg SC	194	0.83	-0.92	0.47 (0.35, 0.64)
	Placebo	191	1.74	----	
*p<0.001 for each dose group compared to placebo Data Source: Study reports Tables 10 and 23					

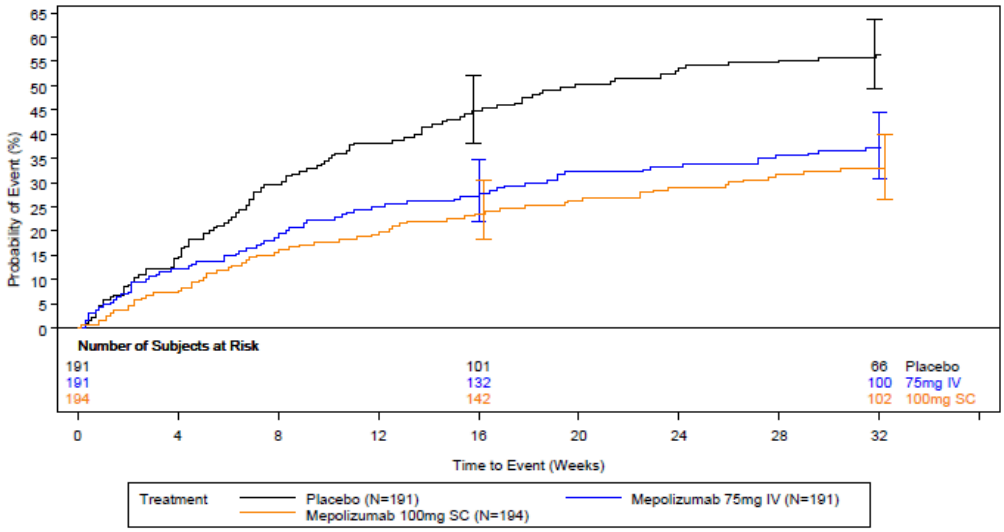
A statistically significant reduction in asthma exacerbations in all mepolizumab treatment arms was seen in both studies. There was no significant benefit of doses higher than 75 mg IV in study 97 and there was no significant difference in exacerbation benefit between the mepolizumab 75 mg IV dose and the 100 mg SC dose in study 88. The rate of exacerbations requiring hospitalizations or ER visit was lower in the mepolizumab treatment groups compared to placebo, but the overall rates of exacerbations requiring hospitalizations or ER visits were low across the treatment groups (shown below in Table 4).

Table 4: Rate of Exacerbations Requiring Hospitalization or ER Visit

Study	Treatment in mg	N	Annualized rate of exacerbation requiring hospitalization or ER visit	Annualized rate of exacerbations requiring hospitalization	Rate Ratio (95% CI) exacerbations requiring hospitalization or ER visit	Rate Ratio* (95% CI) exacerbations requiring hospitalization
97	Mepo 75 mg IV	153	0.17	0.11	0.40 (0.19, 0.81) ¶	0.61 (0.28, 1.33)
	Mepo 250 mg IV	152	0.25	0.12	0.58 (0.30, 1.12)	0.65 (0.31, 1.39)
	Mepo 750 IV	156	0.22	0.07	0.52 (0.27, 1.02)	0.37 (0.16, 0.88) ¶
	Placebo	155	0.43	0.18		
88	Mepo 75 IV	191	0.14	0.06	0.68 (0.33, 1.41)	0.61 (0.23, 1.66)
	Mepo 100 SC	194	0.08	0.03	0.39 (0.18, 0.83)	0.31 (0.11, 0.91) ¶
	Placebo	191	0.20	0.10		
¶True p-value is >0.05 for dose compared to placebo Data Source: Study Reports tables 10 and 23 and Statistical Reviewer program exac studies 88 97 2015 04 17.sas						

Another important assessment in exacerbation studies is the time to first exacerbation. In both studies 97 and 88, mepolizumab-treated subjects had a longer time to first exacerbation compared to patients treated with placebo. The Kaplan-Meier plot below shows the incidence curve for time to first exacerbation in Study 88. A similar trend was seen in study 97.

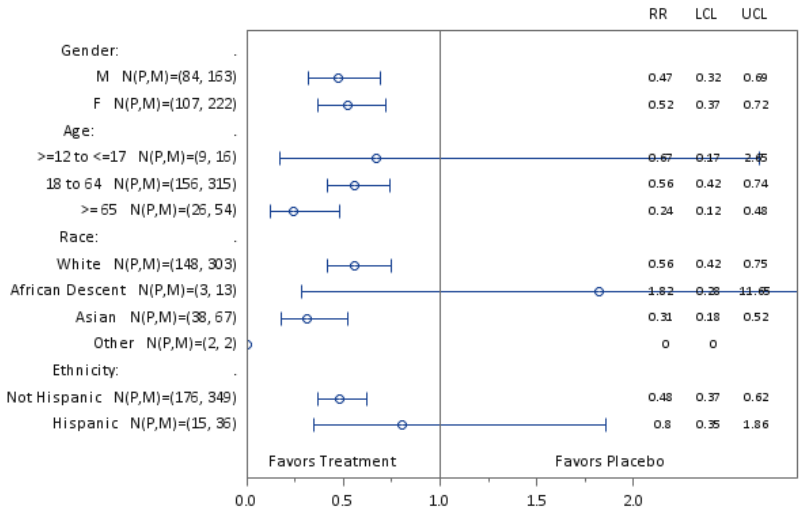
Figure 2. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Trial 88)



Source: Study 88 CSR Figure 4

The reduction in exacerbation was not affected by region, age, or gender. These results are depicted in Figure 3 below. Of note, the point estimate for the exacerbation rate ratio for the adolescent population (12 – 17 years) in trial 88 was similar to that of the adult population. The confidence intervals were wide however and crossed 1 but this is not surprising given the small sample size (n = 25) for the adolescent population.

Figure 3. Exacerbation Rate Ratios by Gender, Age, Race and Ethnicity for Trial 88



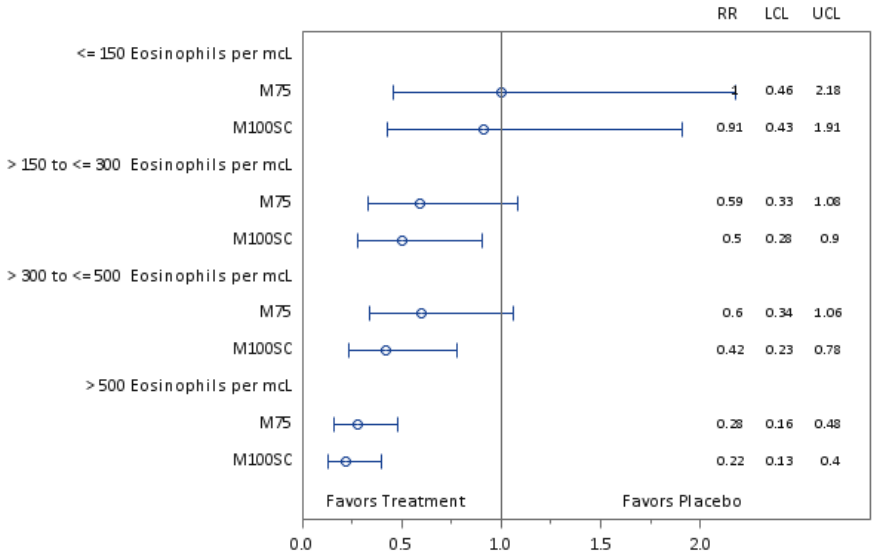
Legend:
P = placebo
M = Mepolizumab
N = number of subjects
RR = rate ratio
LCL = lower confidence limits
UCL = upper confidence limits

Source: Dr. Robert Abugov's Statistical Review Figure 3 page 29

Treatment Modification by Blood Eosinophil Counts
The development program did not include a dedicated interaction study to evaluate the interaction of blood eosinophils and efficacy. However, given the role of IL-5 in the regulation of eosinophils, the biological relevance of an anti-IL-5 therapy such a mepolizumab for asthma has scientific merit and it is reasonable to explore blood eosinophil levels as a potential treatment effect modifier.

From secondary exploratory analyses, the treatment effect (reduction in exacerbation rate) of mepolizumab was greater in patients with higher blood eosinophil levels. The results of this analysis are depicted in Figure 4 below for study 88. Study 97 had a similar trend. Other clinical parameters such as FEV_1 and number of exacerbations in the prior year did not show a similar interaction.

Figure 4. Exacerbation Rate Ratios, by Screening Blood Eosinophil Count (Study 88)



Legend:
M75 = mepolizumab 75 mg IV
M 100 SC = mepolizumab 100 mg SC
RR = rate ratio
LCL = lower confidence limit
UCL = upper confidence limit

Source: Dr. Robert Abugov's Statistical Review Figure 14 page 42

There are ongoing discussions regarding the best approach to present the blood eosinophil interaction information in labeling. There are a number of considerations to keep in mind because the way in which this information is conveyed in the labeling could send the wrong message. Whether a specific eosinophil cutoff should be used to define the patient population with severe persistent asthma and a history of frequent exacerbations for whom mepolizumab would be indicated is an important consideration in this debate. Another point to note is that

the question of whether mepolizumab treatment would be beneficial in patients who would have otherwise met the degree of asthma severity for enrollment but would not have met the blood eosinophil study entry criterion that was pre-specified for these studies, cannot be definitively answered from the data in this program as the studies were not designed to address this question. It is also important to keep in mind the fact that there is no direct correlation between reduction in blood eosinophil levels and clinical efficacy. This was clearly

demonstrated in study 006 where mepolizumab did not show a clinical benefit despite an appreciable and persistent reduction in blood eosinophil count. Of note study 006 had a similar mean eosinophil count at baseline (366 cells/μL)[16] compared to the severe asthma studies. That said, it does appear from these secondary analyses that there is a potential link between baseline blood eosinophil counts and treatment effect in this severe asthma population with frequent exacerbations despite maintenance treatment with high dose ICS with or without oral corticosteroids.

Oral Corticosteroid Reduction

In study 75, mepolizumab treatment resulted in a significant reduction in OCS use. The baseline mean OCS (mg) use was similar in the two treatment groups 13.2 mg in the placebo group and 12.4 in the mepolizumab group. The OCS reduction results are shown in Table 5.

Table 5: Oral Corticosteroid Reduction – Study 75

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

Subjects treated with mepolizumab were able to achieve a greater percent reduction from baseline OCS dose while maintaining asthma control compared to subjects in the placebo arm. The frequency of exacerbations was evaluated in study 75 and showed a favorable trend for the mepolizumab treatment. However, this outcome was included in the study as an "other" endpoint without an adjustment for multiplicity.

Lung Function

Lung function was assessed as the primary efficacy outcome (peak expiratory flow) in the first mepolizumab clinical trial (study 006). This was a 12-week placebo-controlled trial in 362 subjects with asthma who were on a moderate dose of an inhaled corticosteroid and evidence of lung function impairment ($FEV_1 \geq 50\%$ and $\leq 80\%$ predicted) but without clinical or biomarker criteria likely to be indicative of eosinophilic airway inflammation, or a history of exacerbations. The mean eosinophil count at baseline was 366 cells/μL[17]. Subjects received mepolizumab 250 mg and 750 mg IV or placebo once every 4 weeks. The primary endpoint

[16] Study 006 CSR Table 13.8 page 278
[17] Note: Number listed by GSK in the proposed label is a geometric mean. The number 366 is taken from the CSR for study 006 Table 13.8

was the change from baseline of the mean morning domiciliary peak expiratory flow rate recorded in the seven days preceding Week 12. The change from baseline in trough FEV_1 was evaluated as a secondary endpoint. Neither the PEF, nor trough FEV_1 had a significant improvement despite a significant reduction in blood eosinophil counts.

In the severe asthma studies, change from baseline in pre-bronchodilator FEV_1 at Week 52 (study 97), at Week 32 (Study 88), and at week 24 (trial 75) were evaluated as secondary endpoints. In study 97 the change was 61 mL (CI -39,161) for the 75 mg IV dose compared to placebo at Week 52, 98 mL (CI: 11,184) in study 88 (at Week 32) for the 100 mg SC dose, and 114 mL (CI: -42, 271) from baseline at Week 24 in study 75. None of these changes were statistically significant indicating that mepolizumab does not have primary bronchodilator effects. The lung function results are captured in Table xx below (b) (4)

Table 6. Change from Baseline in FEV_1 (mL) in the Trials 06, 97, 88, and 75

	Difference from Placebo in mean Change from Baseline FEV_1 mL (95% CI)		
Trial	Week 12	Week 24	Weeks 32/52
06	-40 (-150,70)	NA	NA
97	10 (-87,108)	5 (-98, 108)	61 (-39, 161)
88	52 (-30,134)	76 (-6, 159)	98 (11, 184)
75	56 (-91, 203)	114 (-42, 271)	NA

Source: Dr. Robert Abugov's Statistical review pages 22 - 23

Patient-Reported Outcome measures

Health-related quality of life using the St Georges Respiratory Questionnaire (SGRQ) was assessed in studies 88 and 75. While SGRQ is used often in COPD development programs, its use in asthma programs is less frequent. However, the SGRQ was developed for use in both asthma and COPD and is also an acceptable instrument for asthma .[18] In both studies, the mepolizumab treatment group achieved an improvement in the total score that exceeded the Minimal Clinical Important Difference (MCID) of 4. In one of the studies (Study 88), the placebo group also achieved an improvement from baseline in the total score that exceeded the MCID of 4 points (9). The responder rate (% of subjects with an improvement of 4 or more) in study 88 was 71% and 68% for the mepolizumab 100 mg SC and 75 mg IV treatment arms respectively compared to 55% for the placebo group. For study 75 the responder rate for the mepolizumab 100 mg SC treatment arm was 58% compared to 41% for placebo. The Asthma Control Questionnaire (ACQ) was also assessed in the three studies. The responder analysis for study 97 showed a similar responder rate for the mepolizumab 75 mg IV treatment arm and placebo (47% compared to 50%). The overall trend for the ACQ for studies 88 and 75 was favorable for mepolizumab. The results for the SGRQ are displayed in Table 7 below (results for the mepolizumab 75 mg IV arm not shown).

[18] Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med 1991; 85 (Suppl B):25 -31*

Table 7. SGRQ Results Study 88 and 75

Study	Treatment (n)	Mean Baseline	Diff from placebo (95% CI)	% with improvement of ≥4	Odds ratio (95% CI)
88	M 100 SC (n=194)	47.7	-7 (-10.2, -3.8)	71%	2.07 (1.33, 3.22)
	Placebo (n =191)	47.2		55%	
75	M 100 SC (n = 69)	50.1	-5.8 (-10.6, -1.0)	58%	1.91 (0.95, 3.82)
	Placebo (n =66)	44.5		41%	
Source: GSK response to IR dated June 22, 2015					

8. Safety

In addition to the safety data from the placebo-controlled efficacy studies outlined in Table1, additional long term safety data are available from two ongoing open label studies with mepolizumab. Study MEA115666 (n =347) is an open-label extension (OLE) of study 97 and study MEA115661 (n=651) is an open-label extension of studies 88 and 75. The dose of mepolizumab in both OLE studies is the dose proposed for marketing (100 mg SC every 4 weeks). While the safety database is relatively small compared to databases of other asthma development programs, it is a reasonable size database considering that this program is not designed to support the full spectrum of asthma severity but rather, a subpopulation of asthmatics.

Along with the usual safety assessments in clinical studies such as adverse event recording, vital signs, physical examination, and clinical laboratory measures, GSK implemented a prospective cardiovascular monitoring strategy in studies 88 and 75 to evaluate for potential cardiovascular signals. This intensive monitoring was driven by the observation of an imbalance in serious adverse events in the cardiovascular system class (SOC) in the high dose (intravenous) mepolizumab group in study 97. The cardiovascular monitoring strategy included an Independent data Monitoring Committee and external adjudication panel to review the cardiovascular safety. In addition, given that the product is a biologic for injection, events of special interest such as hypersensitivity reactions, anaphylaxis, local site reactions, opportunistic infections, malignancies, and immunogenicity were assessed throughout the development program.

Deaths, SAEs, dropouts and discontinuations

There were a total of five (5) deaths reported in the controlled efficacy and safety studies and three (3) deaths to date in the ongoing OLE studies. The number of deaths in the controlled studies is unusual as the occurrence of deaths in an asthma development program is rarely seen. In the controlled studies two of the deaths were in placebo-treated subjects, 2 occurred in the mepolizumab 250 mg IV group, and one occurred in the 750 mepolizumab IV group. There does not appear to be any relationship with mepolizumab, nevertheless, the number of deaths is unusual for an asthma program. [Refer to Dr. Sofia Chaudhry's primary clinical review Section 7.3.1 for narratives].

Events leading to dropouts and discontinuations did not raise any new safety concerns. There were no safety concerns for a cardiovascular safety signal from the intense cardiovascular safety monitoring.

Common Adverse Events

Common adverse events (occurring in ≥ 3% of subjects in a given treatment group) that were seen in the mepolizumab 100 mg SC treatment group included headache, injection site reaction, back pain, fatigue, influenza, urinary tract infection, abdominal pain upper, pruritus, eczema, and muscle spasms. There was no dose response observed for these common adverse events and data from the ongoing OLE studies through the October 27, 2014 safety cutoff date, and with the 120-day safety update do not raise any new concerns.

Adverse Events of special interest, Malignancies, Laboratory findings and Immunogenicity

There was an increase in local injection site reactions in the mepolizumab 100 mg SC treatment group compared to placebo in the controlled clinical studies database. Hypersensitivity reactions [exposure adjusted values] were higher for the 250 mg and 750 mg IV mepolizumab dose compared to placebo. For the 100 mg SC dose, (the dose proposed for marketing) hypersensitivity reactions occurred at a lower frequency compared to placebo. There was one potential case of anaphylaxis but this case is confounded by a prior history of sulfite allergy and exposure to sulfite.

Herpes zoster was the only opportunistic infection reported in more than one subject and reported both in the controlled studies and the ongoing open label extension studies. In addition, 3 reports of esophageal candidiasis were reported in the open label studies through the October 27, 2014 cutoff date. The development program excluded patients with parasitic disease and because eosinophils play a role in the clearance of helminthic infections, patients with pre-existing parasitic infections should be treated prior to starting therapy with mepolizumab. There was one report of parasitic gastroenteritis in one subject receiving mepolizumab 100 mg SC in Study 88, but no cases of parasitic infection has been reported from the open label extension studies through the safety cutoff date.

There were no treatment-related imbalances in malignancies in the controlled studies (3 malignancies in placebo-treated subjects and 2 in mepolizumab-treated subjects). Up to the safety cutoff date, a total of 10 malignancies have been reported but these cases are not suggestive of a malignancy signal for mepolizumab.

Other than the expected decrease in blood eosinophils, there were no concerning findings in the laboratory measures and immunogenicity assessments did not raise any safety concerns.

9. Advisory Committee Meeting

This application was discussed at the Pulmonary, Allergy Drugs advisory committee meeting on June 11, 2015. There were no major safety signals or disagreements with the efficacy

findings between the Division and GSK. The major discussion points at the meeting focused on the role of eosinophil counts in determining initiation of treatment with mepolizumab, the adequacy of the data in adolescents, and the overall risk-benefit assessment to support approval. The committee was advised that the exact wording of the indication statement was undergoing review and will be worked out between the Agency and GSK. The Agency was interested in the Committee's opinion on the concepts to be captured in the Indication statement in the label. The committee voted unanimously (14 yes, 0 no) to approve mepolizumab for adults and voted against approval (4 yes, 10 no) in adolescents 12 to 17 years primarily because of the limited number of adolescent subjects in the development program. However, committee members also stated that there was no compelling evidence that 12 – 17 year olds would respond any differently than adults to mepolizumab. Of note, while there was no major safety or efficacy concern, the majority of the committee members felt that the limited data could not adequately address safety and efficacy in the younger population. Regarding the role of blood eosinophils, the committee endorsed the concept that higher eosinophil counts were predictive of greater benefits. However, there were questions about the use of poorly documented historical values of eosinophil counts to select study subjects.

10. Pediatrics

The pediatric development program for mepolizumab was discussed at the Pediatric Review Committee on three separate occasions. The first two meetings occurred during the development program February 5, 2014 (initial Pediatric Study Plan [iPSP] discussion), and June 11, 2014 (agreed iPSP discussion). The agreed iPSP was communicated to GSK by letter on June 12, 2014.

The third PERC meeting discussion occurred during the BLA review on August 5, 2015 (PREA discussion). The agreed iPSP included a waiver for pediatric 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 – 17 years of age in the adult development program. The severe subset of asthma patients targeted for treatment with mepolizumab is very 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.[19] 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 is reasonable.

The inclusion of pediatric patients in the adult asthma studies prior to completion of the adult program was discussed at the very first PERC meeting. There was the theoretical concern of the unknown potential safety risk of a new biologic being used in children prior to completion of the adult program. The division allayed concerns by pointing out that there was already a

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

reasonable amount of safety data available with this molecule, and other molecules in the same class. Further, there had not been any concerning safety signal observed with this molecule. PERC agreed with the Division's approach to include the adolescent population in the adult development program.

(b) (4)

Safety and PK data to support dose selection would be required to support extending the indication to the 6 to 11 year old population. The PREA requirements were discussed at the PERC meeting on August 5, 2015. The Division proposed that the pediatric requirement was fulfilled for the 12 to 17 year old population and the committee agreed.

A total of 28 adolescent subjects 12 -17 years of age were included in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 88). The demographic and asthma characteristics of the adolescent subjects were similar to the characteristics of the overall population except (as expected) that the duration of asthma was shorter in adolescent subjects (see Table 3). Subset analysis showed a reduction in the rate of exacerbations in adolescents that favored mepolizumab. The point estimate for the reduction in exacerbation rate was similar for the adolescents and the adults although the confidence intervals were wide. There were no safety signals of concern in the adolescents and the overall safety profile was similar to that of the adult population.

For the 6 to 11 year old population, PERC revisited the current agreed upon iPSP that included a safety, PK, and pharmacodynamic study in patients 6 to 11 years of age to evaluate the appropriate dose of mepolizumab that would provide a similar reduction in blood eosinophil (pharmacodynamic endpoint), and collect pharmacokinetic and safety information. The study as currently designed is of 12 weeks treatment duration with dosing of mepolizumab SC (b) (4) (weight-based dosing) (b) (4) The degree of asthma severity for the 6 to 11 year old population is along the same spectrum of disease severity for the adolescent and adult population. In order to be enrolled in the study, subjects must have a diagnosis of severe asthma (as defined by national and international guidelines, i.e. NIH, GINA etc.) for at least 12 months prior to Visit 1 (Screening). These patients must have a well-documented requirement for regular treatment with inhaled corticosteroids (≥ 400 mcg/day of fluticasone propionate (DPI) or equivalent) with or without maintenance oral corticosteroids in the 12 months prior to

Visit 1 and be on current treatment with an additional controller medication for at least 3 months or have a documented failure in the past 12 months of an additional controller medication for at least 3 successive months (e.g. LABAs, theophylline, or leukotriene receptor antagonist), and demonstrate persistent airflow obstruction at either Visit 1 (Screening) or Visit 2. These patients must also meet criteria indicative of eosinophilic airway inflammation that is related to asthma defined by GSK as elevated peripheral blood eosinophil count of ≥

300 cells/µL in the past 12 months OR peripheral blood eosinophil count of ≥ 150 cells/µL at Visit 1 (Screening).[20] Although the study was part of the agreed upon iPSP, the committee noted the lack of long term exposure data in the 6 to 11 year old population and recommended that the sponsor obtain long term safety exposure data in this age group.

In summary, PERC agreed that the pediatric assessment for the 12 -17 year olds was fulfilled, and concurred with the deferral of pediatric assessment for the 6 to 11 year olds, and the waiver for children less than 6 years of age. In communication received from GSK on September 18th in response to the Agency Information Request regarding the PREA PMR, GSK will revise the current safety and PK/PD study in the 6 to 11 year old patients to add a 12-month open label safety extension for patients completing the 12-week portion of the study. This proposal appears reasonable to address PERC's concerns regarding the lack of long term safety data in patients 6 to 11 years of age.

I note the primary reviewer Dr. Sofia's Chaudhry recommendation for additional studies in the 12 – 17 year old population prior to approval. I do not agree with this recommendation as the (b) (4) and the safety findings in the 12 to 17 year old adolescents do not raise any particular safety concerns.

11. Other Relevant Regulatory Issues

Inspections

Two clinical sites were chosen for inspection as they were the largest sites for enrollment in the U.S. The final OSI reports for site #099254 (Johns Hopkins University, Baltimore, MD – study 88) and site #067912 (IPS Research Company, Oklahoma City, OK – study 97) found that the sites adhered to the statutory requirements and FDA regulations and that the data are valid and accurate.

Compliance with Good Clinical Practices

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each complete study report.

Financial Disclosures

GSK provided a list of clinical investigators in the BLA. There were 4 investigators with disclosable financial interests/arrangements as defined in 21 CFR 54.2(a). None of the investigators had proprietary interest in mepolizumab. The 4 investigators with disclosable information recruited a very small sample (< 1%) of the total study population and it is unlikely that any misconduct would impact the study results.

[20] Study protocol submitted to BB-IND 006971

12. Labeling

Proprietary Name

The proposed proprietary name NUCALA has been reviewed and deemed acceptable.

Physician Labeling

The labeling is under review and the substantially complete package insert has been sent to OPDP and OSE. Labeling discussions with GSK are ongoing and there are several labeling issues that need to be resolved. One specific area of labeling that needs internal resolution is regarding representation of the (b) (4) (b) (4) for further discussion. Additionally, the Indication statement will need to be revised (see section 13 Recommendations/Risk Benefit). In our preliminary labeling comments to GSK the Warning/Precaution "opportunistic infections" was added because of the occurrence of herpes zoster infections in the program and in the open label extension studies. (b) (4) In the controlled clinical studies 2 cases of herpes zoster were reported (in adults) who were treated with mepolizumab 100 mg SC compared to no cases in placebo and 5 cases of herpes zoster were reported in the ongoing open label extension studies. (b) (4) Dr. Timothy Robison, pharmacology/toxicology team leader reviewed the available literature that discusses the clinical and preclinical data on this topic and concludes that there is biological plausibility that eosinophils could potentially be involved in the host response to viruses such as Herpes zoster. I concur with Dr. Robison's assessment and "opportunistic infections" will remain as a Warning/Precaution in the label. Please refer to Dr. Timothy Robison's addendum review for further details.

Carton and Immediate Container Labels

The carton and container labeling reviews are ongoing at this time.

Patient Labeling and Medication Guide

There is no need for a REMS or a Medication Guide for this product as there are no major safety signals. GSK included a patient information leaflet and the review is ongoing at this time.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend that NUCALA® (mepolizumab) be approved for use in asthma patients 12 years of age and older. The recommended approved dose and dosing regimen is 100 mg by

subcutaneous administration once every four weeks by a healthcare professional. I recommend that the indication statement be revised from the original proposed.

As noted in the Introduction, GSK's proposed indication statement with the original BLA submission, included a severe asthma population defined as having "severe "eosinophilic asthma" identified by blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/μL in the past 12 months." This statement implies that the term "eosinophilic asthma" and the blood eosinophilic cutoffs for identification are well defined. However, this is not the case. The term "eosinophilic asthma" is not uniformly defined in the academic community and varied blood eosinophil cutoffs have been used when referring to this asthma subtype, and other non-invasive measures (i.e. sputum eosinophils) are also used to define this asthma phenotype.[21] Additionally, GSK's historical eosinophil criterion of 300 cells/ μL in the previous 12 months is problematic for multiple reasons. GSK's submission does not provide substantiation that the historical eosinophil value of 300 cells/μL was obtained in a reliable manner. In fact, in response to a question at the Advisory Committee meeting regarding how this information was captured in the development program, GSK acknowledged the limitation of the database and indicated that information regarding historical eosinophil counts was collected by subject queries. Furthermore, the reliability of a single blood eosinophil count has been questioned in the literature because of the known variability of blood eosinophil counts throughout the day in the same patient.[22]

For these reasons, it would be unacceptable to use the terminology "eosinophilic asthma" in an indication statement in labeling as this would be inconsistent with the labeling regulations. The Indications and Usage section codified at 21 CFR 201.57 (c) (2) states: "This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a *recognized disease or condition*." (Emphasis supplied). Consistent with the understanding that "eosinophilic asthma" is not a uniformly recognized disease or condition, the tenth revision of the International Classification of Diseases (ICD-10) that will replace ICD-9 in October 2015 for physician billing and coding does not include the term "eosinophilic asthma" in the classification of asthma. In ICD-10 asthma is classified as "mild intermittent," "mild persistent," "moderate persistent," or "severe persistent."

I recommend that the Indication statement be revised as follows:

FROM: NUCALA® is indicated for add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/μL in the past 12 months. NUCALA has been shown to reduce exacerbations of asthma in patients with an exacerbation history.

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[21] Lemière C, Ernst Pierre et. al Airway inflammation assessed by invasive and noninvasive means in severe asthma: Eosinophilic and noneosinophilic phenotypes. *J Allergy clin Immunol 2006; 118: 1033-9*
[22] Sheldon Laurence Spector and Ricardo Antonio Tan. Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?" *Journal of Asthma, 2012; 49 (8): 807-810*

TO: NUCALA® is indicated for the add-on maintenance treatment of patients with asthma aged 12 years and older [redacted] (b) (4)

- Risk Benefit Assessment

The submitted data show consistent effect for reduction in exacerbations in a severe persistent asthma population enriched with elevated blood eosinophil levels and with a history of frequent exacerbations despite high dose inhaled corticosteroids and other controller therapies. In addition, the data show that a significant number of subjects who were on continuous oral corticosteroids were able to reduce their dose of OCS. Time to first exacerbation, and exacerbations due to hospitalization and/or ER visits all show a favorable trend with mepolizumab treatment and the patient-reported outcome measures SGRQ and the ACQ showed an overall positive trend. Mepolizumab has demonstrated clinically meaningful efficacy in a severe asthma population with a favorable risk-benefit profile. Patients with severe uncontrolled asthma are more likely to experience frequent asthma exacerbations and hospitalizations because of asthma. Thus the availability of safe and effective asthma therapies targeted to this subpopulation of asthmatics is an important therapeutic advance towards improving clinical outcomes in these patients.

- Recommendation for Postmarketing Risk Management Activities
  None

- Recommendation for other Postmarketing Study requirements

GSK has proposed a voluntary pregnancy registry for NUCALA®. [redacted] (b) (4) . GSK's proposal for the pregnancy registry is reasonable, but there is no compelling reason that the Agency would have asked for a pregnancy registry. The Pediatric and Maternal Health staff (PMHS) made a recommendation that the registry be made a part of a post-marketing commitment so that FDA can track the study and periodically review the outcomes. However, because a pregnancy registry would be considered a safety study it would need to be a PMR based on the PMR/PMC guidance. Given that we do not have safety concerns regarding pregnancy and we would not have otherwise been having this discussion if GSK had not proposed a voluntary registry, there is no need to accept this PMHS recommendation.

PREA-Required Studies
There will be two PREA-required studies in children 6 to 11 years of age with severe asthma as follows:

PMR#1: Conduct a 12 week, randomized, open-label, pharmacokinetic and pharmacodynamic study of mepolizumab in pediatric patients with asthma 6 to 11 years of age (Part A of Study 200363)

Final Protocol Submission:	January 2015 (BBIND 006971) November 2015 (BLA 125-526 and BBIND 006971)
Study Completion:	September 2017
Final Report Submission:	September 2019

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

Final protocol submission date:	November 2015
Study completion date:	March 2019
Final Report submission date:	September 2019

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/s/

LYDIA I GILBERT MCCLAIN
09/23/2015