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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name Mepolizumab
Trade Name Nucala
Therapeutic Class Anti-IL-5 monoclonal antibody
Applicant GlaxoSmithKline

Formulation(s) Lyophilized powder for reconstitution
Dosing Regimen Subcutaneous injection every 4 weeks
Indication(s) Add-on maintenance treatment of severe asthma
Intended Population(s) Asthma

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action from a clinical perspective for mepolizumab 100 mg subcutaneous dosed every 4 weeks is Approval for use in patients in 18 years of age and older and a Complete Response for use in adolescents age 12 to 17 years of age.

1.2 Risk Benefit Assessment

GlaxoSmithKline (GSK) has submitted a Biologics Licensing Application (BLA) for Nucala® in support of mepolizumab, a first-in-class, anti-interleukin 5 monoclonal antibody (anti-IL-5), as a treatment for severe asthma. The dose proposed for marketing is 100 mg subcutaneous every 4 weeks. The proposed indication limits use of the product as “add-on maintenance therapy in patients 12 years of age and older with severe eosinophilic asthma as identified by blood eosinophils ≥ 150 cells/ μ L at initiation of treatment or ≥ 300 cells/ μ L in the past 12 months. Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history.”

Three pivotal efficacy and safety studies have been submitted by GSK in support of this application. These include a 52-week dose-ranging and exacerbation study (Study 97), a 32-week exacerbation study (Study 88) and a steroid reduction study (Study 75). All three studies enrolled a population of severe asthmatics consistent with the criteria outlined in the recently published ATS/ERS Severe Asthma Guidelines¹. The populations were further enriched for patients with evidence of “airway eosinophilic inflammation”, although it is notable that the criteria used to identify eosinophilic inflammation differed between the two exacerbation studies. In Study 97, multiple inclusion criteria² were used to identify these patients, while Studies 88 and 75 utilized specific peripheral blood eosinophil thresholds of ≥ 150 cells/ μ L at the time of treatment initiation or ≥ 300 cells/ μ L in the past 12 months.

The primary endpoint for the exacerbation studies, the annualized rate of asthma exacerbations, used an exacerbation definition that corresponds to a clinically meaningful treatment effect and is consistent with ATS/ERS criteria outlining the

¹ Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.

² Peripheral blood eosinophil count ≥ 300 cells/ μ L in past 12 months, sputum eosinophil count $> 3\%$, FENO > 50 , or rapid loss of asthma control following 50% reduction in steroid dose.

definition of asthma exacerbations for clinical trials³. The primary endpoint in Study 75 evaluated the reduction in oral corticosteroid dose without loss of asthma control.

The 100 mg subcutaneous (SC) dose and route proposed for marketing are supported by the lack of differential dose-response seen in Study 97, similar treatment effects of the 75 mg IV and 100 mg SC dose in Study 88 and supporting PK/PD IV to SC bridging data from Study 92.

Efficacy of the product is supported by data from the two exacerbation studies, both of which demonstrate a statistically significant decrease of approximately 1 exacerbation per year for all evaluated mepolizumab doses beyond that provided by maximum standard of care (placebo group). The oral steroid reduction study provides additional efficacy support for the 100 mg SC dose by demonstrating a statistically significant reduction in oral corticosteroid dose compared to placebo without loss of asthma control.

The safety database for the product is primarily composed of data from the three efficacy and safety studies in addition to longer-term safety data provided by two open-label extension studies. Lingering concerns remain over mepolizumab use and the risk of parasitic disease; however, these concerns can be addressed through a post marketing requirement study. No other major safety signals have emerged from a review of the safety data.

Overall this clinical development program has demonstrated an appropriate risk benefit to support approval of mepolizumab 100 mg SC every four weeks in adult patients with a history of exacerbations despite therapy with high-dose ICS plus an additional controller with or without additional oral corticosteroid treatment who also have applicable peripheral blood eosinophil counts.

While efficacy and safety of the product have been adequately evaluated and demonstrated in an adult population, only limited data in 28 subjects are available in adolescent patients 12 to 17 years of age. In light of the limited data and the unknown relevance of this severe asthma phenotype associated with eosinophilic inflammation in the pediatric population, this review is recommending a complete response for the 12 to 17 year old age range with further pediatric evaluation as PREA PMRs (see Section 1.4 of this review).

³ Reddel, Helen K., et al. "An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice." *American journal of respiratory and critical care medicine* 180.1 (2009): 59-99.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS are recommended for this BLA.

1.4 Recommendations for Postmarket Requirements and Commitments

Discussions regarding Postmarket Requirements (PMR) and Commitments (PMC) remain ongoing at the time of this review.

Lingering concerns remain regarding the risk of parasitic disease with mepolizumab use given the anti-IL-5 effects of this biologic. Given this concern and the prior precedent of requesting a post-marketing study to address this concern for anti-IgE therapy in asthma, this review recommends a PMR in parasitic disease.

In addition, this review recommends additional evaluation in the pediatric population which should be completed as PMRs. While the limited adolescent data in the current clinical program provide preliminary efficacy and safety information, the limited nature of the data do not allow for conclusions to be made regarding the safety and efficacy of the product in this age group⁴. It is further recommended that additional evaluation in patients younger than 12 years of age be outlined as a PMR, but this study should not commence until the adolescent data has been completed and reviewed. Should it be determined that the data are insufficient to support use in the adolescent population, studies in the younger pediatric population may be released.

2 Introduction and Regulatory Background

2.1 Product Information

Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) targeting interleukin-5 (IL-5) and is produced by recombinant DNA technology in Chinese hamster ovary cells.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no treatments specifically approved for the treatment of severe asthma with characteristic peripheral blood eosinophil levels in the United States. However, oral

⁴ Additional analyses of the pediatric data are pending from the sponsor at the time of this review. Recommendations may be altered based on these data.

corticosteroids are typically used in clinical practice to treat asthma refractory to approved therapies.

The majority of approved therapies carry a broad indication statement for the treatment of asthma with the recommended clinical use of the products further outlined in clinical treatment guidelines. However, the approved indication for omalizumab deviates from this standard. Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. Recommended use of omalizumab in the current step-wise treatment approach in clinical practice is further delineated in the clinical treatment guidelines.

2.3 Availability of Proposed Active Ingredient in the United States

To date, mepolizumab has not been approved in the United States or anywhere else in the world.

2.4 Important Safety Issues With Consideration to Related Drugs

Mepolizumab is the first monoclonal antibody targeting IL-5 being evaluated for BLA approval so there are no related products for comparison. As an immunomodulatory monoclonal antibody targeting IL-5, evaluation of systemic and local injection site reactions, neoplasms, and opportunistic infections are of particular interest in this development program. In addition, an imbalance in cardiac Serious Adverse Events (SAEs) was seen in the Phase 2b dose-ranging study (Study 97) prompting the sponsor to include cardiovascular safety in its Adverse Events of Special Interest (AESI). Each of these AESIs is discussed further in Section 6.3.4 of this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Summary of Key Presubmission Regulatory Activities

Date	Interaction	Division Comments:
January 15, 2014	Pre-BLA	<ul style="list-style-type: none">- The adequacy of data supporting the 100 mg SC dose, including bridging information for the 100 mg SC to 75 mg IV dose will be a review issue.- Justification for the proposed restriction of mepolizumab to a subset of asthma patients will be expected. The Division recommends including any data from negative studies in a wider asthmatic population.- The BLA submission and proposed labeling will need to address the potential impact of mepolizumab on underlying

Date	Interaction	Division Comments:
May 4, 2012	EOP2	<p>parasitic disease. A PMR may be required.</p> <p>- The clinical program should define a patient population that can be clearly described in the product label and readily identified in the real-world.</p> <ul style="list-style-type: none"> • Using inclusion criteria based on the ATS Severe Asthma workshop is reasonable; however, concerns were raised regarding the real-world applicability of the specific criteria used to define eosinophilic inflammation. • The clinical program will need to justify the restriction of mepolizumab to a subset of asthma patients. Information from other asthma populations will assist in the risk-benefit assessment and may be included in product labeling to assist clinicians in selecting appropriate patients. • The Division expressed concern regarding defining a phenotype based on a single serum eosinophil measurement and noted that repeat measurements over time may be more reliable. <p>- The clinical program should address the appropriate duration of therapy, i.e. when to discontinue treatment if a reduction in exacerbations has been achieved.</p> <p>- The definition of asthma exacerbation is reasonable.</p> <p>- The current clinical program will not demonstrate a comparative efficacy or safety benefit over corticosteroids.</p>
April 21, 2009	Type B Advice meeting	<p>- The Division agreed that recent published data suggests an asthma population that may benefit from treatment; however, the targeted patient population for the development program was unclear. The Division recommended evaluating mepolizumab in a range of asthma severity.</p> <p>- The range of proposed doses appears reasonable for the dose-ranging study.</p> <p>- The Division agrees with the evaluation of exacerbation data in addition to lung function data; however, the exacerbation definition should incorporate objective measures to account for variability in the exacerbation</p>

Date	Interaction	Division Comments:
		identification. - Proposed Phase 2b dose-ranging study may serve as a pivotal study if the studied population reflects the intended target population. - If the targeted population is defined in part by sputum eosinophil measurements, data to support and validate the sputum eosinophil measurement will be expected.
February 23, 2006	Advice meeting	- A clinical development program should include adequate and well-controlled trials in patients with less severe forms of asthma to address whether the product is safe and effective in this population.
February 24, 1997	IND safe to proceed	IND opened

2.6 Other Relevant Background Information

Clinical Background: Severe Asthma

Asthma is a chronic inflammatory disorder of the airways, the diagnosis and management of which are outlined in several consensus documents (National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma⁵ [NAEPP EPR3 report] and the Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, 2013⁶ [GINA guidelines]).

While the majority of patients are successfully managed with a step-wise treatment approach, a subset of patients remains uncontrolled despite maximal medical management. Initial efforts to establish criteria defining a “severe refractory asthma” phenotype were published in 1999/2000^{7,8} with updated guidelines defining a “severe

⁵ National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. August 2007. NIH publication no. 07-4051.

⁶ Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2013. Website accessed April 28, 2015: <http://www.ginasthma.org/>.

⁷ Chung KF, et al. “Difficult/therapy resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy Resistant Asthma. European Respiratory Society” Eur Respir J 1999; 13(5): 1198-1208.

⁸ “Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions.” American Thoracic Society. Am J Respir Crit Care Med 2000; 162(6): 2341-2351.

asthma” phenotype published more recently (International ERS/ATS Severe Asthma guidelines⁹).

The International ERS/ATS guidelines define severe asthma as patients with a confirmed asthma diagnosis which requires treatments with high dose inhaled corticosteroids (ICS) plus LABA or leukotriene modifier/theophylline¹⁰ therapy to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy. Additionally, the guidelines outline that patients who do not meet the aforementioned criteria, but whose asthma worsens when corticosteroids are tapered, also meet the definition of severe asthma.

In these guidelines, “uncontrolled asthma” is defined as meeting any of the four following criteria:

- Poor symptom control: ACQ consistently > 1.5 or ACT < 20 (or “not well controlled” by NAEPF or GINA guidelines) over 3 months of evaluation
- Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year
- Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
- Airflow limitation: FEV1 <80% predicated (in the presence of a reduced FEV1/FVC) with both short- and long-acting bronchodilators withheld

Beyond categorizing asthma by severity, there is an active body of research working to identify additional asthma phenotypes and endotypes using various biomarkers. One approach was conducted by the Severe Asthma Research Program (SARP) which employed statistical modeling to identify asthma clusters. While 5 subgroups were identified, overlap between the groups was seen with respect to identifying biomarkers¹¹. This overlap exemplifies the heterogeneity seen within asthma and difficulties with further sub-classification of the disease. While alternative approaches have been outlined in the academic literature, to date, there are no consensus guidelines outlining the identification or management of specific severe asthma subgroups.

3 Ethics and Good Clinical Practices

⁹ Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-373.

¹⁰ and/or systemic corticosteroids for ≥ 50% of the previous year

¹¹ Moore et al “Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program” *Am. J. of Respiratory and Cri Car Med*; Vol 181.4 (2010):315-323.

3.1 Submission Quality and Integrity

This BLA was appropriately indexed and complete to permit review. Two clinical sites were chosen for inspection as they were largest sites for enrollment in the United States.

Table 2: Sites Identified for OSI Audit

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site # 067912 Jeremy Cole, MD IPS Research Company 1111 North Lee, Suite 400 Oklahoma City, OK 405 2358188 (main #) jcole@ipsresearch.com	MEA112997	10	Clinically significant exacerbations
Site# 099254 Mark Liu, MD John Hopkins University 5501 Hopkins Bayview Circle Baltimore, MD 21224 410 550 2505 (main #) mcl@jhmi.edu	MEA115588	9	Clinically significant exacerbations

Final OSI reports for Site #099254 and Site #067912 found that these sites adhered to the statutory requirements and FDA regulations and that the data are valid and accurate.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each complete study report.

3.3 Financial Disclosures

A financial disclosure checklist is attached in the appendix of this review. As each investigator contributed only a limited number of subjects for each study, the overall contribution of each site to the totality of the data from this program is small. Any potential for improper conduct at each site would be unlikely to affect the efficacy or safety outcomes of this BLA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Mepolizumab will be supplied as a sterile, preservative-free, lyophilized powder for reconstitution and SC injection in cartons of 1 single-use glass vials with a rubber stopper (not made with natural rubber latex) and a flip-off seal. Each 10-ml vial contains 100 mg of mepolizumab. It is a sterile, lyophilized powder for injection. Following reconstitution with Sterile Water for Injection, USP, each single-use vial will deliver 100 mg/ml mepolizumab in 1 mL, 160 mg/mL sucrose, 7.14 mg/mL sodium phosphate dibasic heptahydrate, and 0.67 mg/mL polysorbate 80, with a pH of 7.0.

The CMC recommendations for this application remain pending at the time of this clinical review.

4.2 Clinical Microbiology

The final CMC recommendations for this application remain pending at the time of this clinical review.

4.3 Preclinical Pharmacology/Toxicology

Preliminary recommendations from the nonclinical team are for Approval of this BLA; however, final recommendations are pending at the time of this review. Details of the nonclinical pharmacology toxicology information can be found in the nonclinical review by Dr. Tim Robison.

In summary, long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab, nor has the mutagenic potential been evaluated. However, no evidence of defective tumor surveillance is seen in IL-5 deficient mice or eosinophil-deficient mice. IV and SC administration of mepolizumab in monkey was associated with prolonged reductions in peripheral and lung eosinophil counts, with no associated toxicity.

4.4 Clinical Pharmacology

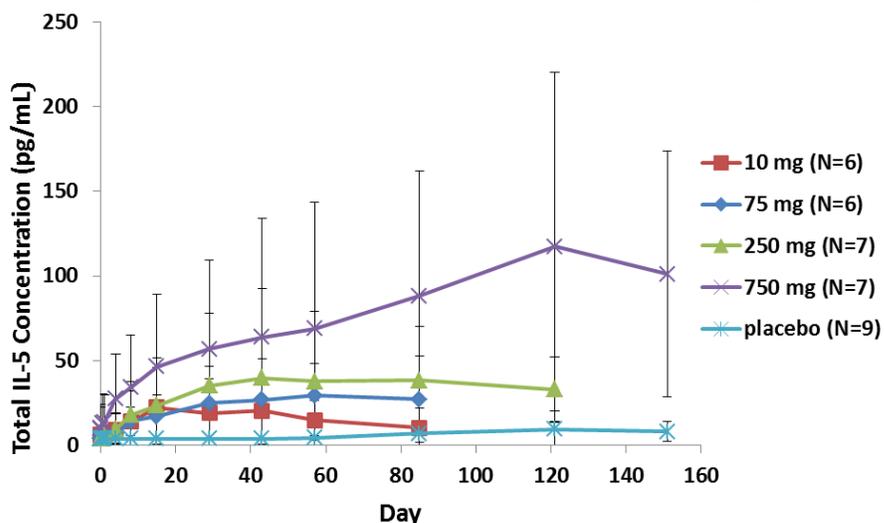
4.4.1 Mechanism of Action

Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) targeting interleukin-5 (IL-5). IL-5 is a cytokine important in the growth, differentiation, recruitment, activation and survival of eosinophils. Mepolizumab binds to the alpha chain of the IL-5 receptor complex on eosinophil cells surfaces and blocks the binding of IL-5 to the receptor, thus inhibiting IL-5 signaling. Multiple cell types, including eosinophils, are involved in asthmatic inflammation.

4.4.2 Pharmacodynamics

In a single-dose study in healthy Japanese males, mepolizumab treatment demonstrated an increase in total serum IL-5 levels in a dose-dependent fashion. Total IL-5 levels were largely unchanged in the placebo group, and free IL-5 levels were essentially undetectable with or without mepolizumab treatment (Figure 1).

Figure 1: Mean (\pm SE) serum total IL-5 concentrations in healthy Japanese males: Study 05

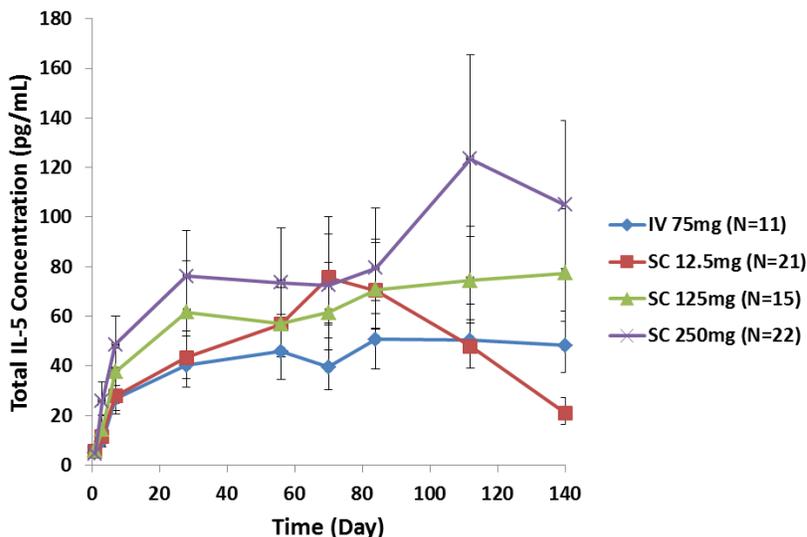


Source: Clinical Pharmacology Briefing Document Figure 4

To support its proposed subcutaneous dosing, the sponsor conducted a pharmacokinetic/pharmacodynamic (PK/PD) IV to SC study (Study 92), a multicenter, open-label, dose-ranging study to determine the PK and PD of mepolizumab administered intravenously or subcutaneously to adult asthmatic subjects with elevated blood eosinophil levels. Subjects were randomized to one of four treatment arms: 12.5 mg SC, 125 mg SC, 250 mg SC or 75 mg IV. Each treatment was administered every 4 weeks for a total of 3 doses. Blood samples for safety, PD, PK, biomarkers and immunogenicity analyses were assessed. A total of 66 subjects completed the study.

In Study 92, an increase in total IL-5 levels was seen following mepolizumab treatment; however, a dose-response relationship was not clearly demonstrated. This study did not include a placebo arm (Figure 2).

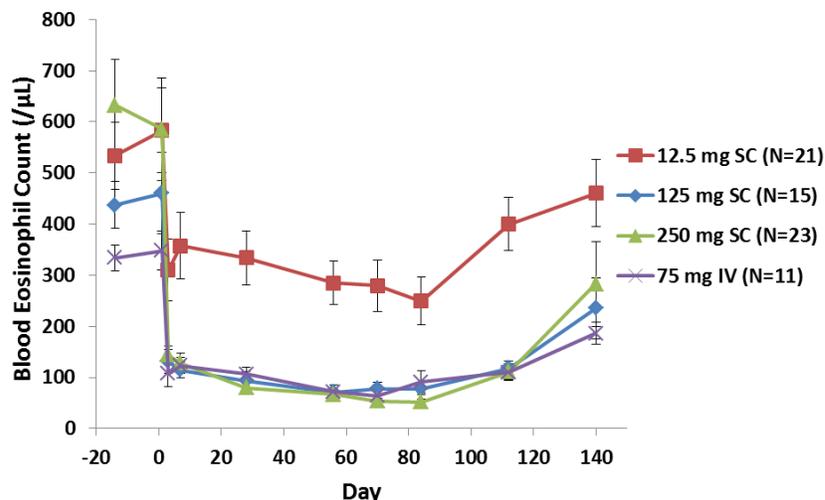
Figure 2: Mean (\pm SE) serum total IL-5 concentrations: Study 92



Source: Clinical Pharmacology Briefing Document: Figure 5

A reduction was seen in blood eosinophil levels in a dose dependent fashion with greater treatment effect noted for doses > 12.5 mg SC every 4 weeks (Figure 3).

Figure 3: Mean (\pm SE) absolute blood eosinophil counts over time: Study 92

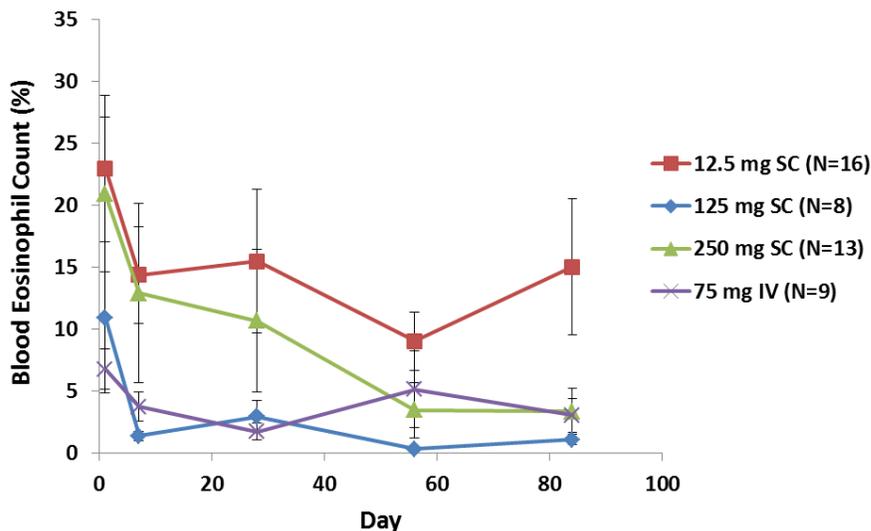


Source: Clinical Pharmacology Briefing Document: Figure 1

There was a general trend towards a reduction in sputum eosinophil counts following mepolizumab treatment in Study 92 (Figure 4). However, the sputum eosinophil counts

(%) at baseline (pre-dose on Day 1) were not balanced between four active treatment groups. The largest decrease from baseline was observed in the mepolizumab 250 mg SC groups, with smaller decreases in the mepolizumab 12.5 mg SC group.

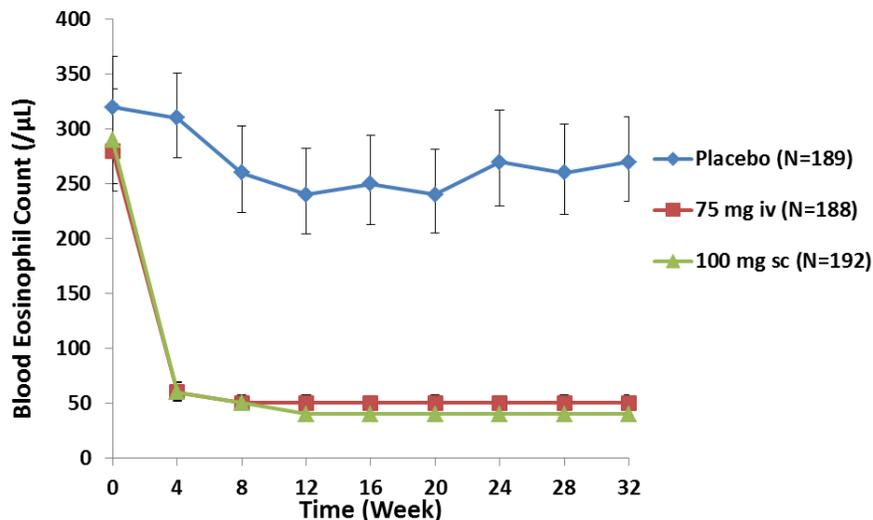
Figure 4: Mean (\pm SE) sputum eosinophil counts (%) over time: Study 92



Source: Clinical Pharmacology Briefing Document: Figure 3

In Study 88, following 100 mg SC mepolizumab treatment every four weeks for 32 weeks, blood eosinophils demonstrated an 86% decrease from baseline for mepolizumab treated subjects compared to a 16% decrease by placebo. The plateau phase of blood eosinophil reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period (Figure 5).

Figure 5: Mean (\pm SE) absolute blood eosinophil counts over time: Study 88



Source: Clinical Pharmacology Briefing Document: Figure 2

4.4.3 Pharmacokinetics

Dose-proportional pharmacokinetics are seen following SC doses of 12.5 to 250 mg. Following SC administration mepolizumab was absorbed with a median time to reach maximal plasma concentration (T_{max}) of 4 to 8 days with an absolute bioavailability of 64%, 71%, and 75% for the abdomen, thigh or arm of healthy subjects. A 2-fold accumulation at steady state was seen following repeat SC administration every 4 weeks. The mean volume of distribution was 55 to 85 mL/kg. This humanized IgG1 monoclonal antibody is degraded by proteolytic enzymes widely distributed in the body. The mean systemic clearance for a single IV administration ranged from 1.9 to 3.3 mL/day/kg and a mean terminal $\frac{1}{2}$ life of approximately 20 days. Following SC administration, the mean terminal $\frac{1}{2}$ life ranged from 16 to 22 days, with an estimated systemic clearance of 3.1 mL/day/kg demonstrated by population pharmacokinetic analysis.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Key clinical studies

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
Pivotal Efficacy and Safety Studies							
MEA112997 (Study 97) <i>Nov 2009 to Dec 2011</i>	MC, R, DB, PC, PG,	52 weeks	severe asthma with eosinophilic inflammation*	153 152 156 155	Mepo 75 IV Mepo 250 IV Mepo 750 IV Placebo IV	Annualized rate asthma exacerbation	81 centers in 13 countries ¹ <i>US: n = 78(13%)</i>
MEA115588 (Study 88) <i>Oct 2012 to Jan 2014</i>	MC, R, DB, DD, PC, PG,	32 weeks	severe asthma with eosinophilic inflammation*	194 191 191	Mepo 100 SC Mepo 75 IV Placebo	Annualized rate asthma exacerbation	119 centers in 16 countries ² <i>US: n= 67 (12%)</i>
MEA115575 (Study 75) <i>Oct 2012 to Dec 2013</i>	MC, R, PC, PG,	24 weeks	severe asthma with eosinophilic inflammation*	69 66	Mepo 100 SC Placebo	Reduction in steroid dose while maintaining asthma control	38 centers in 10 countries ³ <i>US: n = 7 (5%)</i>
Long-term Safety Studies							
MEA115666 (Study 66) <i>Sept 2012 –</i>	OLE	~ 3.5 years <i>ongoing at time of submissio n</i>	Subjects from Study 97 12 month break	347	100 mg SC	Safety	65 centers in 13 countries ⁴ <i>US: n = 30 (9%)</i>
MEA115661 (Study 61) <i>May 2013 --</i>	OLE	52 weeks <i>ongoing at time of submissio n</i>	Subjects from Studies 88 & 75 No break in treatment	651	100 mg SC	Safety	139 centers in 19 countries ⁵ <i>US: n = 66 (10%)</i>
Supplemental Studies							

Clinical Review
Sofia Chaudhry, MD
BLA 125526
NUCALA (mepolizumab)

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
MEA114092 (Study 92) <i>Feb 2011 to Sept 2014</i>	R, OL, IV to SC bridging study	12 weeks	Asthmatics	21 15 23 11	Mepo 12.5 SC Mepo 125 SC Mepo 250 SC Mepo 75 IV	PK/PD	11 centers in 4 countries ⁶ US: n = 5 (7%)
SB- 240563/006 (Study 06) <i>Feb 1999 to Oct 1999</i>	MC, R, DB, PC, PG	12 weeks	≥ 18 – 55 year old asthmatics - FEV1 ≥ 50% and ≤ 80% - On ICS controller therapy - No exacerbation requirement - No eosinophil inflammation requirement	120 116 126	Mepo 250 IV Mepo 750 IV Placebo	peak expiratory flow	55 centers in 5 countries ⁷ US: n = 211 (58%)

Study	Design	Duration	Population	N	Treatment Arms	Primary Efficacy Assessment	Study Sites (US subjects)
<p>* Additional enrichment criteria identified by the sponsor as indicative of airway eosinophilic inflammation. See Table 3 for the specific enrichment criteria used in each study.</p> <p>¹ Argentina (4), Australia (5), Canada (5), Chile (4), France (5), Germany (9), Korea (2), Poland (5), Romania (5), Russian Federation (8), UK (5), Ukraine (7), United States (17)</p> <p>² Argentina (7), Australia (3), Belgium (4), Canada (10), Chile (3), France (8), Germany (10), Italy (8), Japan (18), Republic of Korea (11), Mexico (1), Russian Federation (4), Spain (5), Ukraine (5), United Kingdom (5), and USA (18)</p> <p>³ Germany (8), France (5), Czech Republic (5), USA (5), United Kingdom (4), Australia (3), Canada (3), Netherlands (2), Poland (2), Mexico (1)</p> <p>⁴ United States (19), Japan (18), Germany (12), Canada (11), France (11), Korea (10), Italy (8), Argentina (7), United Kingdom (5), Czech Republic (5), Spain (5), Australia (4), Belgium (4), Russian Federation (4), Ukraine (4), Chile (3), Mexico (2), Netherlands (2), Poland (2)</p> <p>⁵ United States (11), Germany (8), Russian Federation (7), Australia (5), Romania (4), Ukraine (5), United Kingdom (5), Argentina (4), Canada (4), Chile (4), France (4), Korea (2), Poland (2)</p> <p>⁶ United States (1), Germany (4), Estonia (2), France (3)</p> <p>⁷ United States (30), France (10), Germany (9), Netherlands (2), UK (4)</p> <p>MC = multi-center, R = randomized, PC = placebo-controlled, PG = parallel-group, OLE= open label extension, OL = open-label; PK = pharmacokinetic, PD = pharmacodynamic, yo= years old, mepo = mepolizumab, IV = intravenous, SC = subcutaneous</p>							

Table 4: Key inclusion criteria from pivotal efficacy studies: Studies 97, 88, 75

	Study 97	Study 88	Study 75
Baseline asthma therapy	High dose ICS + controlled therapy ± oral corticosteroids		High dose ICS + controller + oral corticosteroids
Exacerbation history	≥ 2 exacerbations/year		No exacerbation history requirement
Eosinophilic airway inflammation criteria	<ul style="list-style-type: none"> • Serum eos ≥ 300 or • Sputum eos ≥ 3% or • FENO ≥ 50 ppb or • Loss of asthma control after a ≤ 25% reduction in ICS/OCS 	<ul style="list-style-type: none"> • Serum eos ≥ 150 at screening or • Serum eos ≥ 300 in past 12 months 	<ul style="list-style-type: none"> • Serum eos ≥ 150 at screening or • Serum eos ≥ 300 in past 12 months
ICS = inhaled corticosteroid, eos = eosinophil, FENO = Fractional exhaled Nitric Oxide, OCS = oral corticosteroids			

5.2 Review Strategy

The key studies from the applicant's BLA for mepolizumab discussed in this review are outlined in Table 3. Key efficacy studies include Study 97, a pivotal dose-ranging and exacerbation efficacy study, Study 88, a second exacerbation study, and Study 75, a steroid-reduction study. Supplemental data are drawn from Study 06, an earlier, lung function study in less severe asthmatics that failed to demonstrate a treatment effect, and Study 92, a PK/PD, IV to SC bridging study. The safety database is composed of data from the three pivotal efficacy studies and supplemented by two, open-label extension studies providing longer-term safety data, Studies 61 and 66.

The targeted patient population for mepolizumab has continued to evolve over the course of its clinical development program. An early study, Study 06, in less severe asthma failed to demonstrate a beneficial impact on lung function¹² (see Sections 5.17 and 6.5.2 of this document). However, further evaluation in an investigator-sponsored study of mepolizumab in 61 patients with a history of 2 exacerbations requiring oral steroids and elevated sputum eosinophil counts > 3% on at least occasions in the previous 2 years provided initial evidence that mepolizumab decreased the number exacerbations in a more selective patient population¹³.

Based on these data, the applicant conducted Study 97, a 52-week exacerbation and dose-ranging study in severe asthma further enriched for subjects with evidence of eosinophilic inflammation. In this study eosinophilic inflammation was defined using multiple biomarkers, including peripheral blood eosinophil counts, sputum eosinophilia, elevated Fractional exhaled Nitric Oxide (FENO), or loss of asthma control with reduction in corticosteroid dosing. Based on the positive results from Study 97, the applicant conducted a second exacerbation study, Study 88, and a steroid reduction study, Study 75, both of which further used criteria defining eosinophilic inflammation that was further refined (see Table 4 for an overview of the inclusion criteria for the pivotal efficacy studies).

¹² Flood-Page, Patrick, et al. "A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma." *American journal of respiratory and critical care medicine* 176.

¹³ Haldar, Pranabashis, et al. "Mepolizumab and exacerbations of refractory eosinophilic asthma." *New England Journal of Medicine* 360.10 (2009): 973-984.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study MEA112997: Phase 2 Dose Finding Study (Study 97)

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma

Study Centers: Eighty-one centers in 13 countries: Argentina (4), Australia (5), Canada (5), Chile (4), France (5), Germany (9), Korea (2), Poland (5), Romania (5), Russian Federation (8), UK (5), Ukraine (7), United States (17)

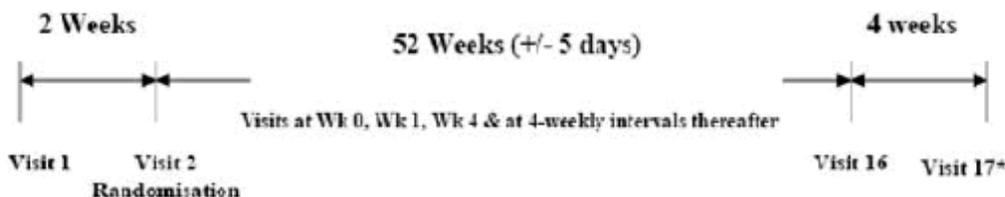
Study Dates: November 9, 2009 – December 5, 2011

Study Design

The study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the effect of mepolizumab on exacerbation rates in adult and adolescent subjects ≥ 12 years of age with asthma requiring treatment with high dose ICS for the prior 12 months (with or without corticosteroids) plus an additional controller medication (LABA, LTRA, or theophylline). Subjects were also required to meet at least one of several criteria the sponsor selected as biomarkers that may be indicative of eosinophilic inflammation.

Following an initial screening visit, subjects underwent a 2-week run-in period during which the subject's maintenance asthma medications remained unchanged. Subjects were randomized (stratified by maintenance oral corticosteroid use) to one of four treatment groups in a 1:1:1:1 fashion at the randomization visit (Visit 2). Treatment arms, given in addition to stable background therapy, included: mepolizumab 75 mg IV, 250 mg IV, 750 mg IV, or placebo. Treatment was administered every four weeks for 48 weeks providing for 52 weeks of treatment. Following a four-week safety follow-up period, subjects attended a follow-up visit at Visit 17 and returned to the clinic to provide a blood sample 24 weeks after the last dose of study medication for immunogenicity testing.

Figure 6: Study 97 Schematic



Source: Study 97 CSR Figure 1

The primary efficacy endpoint was the rate of exacerbations defined by the following criteria:

- Worsening of asthma which in the investigator's opinion requires use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For subjects on maintenance oral corticosteroids, an exacerbation requiring oral corticosteroids was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days.

In attempt to standardize the clinical decision defining an exacerbation, the investigator was instructed to take into account changes from baseline in one or more of the following parameters recorded in the subject's e-Diary:

- A decrease in morning peak flow
- An increase in the use of rescue medication
- Increases in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use
- An increase in overall asthma symptom score

Study Population

The inclusion/exclusion criteria for this study allowed for enrollment of subjects with severe refractory asthma ≥ 12 years of age with documented asthma requiring treatment with high dose ICS with or without maintenance oral corticosteroids in the prior 12 months plus an additional controller medication. Subjects had to have a history of ≥ 2 exacerbations requiring treatment with systemic corticosteroids in the prior 12 months and were further required to meet criteria the sponsor had chosen to indicate evidence of eosinophilic airway inflammation.

Of note, there was no requirement that patients be symptomatic on background therapy as assessed by a daily asthma symptom assessment during the 2-week run-in period. The key inclusion, exclusion, and randomization criteria for the study are outlined below.

Key Inclusion Criteria

- Male or female non-smoking subjects ≥ 12 years of age with a minimum weight of 45 kg
- Evidence of asthma as documented by:
 - Airway reversibility ($FEV_1 \geq 12\%$ and 200 ml) at Visit 1 or Visit 2 or documented in the previous 12 months OR

- Airway hyperresponsiveness (PC_{20} of < 8 mg/ml or $PD_{20} < 7.8$ μ mol methacholine/histamine) documented in past 12 months OR
- Airflow variability in clinic $FEV_1 \geq 20\%$ between two consecutive clinic visit documented in the 12 months prior to Visit 1 (FEV_1 recorded during an exacerbation will not be valid) OR
- Airflow variability as indicated by $> 20\%$ diurnal variability in peak flow observed on ≥ 3 days during run-in
- Clinical features of severe refractory asthma similar to those outlined in the ATS Workshop on Refractory Asthma¹⁴ for ≥ 12 months prior to Visit 1 and mandated by meeting the following inclusion criteria
 - Treatment with high dose ICS (with or without oral corticosteroids) in the 12 months prior to Visit 1
 - Treatment with an additional controller medication (LABA, LTRA, or theophylline) in the 12 months prior to Visit 1
 - Persistent airflow obstruction with pre-bronchodilator $FEV_1 < 80\%$ at Visit 1 or Visit 2 or peak flow diurnal variability of $> 20\%$ on 3 or more days during run-in
 - History of ≥ 2 exacerbations requiring treatment with oral corticosteroids in the prior 12 months despite use of high-dose ICS and additional controller medications. For patients receiving maintenance OCS with high-dose ICS plus controller, the OCS treatment for exacerbation must be a two-fold or greater increase in dose of OCS.
- Airway inflammation likely to be eosinophilic in nature
 - Elevated peripheral blood eosinophil count ≥ 300 cells/ μ L OR
 - Sputum eosinophil $\geq 3\%$ OR
 - Fractional exhaled Nitric Oxide ≥ 50 ppb (performed at Visit 1 or Visit 2 pre randomization) OR
 - Prompt deterioration of asthma control following a $\leq 25\%$ reduction in regular maintenance dose of inhaled or oral corticosteroid dose in previous 12 months

Key Exclusion criteria

- Current smokers or subjects with smoking history ≥ 10 pack years
- Clinically important lung conditions other than asthma
- Subjects who have received Xolair or any other biological for the treatment of inflammatory disease within 130 days of Visit 1
- Regular use of oral or systemic corticosteroids for diseases other than asthma within the past 12 months
- Subjects with parasitic infection within 6 months of Visit 1

¹⁴ "Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions." American Thoracic Society. Am J Respir Crit Care Med 2000; 162(6): 2341-2351.

- Subjects with clinically significant cardiovascular, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematologic, or any other system abnormalities that are uncontrolled with standard treatment

Key Randomization Criteria Following Run-in

- No changes in asthma medication (excluding rescue salbutamol/albuterol MDI provided at Visit 1) during run-in
- No respiratory tract infection that led to a change in asthma management and no exacerbations during run-in (defined as worsening asthma requiring systemic corticosteroids and/or ER visit or hospitalization)

Investigational Treatment

- Mepolizumab 75 mg IV
- Mepolizumab 250 mg IV
- Mepolizumab 750 mg IV
- Matching IV placebo

Withdrawal Criteria

- Investigator/subject discretion
- Meeting specific ECG or LFT withdrawal criteria

Study Assessments

The timing of the key efficacy and safety assessments evaluated in this study are summarized in Table 5.

Table 5: Key efficacy and safety assessments: Study 97

	Screen/ run-in	Random- ization	Treatment				Early with- drawal	End of Therapy	F/U
Visit	1	2	3	4	5- 14	15		16	17
Week	-2 ± 2d	0	1±2 d	4±5 d	8- 44	48± 5d		52±5d	56±5 d
Efficacy									
Exacerbation review		X	x	x	x	x	x	x	
Spirometry	x	X	x	x	x	x	x	x	
ACQ		X		x	x	x	x	x	
eDiary data review (PEF, symptoms)		X	x	x	x	x	x	x	
Safety									
Concomitant meds	x	X	x	x	x	x	x	x	
PE	x						x	x	

	Screen/ run-in	Random -ization	Treatment				Early with- drawal	End of Therapy	F/U
VS	x	X	x	x	x	x	x	x	
12-lead ECG	x				x		x		x
AE		X	x	x	x	x	x	x	x
SAE	x	X	x	x	x	x	x	x	x
Laboratory									
Hematology	x	X		x	x	x	x	x	x
Chemistry	x	X		x	x	x	x	x	
UA	x			x	x	x	x	x	
Blood eosinophils	x	X		x	x	x	x	x	x
Immunogenicity		X			x	x	x		x
Source: Study 97 Protocol Table 3									

Efficacy Endpoints:

Primary Efficacy Endpoint

- Frequency of exacerbations defined by worsening of asthma which in the investigators opinion required oral/systemic corticosteroids¹⁵ and/or hospitalization and/or ED visit

Secondary Efficacy Endpoints

- Time to first clinically significant exacerbation
- Frequency of exacerbations requiring hospitalization (including intubation and admittance to an intensive care unit) or ED visit
- Frequency of Investigator-defined exacerbations
- Time to first Investigator-defined exacerbation
- Mean change from baseline in clinic pre-bronchodilator FEV1 over the 52-week treatment period
- Mean change from baseline in clinic post-bronchodilator FEV1 over the 52-week treatment period
- Mean change from baseline in Asthma Control Questionnaire (ACQ) score
- Time to first exacerbation requiring hospitalization or ED visit

¹⁵ For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

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 awakening due to asthma symptoms requiring rescue medication use
- Increase in overall asthma symptom score

Pre-specified Statistical Methods

Exacerbation rates were analyzed using a generalized linear model with negative binomial distribution having independent factors treatment, OCS usage at baseline, region, number of exacerbations in year prior to study, and baseline disease severity (% predicted FEV1). The planned offset was logarithm of time followed for exacerbations. Type I error across doses for the rate of exacerbations, the primary endpoint was controlled by first testing for a linear trend across doses, including placebo and following with tests of each dose versus placebo only if the overall trend was significant. Control of type I error across doses in the secondary endpoints was achieved with a truncated Hochberg procedure. Endpoints were tested in the hierarchical order listed below.

1. Rate of exacerbations
2. FEV1 pre-bronchodilator at week 52
3. AQLQ at week 52
4. Rate of exacerbations requiring hospitalizations or emergency department visits
5. ACQ-6 at week 52

4.1.2 Study MEA115588: Phase 3 Exacerbation Study (Study 88)

Title: A randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma

Study Centers: A total of 119 centers in 16 countries randomized and treated subjects: Argentina (7), Australia (3), Belgium (4), Canada (10), Chile (3), France (8), Germany (10), Italy (8), Japan (18), Republic of Korea (11), Mexico (1), Russian Federation (4), Spain (5), Ukraine (5), United Kingdom (5), and USA (18).

Study Dates: October 2, 2012- January 18, 2014

Study 88 was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study in a severe asthma population enriched for markers the sponsor has identified as indicative of eosinophilic inflammation. While similarly designed to Study 97, there were several key differences in the study design which are outlined below.

Similar to Study 97, the targeted study population in Study 88 included adults and adolescents 12 years of age and older with severe asthma defined by use of high dose ICS therapy plus an additional controller therapy who experienced ≥ 2 exacerbations in the prior year requiring treatment with systemic corticosteroids. However, in contrast to Study 97, Study 88 relied on different criteria to enrich for evidence of eosinophilic inflammation. In this case, the sponsor enrolled subjects with a peripheral blood value \geq

300 cells/ μ L in the prior 12 months or an elevated peripheral blood eosinophil count \geq 150 cells/ μ L at Visit 1 (screening) related to asthma.

The same primary endpoint used in Study 97, the annual rate of exacerbations, was used in this study; except the study had a shorter treatment period of 32 weeks compared to the 52 weeks evaluated in Study 97. The study also evaluated both a 75 mg IV and 100 mg SC mepolizumab doses in addition to matching placebo.

Pre-specified Statistical Methods

Exacerbation rates were analyzed using a generalized linear model with negative binomial distribution having independent factors treatment, OCS usage at baseline, region, number of exacerbations in year prior to study, and baseline disease severity (% predicted FEV1). The planned offset was logarithm of time followed for exacerbations.

Type I error over multiple doses and endpoints was controlled using a truncated Hochberg procedure conducted at the one-sided 0.025 level of significance. Significance for an endpoint was declared if both doses compared to placebo were significant at the unadjusted 0.025 level or if at least one dose compared to placebo was significant at the unadjusted 0.0125 level. If both of the dose comparisons to placebo for an endpoint were significant at the one-sided unadjusted 0.025 level, then the next endpoint in the hierarchy provided below was tested. The gamma parameter for the Hochberg procedure was 1:

1. Exacerbation rate
2. Rate of exacerbations requiring hospitalization or ED visit
3. Rate of exacerbations requiring hospitalization
4. Δ Trough FEV1 W32
5. Δ SGRQ at W32

4.1.3 Study MEA115575: Steroid Reduction Study (Study 75)

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects with Severe Refractory Asthma

Study Centers: 38 centers in 10 countries: Germany (8), France (5), Czech Republic (5), USA (5), United Kingdom (4), Australia (3), Canada (3), Netherlands (2), Poland (2), Mexico (1)

Study Dates: October 29, 2012 – December 12, 2013

Study Design:

The study was a multicenter, randomized (stratified by previous oral corticosteroid use of less or more than 5 years), placebo-controlled, double-blind, parallel-group designed study with a 24-week treatment period. With the exception of oral corticosteroid dose titration, all subjects remained on their existing maintenance asthma therapy throughout the duration of the study. The study included 4 study periods which are outlined below:

1. Oral corticosteroid optimization phase used to titrate a subject to the lowest oral corticosteroid dose that maintained control of their symptoms (3- 10 weeks duration): A recommended dose titration schedule was provided, but not required, for use by investigators (Table 6).
2. Induction phase (4 weeks duration): Subjects received their first dose of blinded investigational treatment and remained on their optimized oral corticosteroid dose.
3. Oral corticosteroid reduction phase (16 weeks duration): 5 doses of investigational product were administered during this phase. Investigators were provided with recommended OCS dose titration schedule and assessed subjects for dose reduction every 4 weeks (Table 7).
4. Maintenance (4 weeks duration): No further oral corticosteroid dose adjustments were made during this phase. Subjects who met eligibility criteria were offered enrollment in a 12-month open-label extension study (Study 61).

Table 6: Optimization phase OCS dose titration schedule

Sequential Time Course	Prednisone/prednisolone Optimisation Phase								
	Oral Corticosteroid Dose (mg/day)								
Visit 2 starting dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1 st dose reduction (Visit 2)	30.0	25.0	20.0	15.0	12.5	10.0	7.5	5.0	5.0
+ 1 Week	25.0	20.0	15.0	12.5	10.0	7.5	5.0		
+ 1 Week	20.0	15.0	12.5	10.0	7.5	5.0			
+ 1 Week	15.0	12.5	10.0	7.5	5.0				
+ 1 Week	12.5	10.0	7.5	5.0					
+ 1 Week	10.0	7.5	5.0						
+ 1 Week	7.5	5.0							
+1 Week	5.0								

Source: Study 75 Protocol Table 1

A suggested OCS tapering schedule (Table 7) was provided to study sites for OCS reduction unless one or more of the following occurred:

- Mean AM peak PEF < 80% of the baseline stability limit
- Mean asthma-related night time awakenings > 50% increase over the baseline period (per night), > 150% of the baseline mean
- Rescue medication use requiring ≥ 4 puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or ≥ 12 puffs of any one day in the prior week

- Change in ACQ5 $\geq +0.5$ from the prior months OCS dose assessment
- Symptoms of adrenal insufficiency

Table 7: Reduction phase OCS titration schedule: Study 75

Sequential Time Course	Prednisone/Prednisolone Reduction Phase								
	Oral Corticosteroid Dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10.0	7.5	5.0
1 st dose reduction	25.0	20.0	15.0	10.0	10.0	10.0	5.0	5.0	2.5
+ 4 Weeks	15.0	10.0	10.0	5.0	5.0	5.0	2.5	2.5	1.25
+ 4 Weeks	10.0	5.0	5.0	2.5	2.5	2.5	1.25	1.25	0
+ 4 Weeks	5.0	2.5	2.5	1.25	1.25	1.25	0	0	0
+ 4 Weeks	2.5	2.5	2.5	0	0	0	0	0	0

1. *Subject taking 1.25mg/day should take this as 2.5mg administered every other day

Source: Study 75 Protocol Table 2

Study Population

The inclusion/exclusion criteria allowed for enrollment of subjects ≥ 12 years of age with asthma with a documented requirement for regular treatment with maintenance systemic corticosteroids (5 to 35 mg/day prednisone or equivalent) and high-dose-ICS in the 6 months prior to screening. Subjects also had to be receiving current treatment with an additional controller medication for at least 3 months or have documentation of failure with an additional controller medication for at least 3 consecutive months during the prior 12 months and demonstrate evidence of asthma and persistent airflow obstruction. As with Studies 97 and 88, the sponsor further enriched the population with markers it believes are indicative of airway eosinophilic inflammation. The eosinophilic inflammation enrichment criteria were the same as those outlined in Study 88 and required subjects to have a history of an elevated peripheral blood eosinophil count ≥ 300 cells/ μ L related to asthma within the previous 12 months or a peripheral blood eosinophil count ≥ 150 cells/ μ L at screening Visit 1. In this study, subjects had to achieve a stable dose of OCS, defined as 2 weeks on the same OCS dose between 5 and 35 mg/day of OCS, during the optimization period. Subjects were not required to have an exacerbation history.

Investigational Treatment

- Mepolizumab 100 mg SC every 4 weeks
- Matching placebo

Efficacy Endpoints

Primary

- Percent reduction of OCS dose during weeks 20-24 compared to baseline dose, while maintaining asthma control

Secondary (with no correction for multiple endpoints)

- Proportion of subjects who achieve a 50% reduction or greater in their daily OCS dose, compared to baseline dose, during weeks 20-24 while maintaining asthma control
- The proportion of subjects who achieve a reduction of their daily OCS dose to less than or equal 5 mg during weeks 20-24, while maintaining asthma control
- The proportion of subjects who achieve a total reduction of OCS dose during weeks 20-24, while maintaining asthma control
- Median percentage reduction from baseline in daily OCS dose during weeks 20-24 while maintaining asthma control

Notably, the annualized rate of exacerbations, FEV1, SGRQ and ACQ were evaluated as “other endpoints” in this study.

Pre-Specified Statistical Methods

Comparison of mepolizumab to placebo for percent reduction of daily prednisone dose while maintaining asthma control was analyzed using a proportional odds model with the following categories of percent reduction: 0%, >0% to <50%, 50% to <75%, 75% to 90%, and 90% to 100%. The model included independent variables treatment, number of years on OCS (< 5 years, ≥ 5 years), region, and baseline OCS dose.

4.2 Long-term Safety Studies

4.2.1 MEA115661 Open Label Extension for subjects enrolled in Studies 88 and 75 (Study 61)

- Title: A multi-center, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA115588 or MEA115575 studies
- Study Centers: 139 centers in 19 countries: United States (19), Japan (18), Germany (12), Canada (11), France (11), Korea (10), Italy (8), Argentina (7), United Kingdom (5), Czech Republic (5), Spain (5), Australia (4), Belgium (4), Russian Federation (4), Ukraine (4), Chile (3), Mexico (2), Netherlands (2), Poland (2)
- Study Dates: May 21, 2013 – on-going (interim report data cutoff date: Feb 28, 2014)

This study was a multicenter, open-label, long-term safety study of mepolizumab 100 mg SC every 4 weeks on continued background standard of care in subjects who completed Study 88 or study 75. The study was 52 weeks in duration and subjects with a history of life-threatening disease and a history of improved asthma disease control

while receiving mepolizumab are eligible for extended treatment in Study 201312, an open-label access study in patients from Study 61 with a history of life-threatening/seriously debilitating asthma who have demonstrated a positive mepolizumab treatment response. Data from Study 201312 were not available at the time of BLA submission and only limited safety data from this study were provided in the 120-day safety update.

4.2.2. MEA115666 Open Label Extension for subjects enrolled in Study 97 (Study 66)

Title: A multi-center, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997

Study Centers: 65 centers in 13 countries: United States (11), Germany (8), Russian Federation (7), Australia (5), Romania (4), Ukraine (5), United Kingdom (5), Argentina (4), Canada (4), Chile (4), France (4), Korea (2), Poland (2)

Study Dates: September 28, 2012 – on-going (interim report data cutoff date: Feb 28, 2014)

This study was a multicenter, open-label, long-term safety study of mepolizumab 100 mg SC every 4 weeks on continued background standard of care in subjects who completed Study 97. All enrolled subjects had a gap of at least 12 months from the last dose of double-blind study medication in Study 97 to enrollment in Study 66. Mepolizumab was dosed every 4 weeks until either: 1) the risk/benefit profile is no longer positive in the opinion of the investigator, 2) subject's physician withdraws the subject, 3) the subject withdraws consent, 4) sponsor discontinues development, 5) the sponsor discontinues the study in the relevant country, or 6) mepolizumab becomes commercially available in the relevant participating country.

6 Review of Efficacy

Efficacy Summary

The key efficacy studies in the mepolizumab clinical development program include a pivotal, 52-week, dose-ranging and exacerbation study (Study 97), a second, 32-week, exacerbation study (Study 88), and a steroid-reduction study (Study 75).

Studies 97 and 88 enrolled subjects with severe asthma on background ICS + controller therapy with a history of exacerbations and were further enriched with biomarkers the sponsor has identified as indicative of eosinophilic inflammation. Study 97 used the broadest criteria to identify these patients and included patients with elevated peripheral blood or sputum eosinophils, elevated FENO, or loss of control with reduction in steroid dosing. This study evaluated the annualized rate of exacerbations for three IV doses of mepolizumab against placebo: 75 mg IV, 250 mg IV, and 750 mg IV.

The sponsor subsequently included specific peripheral blood eosinophil cutoffs of ≥ 150 cells/ μ L at screening or history of counts ≥ 300 cells/ μ L into Study 88. Study 88 evaluated the annualized rate of exacerbations for mepolizumab 75 mg IV treatment and 100 mg SC against placebo. Study 75, an oral corticosteroid reduction study, used the same eosinophilic inflammation enrichment strategy and evaluated the effect of mepolizumab 100 mg SC against placebo on oral corticosteroid steroid dose reduction without loss of asthma control. Of note, this study did not require an exacerbation history, which is reasonable as subjects were maintained on chronic corticosteroids prior to enrolment.

The positive treatment effect with a lack of a dose-response seen in Study 97, along with the similar treatment response between the 75 mg IV and 100 mg SC treatment arms in Study 88 and data from the PK/PD Study 92 provides support for the 100 mg SC mepolizumab dose and route proposed for marketing.

Efficacy support for mepolizumab is provided by the two exacerbation studies, each of which demonstrated statistically significant reductions in exacerbations for all of the evaluated mepolizumab doses. Supplemental efficacy support for the 100 mg SC dose is provided by Study 75 which demonstrated a statistically significant reduction in oral corticosteroid dose without loss of asthma control for subjects treated with 100 mg SC compared to placebo.

In addition to the efficacy data from the pre-specified analyses of the total enrolled population, the Agency and sponsor conducted multiple exploratory analyses to gain a better understanding of the treatment modification effect by peripheral blood eosinophil counts. Such analyses were discussed with the sponsor at the end-of-phase 2 meeting, which included a discussion of selecting blood eosinophils as a likely predictive biomarker. Statistical methods for this purpose were discussed internally prior to marketing application submission. Overall, the data suggest a strong trend towards an improved treatment response with higher levels of peripheral blood eosinophil counts obtained in close proximity to treatment initiation. These exploratory data should be considered within the context of the inherent variability that is observed in peripheral blood eosinophil measurements over time due to unknown intrinsic factors within an individual and the imprecision in measurements. However, it should be noted that the

positive association is seen within the context of this variability, suggesting that the overall association may actually be higher than what is seen in the data.

Overall, this review finds that efficacy has been demonstrated for mepolizumab in the highly select patient population evaluated in its severe asthma program. While final labeling language remains a review issue, this review recommends approval in patients 18 years of age and older.

While the efficacy of the product is demonstrated in the overall targeted patient population, this review is recommending further PREA required studies in adolescents and younger pediatric patients (See Section 1.4). These issues were raised and discussed during the June 11, 2015 Pulmonary Allergy Drugs Advisory Committee Meeting and these recommendations are consistent with the panel's discussion and recommendation.

This review does not favor inclusion of the specific threshold values into the indication statement as the data from this single drug development program do not appear sufficient to clinically define a new severe asthma phenotype based on specific peripheral blood eosinophil thresholds and no corresponding major safety concerns have been identified that would support imposing a strict limitation of use. While gaps in the program exist in determining which patients would not benefit from treatment, the program has clearly identified a patient population that does benefit from treatment. To that end it is important, that an informative product label be written to assist clinician's use of the product. This can be accomplished using more general language in the indication statement with the specific eosinophil enrichment criteria used in this program outlined in Section 14 of the product label. This approach informs clinicians that asthma severity and peripheral blood eosinophil counts should be taken account when considering this therapy, but as clinical guidelines do not yet exist regarding the identification and management of specific subsets of severe asthma patients, this approach allows for use of the clinician's judgment in determining which of their patients may benefit. Ultimately, it is anticipated that the academic and practicing community will establish specific criteria to identify this new specific asthma phenotype; however this will likely be done when data from the multiple ongoing programs evaluating "eosinophilic asthma" are available. Additional discussion regarding the proposed product label for this product can be found in Section 9.2 of this review.

6.1 Indication

The current proposed indication for mepolizumab is for the add-on maintenance treatment of patients ages 12 years of age and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/ μ L at initiation of treatment or blood eosinophils greater than or equal to 300 cells/ μ L in the past 12

months. The indication statement further stipulates that mepolizumab has been shown to reduce exacerbations of asthma in patients with an exacerbation history.

6.1.1 Methods

This review focuses on the efficacy results from three pivotal efficacy and safety studies: Study 97, Study 88, and Study 75. Additional efficacy data from Study 06 are reviewed in Section 6.1.10 to provide contextual information regarding use of the product in a less severe asthma population. Details of the study designs for each of the pivotal studies can be found in Section 5, the study design for Study 06 is summarized in Section 6.1.10.

6.1.2 Demographics

Overall the age, gender, race and asthma severity were similar across treatment groups within each pivotal study. Subjects were more commonly female (59%) and White (85%) with a mean age of 49 years. The mean duration of asthma was 19 years, over 90% were taking ICS/LABAs, and 38% of subjects were taking maintenance OCS. Despite maximum standard of care therapy, over half the subjects had experienced ≥ 3 exacerbations in the prior year. The majority of subjects had never smoked (74%).

Overall, an underrepresentation of subjects of African Heritage and adolescents age 12 to 17 years old are evident in this development program. The enrollment of these subgroups relative to the US population and the efficacy data for these subgroups are discussed in Section 5.1.6.

Table 8: Baseline demographics and disease characteristics: Study 97

	Mepolizumab			
	Placebo IV N = 155	75 IV N = 153	250 IV N = 152	750 IV N = 156
Age (years)				
Mean (range)	46 (20-68)	50 (23-69)	49 (15-74)	49 (19-69)
Sex (n, %)				
Female	97(63)	104 (68)	93(61)	93 (60)
Male	58 (37)	49 (32)	59 (39)	63 (40)
Race (n,%)				
White	140 (90)	139 (91)	135 (89)	140 (90)
Asian	8 (5)	9 (6)	7 (5)	10 (6)
African Heritage	6 (4)	5 (3)	8 (5)	5 (3)
American Indian or Al. Native	0	0	0	1 (<1)
Native Hawaiian or	1(<1)	0	0	0

	Mepolizumab			
	Placebo IV N = 155	75 IV N = 153	250 IV N = 152	750 IV N = 156
Pacific Islander				
Other	0	0	2(1)	0
Ethnicity (n, %)				
Hispanic or Latino	16 (10)	15 (10)	14 (9)	16 (10)
Not Hispanic or Latino	139 (90)	138 (90)	138 (91)	140 (90)
Asthma Duration (n, %)				
≥ 1 to < 10 years	51	43	38	55
≥ 10 years to < 20 years	40	44	42	36
≥ 20 years	64	66	72	65
Post-bronchodilator % Predicated FEV1				
Mean	71.4	70.0	70.3	70.4
FEV1/FVC ratio (%)				
Mean	0.66	0.67	0.66	0.68
% reversibility (%)				
Mean	26.8	22.6	25.6	23.9
Smoking Status n (%)				
Never smoked	121 (78)	122 (80)	121(80)	119 (76)
Former smoker	34 (22)	31 (20)	31 (20)	37 (24)
Baseline Eosinophil Count, cells/μL (SD)				
Baseline	418 (372)	367 (350)	390 (435)	361 (310)

Source: Study 97 CSR Table 8, 5.15, 5.18, FDA Statistical Reviewer Analysis

Table 9: Baseline demographics and disease characteristics: Study 88

	Mepolizumab		
	Placebo N = 191	100 SC N = 194	75 IV N = 191
Age (years)			
Mean (range)	49(12-76)	51(12-81)	50(13-82)
Sex (n, %)			
Female	107(56)	116(60)	106(55)
Male	84 (44)	78 (40)	85 (45)
Race (n,%)			
White	148 (77)	152 (78)	151 (79)
Asian	38 (20)	34 (18)	33 (17)
African Heritage	3 (2)	7 (4)	6 (3)
Amer. Indian or Alaska Native	0	1 (<1)	0
Native Hawaiian or	0	0	0

	Mepolizumab		
	Placebo N = 191	100 SC N = 194	75 IV N = 191
Pacific Islander			
Other	2	0	1
Ethnicity (n, %)			
Hispanic or Latino	15 (8)	18 (9)	18 (9)
Not Hispanic or Latino	176 (92)	176 (91)	173 (91)
Asthma Duration (n, %)			
≥ 1 to < 10 years	47(25)	40(21)	52(27)
≥ 10 years to < 20 years	71(37)	61(31)	58(30)
≥ 20 years	73(38)	93(48)	81(42)
% predicated post-bronchodilator FEV1			
mean	72.3	69.9	70.5
FEV1/FVC ratio (%)			
mean	0.67	0.66	0.67
% reversibility FEV1 (%)			
mean	27.2	28.7	27.2
Smoking History (n, %)			
Never smoked	134 (70)	144 (74)	139 (73)
Former smoker	57 (30)	50 (26)	52 (27)
Eosinophil Inclusion Criteria, n (%)			
≥ 300 cells/μL	121 (63)	146 (75)	130 (68)
≥ 150 cells/μL	167 (87)	155 (80)	155 (81)
Exacerbations in prior year			
mean	3.6	3.8	3.5
Baseline Eosinophil Count, cells/μL (SD)			
mean	460 (450)	451 (437)	417 (399)

⁺ one subject in Korea was incorrectly noted as being Hispanic/Latino
Source: Study 88 CSR Tables 6, 7, 8, 9, FDA Statistical Reviewer Analysis

Table 10: Baseline demographics and disease characteristics: Study 75

	Placebo N = 66	Mepo 100 SC N = 69
Age (years)		
Mean (range)	50 (28-70)	50 (16-74)
Sex (n, %)		
Female	30 (45)	44 (64)
Male	36 (55)	25 (36)
Race (n,%)		

	Placebo N = 66	Mepo 100 SC N = 69
White	61 (92)	67 (97)
Asian	2 (3)	1 (1)
African Heritage	0	0
American Indian or Alaska Native	1 (2)	0
Native Hawaiian or Pacific Islander	1 (2)	0
Other	1 (2)	1 (1)
Ethnicity (n, %)		
Hispanic or Latino	3 (5)	2 (3)
Not Hispanic or Latino	63 (95)	67 (97)
Asthma Duration (n, %)		
≥ 1 to < 10 years	19 (29)	23 (33)
≥ 10 years to < 20 years	20 (30)	17 (25)
≥ 20 years	27 (41)	29 (42)
Post-bronchodilator % predicated FEV1		
mean	67.6	71.8
FEV1/FVC ratio (%)		
mean	0.64	0.67
% reversibility FEV1 (%)		
mean	23.7	24.9
Smoking History, (n, %)		
Never smoked	41 (62)	41 (59)
Former smoker	25 (38)	28 (41)
Duration of OCS use at baseline, n (%)		
<5 years	35 (53)	35 (51)
≥ 5 years	31 (47)	34 (49)
Daily OCS dose, (mg) at baseline		
Mean (range)	13 (5-35)	12 (5-35)
Eosinophil Inclusion Criteria, n (%)		
≥ 300 cells/μL within 12 months	42 (64)	50 (72)
≥ 150 cells/μL at Baseline	60 (91)	61 (88)
Exacerbations in Prior Year		
Mean	2.9	3.3
Baseline Eosinophil Count, cells/μL (SD)		
Mean	347 (303)	413 (386)

Source: Study 75 CSR Table 9, 10, 11, 12, 13, 5.21, FDA Statistical Reviewer Analysis

All subjects enrolled in the severe asthma studies were on concomitant asthma therapy prior to enrollment. As outlined in the protocols, all subjects were taking background high dose ICS in addition to other asthma controller therapies. In keeping with clinical practice, the majority were taking an ICS/LABA, with many taking an additional

controller medication (Table 11). Per the protocols, the background therapy was maintained throughout the run-in and treatment periods.

Table 11: Respiratory medications prior to run-in: Studies 97, 88, 75

	Placebo	Mepolizumab			
		100 SC	75 IV	250 IV	750 IV
Study 97					
Asthma Meds prior to run-in					
ICS + LABA alone	86 (55)	--	92 (60)	80 (53)	94 (60)
ICS + LABA + additional controller	63 (41)	--	50 (33)	61 (40)	57 (37)
ICS + non-LABA controller	1 (<1)	--	3 (2)	2 (1)	0
Study 88					
Asthma Meds Prior to run-in					
ICS + LABA alone	76 (40)	72 (37)	80 (42)	--	--
ICS + LABA + additional controller	110 (58)	119 (61)	102 (53)	--	--
ICS + non-LABA controller	1 (<1)	0	3 (2)	--	--
Study 75					
Asthma Meds Prior to run-in					
ICS + LABA alone	24 (36)	29(42)	--	--	--
ICS + LABA + additional controller	41 (62)	40 (58)	--	--	--
ICS + non-LABA controller	1(2)	0	--	--	--
Source: January 20, 2015 Response to Clinical Information Request Tables 1,2,3					

6.1.3 Subject Disposition

No imbalances in the rates of treatment withdrawal across treatment arms in each of the pivotal efficacy and safety studies are seen.

	Placebo	Mepolizumab			
		100 SC	75 IV	250 IV	750 IV
Study 97 n, (%)					
Randomized	155	--	153	152	156
Completed	127 (82)	--	129 (84)	131 (86)	133 (85)
Withdrawn	28 (18)	--	24 (16)	21 (14)	23 (15)
Adverse event ¹	6 (4)	--	5 (3)	8 (5)	9 (6)
Adverse event ²	5 (3)	--	4 (3)	7 (5)	8 (5)
Lab abnormality	1 (<1)	--	1 (<1)	1 (<1)	1 (<1)
Lack of efficacy	8 (5)	--	6 (4)	4 (3)	4 (3)
Protocol deviation	1 (<1)	--	1 (<1)	0 (0)	0 (0)
Lost to follow up	1 (<1)	--	1 (<1)	4 (3)	0 (0)

Investigator discretion	1 (<1)	--	3 (2)	3 (2)	3 (2)
Withdrew consent	11 (7)	--	8 (5)	2 (1)	7 (4)
Study 88					
Randomized	191	194	191	--	--
Completed	179 (94)	185 (95)	175 (92)	--	--
Withdrawn	12 (6)	9 (5)	16 (8)	--	--
Subject discretion	5 (3)	4 (2)	9 (5)	--	--
Adverse event	4 (2)	1 (<1)	0 (0)	--	--
Lack of efficacy	1 (<1)	2 (1)	1 (<1)	--	--
Lost to follow up	0 (0)	2 (1)	2 (1)	--	--
Protocol deviation	0 (0)	0 (0)	3 (2)	--	--
Physician discretion	2 (1)	0 (0)	1 (<1)	--	--
Study 75					
Randomized	66	69	--	--	--
Completed	62 (94)	66 (96)	--	--	--
Withdrawn	4 (6)	3 (4)	--	--	--
Adverse Event	3 (5)	3 (4)	--	--	--
Withdrew consent	1 (2)	0	--	--	--
¹ adverse event leading to permanent discontinuation of investigational product or withdrawal from study					
² subjects with "adverse event" as primary reason for withdrawal					
Source: FDA Statistical Reviewer Analysis					

Treatment Compliance

All IV and SC doses were administered within the study centers; therefore subject compliance with treatment is not in question. The table below summarizes the mean and median number of treatments administered for each treatment group within each study. No imbalances across treatment groups are noted.

Table 12: Number of treatments administered

	Placebo	Mepolizumab			
		100 SC	75 IV	250 IV	750 IV
Study 97					
Mean	11.6	--	11.8	12.0	11.8
Median	13	--	13	13	13
Study 88					
Mean	7.7	7.7	7.6	--	--
Median	8	8	8	--	--
Study 75					
Mean	5.9	5.8	--	--	--
Median	6	6	--	--	--

		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
Source: Study 97 CSR Table 9, Study 88 CSR Table 10, Study 75 CSR Table 15					

6.1.4 Analysis of Primary Endpoint(s)

6.1.4. Exacerbations: Studies 97, 88, 75¹⁶

The annualized rate of exacerbations was evaluated as the primary efficacy endpoint in Studies 97 and 88 and evaluated as an “other endpoint” in Study 75. This endpoint was not adjustment for multiplicity in Study 75 therefore results are nominally significant.

Both Studies 97 and 88 demonstrated a statistically significant reduction in exacerbations with similar effect sizes demonstrated in each study. A numeric reduction in exacerbations is also seen in mepolizumab treated subjects compared to placebo in Study 75 (Table 13).

No dose response is evident from the data in Study 97 and similar effect sizes are seen between IV and SC treatment arms in Study 88. Notably, Study 88 was the only pivotal exacerbation study to evaluate the direct effect of the subcutaneous dosing on the exacerbation rate. The effect size between the two routes of administration in Study 88, along with data from the OCS withdrawal study (Study 75) and the results of the PK/PD study (Study 92), provide support for the efficacy of the chosen dose for marketing.

Table 13: The annual rate of exacerbations for Studies 97, 88, 75

		Mepolizumab			
	Placebo	100 SC	75 IV	250 IV	750 IV
Study 97					
N	155	--	153	152	156
Exacerbation/year	2.40	--	1.24	1.46	1.15
Δ placebo	--	--	-1.16	-0.94	-1.24
p-value	--	--	<0.0001	0.0006	<0.0001
Study 88					
N	191	194	191	--	--
Exacerbation/year	1.75	0.81	0.93	--	--
Δ placebo	--	-0.92	-0.81	--	--
p-value	--	<0.0001	<0.0001	--	--
Study 75					
N	66	69	--	--	--

¹⁶ exacerbations were not evaluated as the primary endpoint in Study 75 but as an “other endpoint”

	Mepolizumab				
	Placebo	100 SC	75 IV	250 IV	750 IV
Exacerbation/year	2.12	1.44	--	--	--

Source: FDA Statistical Reviewer Analysis and Modifications of Study 75 CSR Table 28

Exploratory analyses of the exacerbation data by eosinophil count

As noted above, the sponsor's development program demonstrates a consistent, statistically significant treatment effect on exacerbations in a population of severe asthmatics with a history of exacerbations further enriched for evidence of eosinophilic inflammation.

This is in contrast to an initial proof-of-concept study evaluating a pilot formulation of mepolizumab in a broader population of asthmatics. Study 06, discussed in Section 5.1.7, failed to demonstrate a lung function benefit in less severe asthma, despite a reduction in blood eosinophils¹⁷. However, further evaluation in an investigator-sponsored study of mepolizumab in 61 patients with a history of at least 2 exacerbations requiring oral steroids and elevated sputum eosinophil counts > 3% on at least one occasion in the previous 2 years provided initial proof-of-concept support that mepolizumab decreased the number exacerbations in a more selective patient population¹⁸.

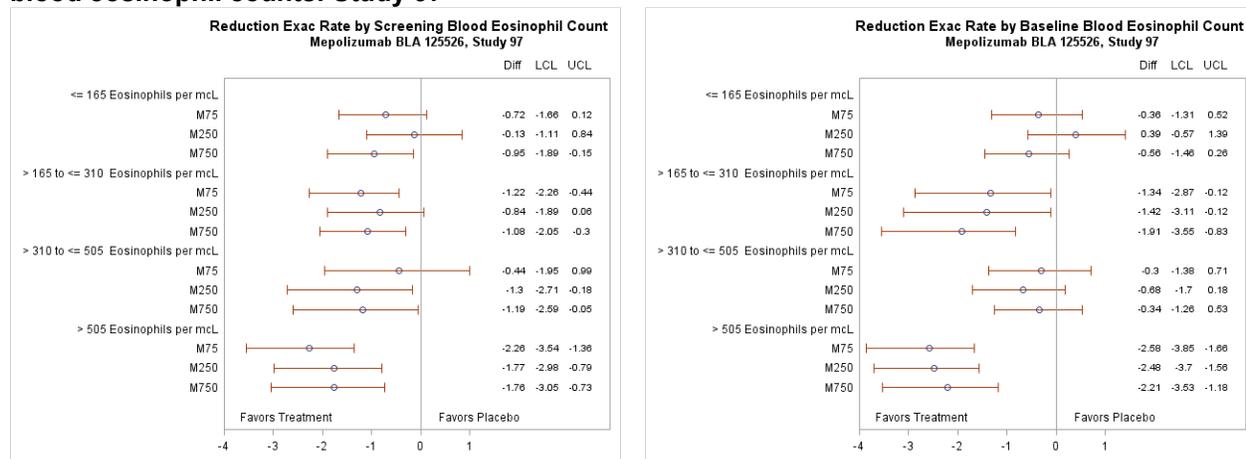
Subsequently, the sponsor conducted Study 97 using a broader set of inclusion criteria to identify patients with evidence of eosinophilic inflammation. Based on these results, the sponsor further refined the enrichment criteria for eosinophilic inflammation in Studies 88 and 75. Notably, the overall design of the program provides only limited data in patients with severe asthma with an exacerbation history who fail to meet the specific peripheral blood eosinophil thresholds applied in the phase 3 program.

An analysis of exacerbation data by screening and baseline eosinophil count from Studies 97 and 88 by the Agency strongly suggests that the mepolizumab treatment effect increases as an individual's peripheral blood eosinophil count increases (Figure 7, Figure 8).

¹⁷ Flood-Page, Patrick, et al. "A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma." *American journal of respiratory and critical care medicine* 176.11 (2007): 1062-1071.

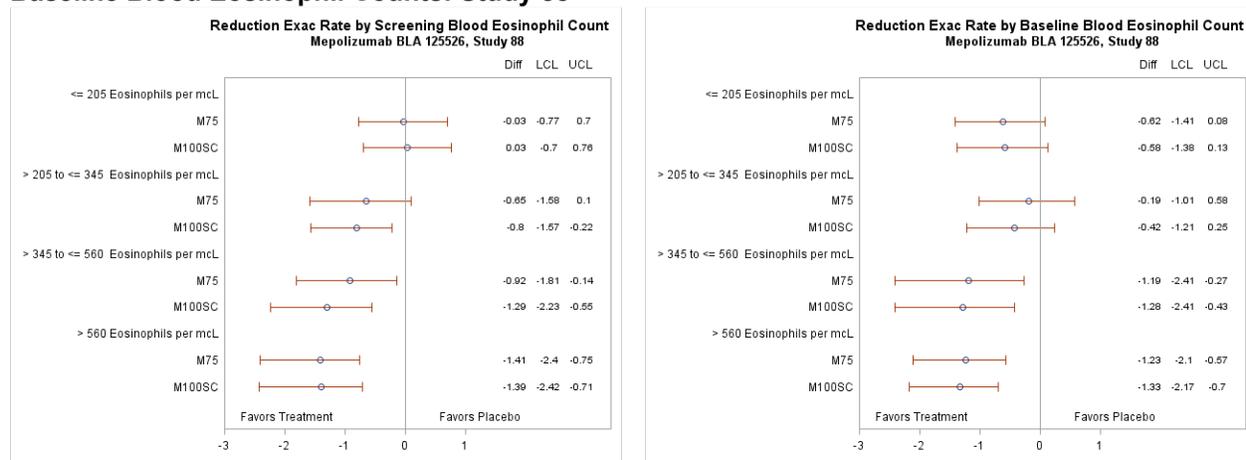
¹⁸ Haldar, Pranabashis, et al. "Mepolizumab and exacerbations of refractory eosinophilic asthma." *New England Journal of Medicine* 360.10 (2009): 973-984.

Figure 7: Difference between treatment and placebo exacerbation rates, by screening and baseline blood eosinophil counts: Study 97



Source: FDA Statistical Reviewer Analyses

Figure 8: Difference between Treatment and Placebo Exacerbation Rates, by Screening and Baseline Blood Eosinophil Counts: Study 88



Source: FDA Statistical Reviewer Analyses

In addition, the sponsor's analysis of the exacerbation data from Study 88 categorized by inclusion criteria suggests a trend for greater treatment effect for subjects meeting the eosinophil cutoff at initiation than for subjects enrolled based on a historical value alone (Table 14). However, that trend was not statistically significant, with the analysis possibly hampered by loss of power due to dichotomization of the integer/continuous eosinophil measurement.

Table 14: Exploratory Analyses of the primary endpoint: the annual rate of exacerbations by blood eosinophil inclusion criterion for Study 88

	Placebo N = 191	Mepo 100 SC	Mepo 75 IV
≥ 300 cells/μL in the previous 12 months <u>OR</u> ≥ 150 cells/μL at screening			
Only met ≥ 150 cells/μL at screening			
N	69	48	59
Rate/year	1.92	0.51	0.54
Only met ≥ 300 cells/μL in prior 12 months			
N	23	39	34
Rate/year	1.52	1.25	1.62
Met both criteria: ≥ 300 cells/ μL in previous 12 months AND ≥ 150 cells/μL at screening			
N	98	107	96
rate/year	1.62	0.74	0.98
Source: April 3, 2015 GSK Errata to BLA 125526 Module 1.11.3 Page 42-43 (Source Table 6.17, 6.18, and 6.19)			

While strong trends are seen for a positive treatment modification effect by peripheral blood eosinophil count, the underlying lability of the peripheral blood eosinophil counts should be considered when evaluating these data. Several publications have documented the variability in counts obtained within an individual in a single day as well as over time^{19,20,21}. This finding is further substantiated by data from this program which provided both screening and baseline peripheral blood eosinophil counts in individual subjects. The Agency's statisticians evaluated these data for Studies 97²² and 88²³ and found that 34% of individuals in Study 97 crossed out of the lowest eosinophil quartile into a higher quartile between screening and baseline measurements.

A second factor to consider is that while a complete blood cell count (CBC) with differentiation is a standard and widely available clinical laboratory test, there is an inherent imprecision in the obtained measurements, particularly for automated counters. Use of the central laboratory by this program would limit some of the inter-machine variability that would likely be seen in general clinical practice; although, this use cannot

¹⁹ Acland JD, Gould AH. Normal variation in the count of circulating eosinophils in man. *J Physiol* 1956; 133:456–466.

²⁰ Spector, Sheldon Laurence, and Ricardo Antonio Tan. "Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?." *Journal of Asthma* 49.8 (2012): 807-810.

²¹ Tatai K, Ogawa S. A study of diurnal variation in circulating eosinophils especially with reference to sleep in healthy individuals. *Jpn J Physiol* 1951; 1:328–331.

²² Screening and baseline values were obtained 1 to 6 weeks apart

²³ Screening and baseline values were obtained 1 week apart

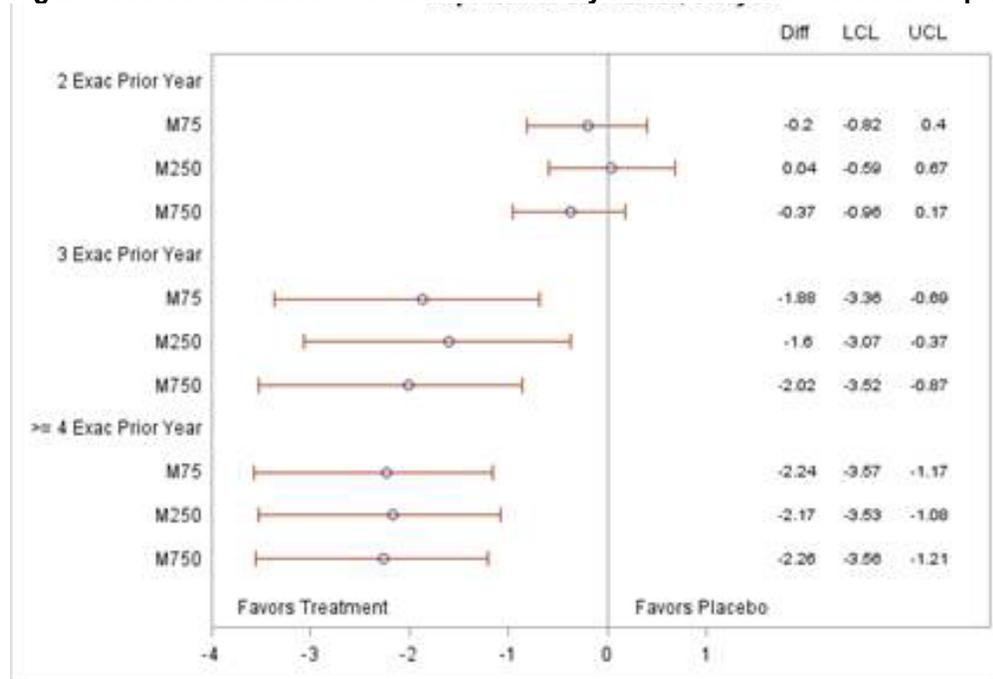
account for any additional imprecision due to intra-machine variability. Thus, the generalizability of the eosinophil data to a real-world situation is unknown.

Both of these factors speak to an underlying lability in peripheral blood eosinophil measurements. Although, it should be noted that the treatment interactions effects calculated by the Agency's statistical team are seen *despite* this variability indicating that the actual effect may be stronger than what is seen in the data.

Providing the community with data regarding the eosinophil effect of the exacerbation rate in Section 14 of the product label should assist clinicians in making appropriate decisions for his/her individual patient. Furthermore this lability speaks against defining specific threshold values in the Indication Statement until additional data regarding this clinical phenotype are made available, and the clinical and academic communities have weighed in on the appropriate defining characteristics for this asthma phenotype.

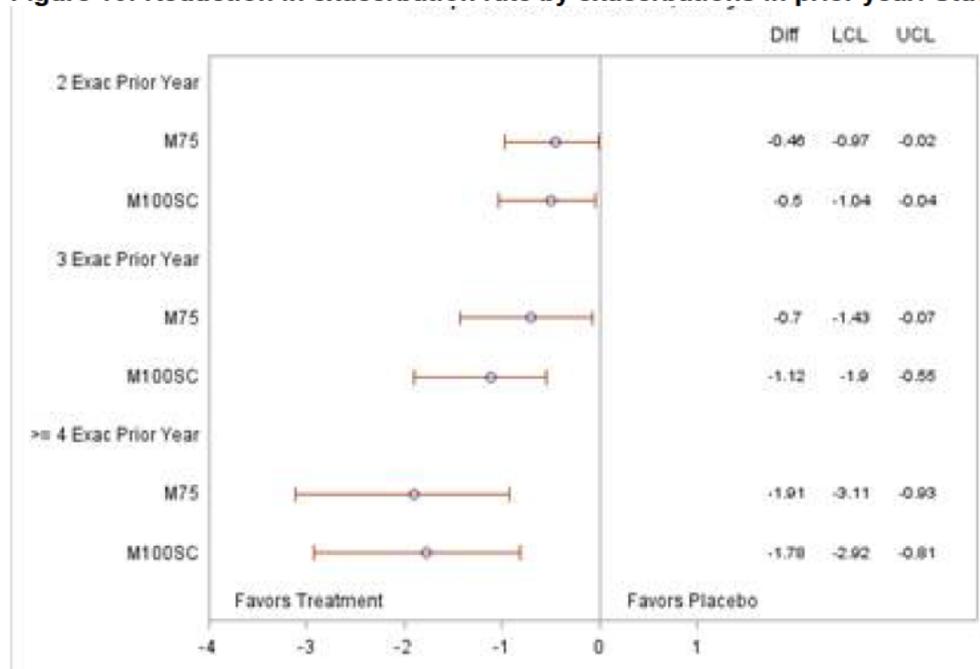
In addition to the analysis of treatment modification by eosinophil count, the Agency's statistical team also evaluated the impact of a patient's exacerbation history which can be used a rough marker for the underlying severity of their disease. This exploratory analysis by the Agency suggests a numerical trend towards an increased treatment response as a patient's exacerbation history increases (Figure 9 and Figure 10); however, this relationship is uncertain in that the treatment-by-number-of-previous-exacerbations is not significant (Study 97 $p=0.067$, Study 88 $p=0.42$).

Figure 9: Reduction in rate of exacerbations by number of exacerbations in prior year: Study 97



Source: FDA Statistical Reviewer Analysis

Figure 10: Reduction in exacerbation rate by exacerbations in prior year: Study 88



Source: FDA Statistical Reviewer Analysis

Finally, the heterogeneity of severe asthma must be considered. As shown in Table 14, additional factors such sputum eosinophilia $\geq 3\%$, exhaled nitric oxide ≥ 50 ppb, and deterioration of asthma control following at least a 25% reduction in corticosteroid use, were examined. Numerical beneficial trends for mepolizumab were observed in these subgroups; however no statistically significant interactions between any subgroup and treatment were identified. These data provide support for providing clinical definition of the asthma phenotype in the Indication, but there is no data at this time to suggest that data from these other biomarkers are sufficient to define the phenotype.

Table 15: Exploratory analysis of the primary endpoint: rate of exacerbations by inclusion criterion for Study 97

	Placebo N=155	Mepolizumab		
		75 IV N=153	250 IV N = 152	750 IV N=156
Blood eosinophil ≥ 300 cells/ μ L related to asthma*				
N	96	85	93	91
Exacerbation rate per year	2.22	1.08	1.16	1.22
Sputum eosinophilia $\geq 3\%$ *				
N	16	18	16	14
Exacerbation rate per year	2.03	1.13	0.96	1.40
Exhaled nitric oxide ≥ 50 ppb*				

	Mepolizumab			
	Placebo N=155	75 IV N=153	250 IV N = 152	750 IV N=156
N	70	61	57	74
Exacerbation rate per year	2.83	1.25	1.5	0.92
Deterioration of asthma control following at least a 25% reduction in corticosteroid use*				
N	48	46	41	47
Exacerbation rate per year	2.57	1.04	1.48	0.88
Source: Study 97 CSR Table 11				
* Tests for treatment by subgroup interaction each are not statistically significant				

The Agency also evaluated the effect of other potential treatment modifiers (including screening FEV1 reversibility, FENO, baseline percent predicated FEV1, and ACQ). None of these factors appeared to impact the treatment effect (data not shown).

Additional sensitivity analyses of exacerbation data: Studies 97, 88

Exacerbations requiring hospitalizations or ER visit and exacerbations requiring hospitalization: Studies 97 and 88

While overall rates are low, the data for exacerbations requiring hospitalization or ER visit or hospitalization alone are consistent with the primary endpoint (Table 16). Similar trends are seen in Study 75 (data not shown).

Table 16: Rate of exacerbations requiring hospitalization or ER visit or hospitalization alone: Studies 97 and 88

	Placebo	Mepolizumab			
		100 SC	75 IV	250 IV	750 IV
Study 97					
Exacerbations requiring hospitalization or ER visit					
N	155	--	153	152	156
Rate per year	0.43	--	0.17	0.25	0.22
Exacerbations requiring hospitalization					
N	155	--	153	152	156
Rate per year	0.18	--	0.11	0.12	0.07
Study 88					
Exacerbations requiring hospitalization of ER visit					
N	191	194	191	--	--
Rate per year	0.20	0.08	0.14	--	--
Exacerbations requiring hospitalization					
N	191	194	191	--	--

	Mepolizumab				
	Placebo	100 SC	75 IV	250 IV	750 IV
Rate per year	0.10	0.03	0.06	--	--

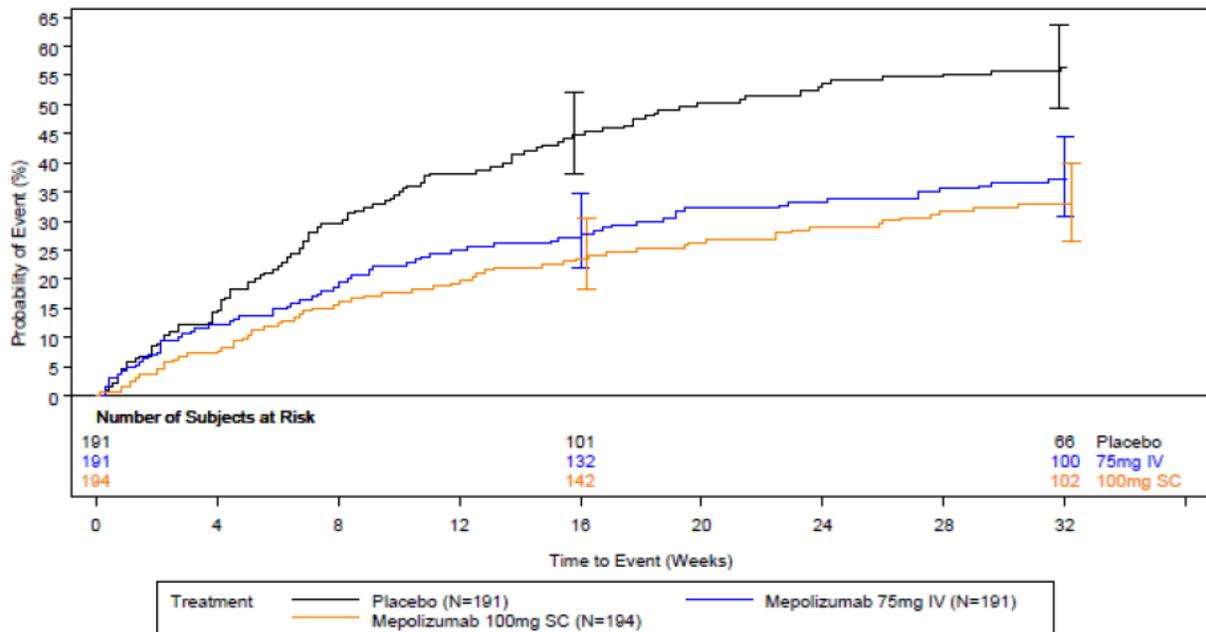
Source: FDA Statistical Reviewer Analysis

Time to First Exacerbation: Studies 97, 88

Consistent with the primary endpoint, mepolizumab treated subjects demonstrated an increased time to first exacerbation in Studies 97 and 88 (Figure 11, Figure 12).

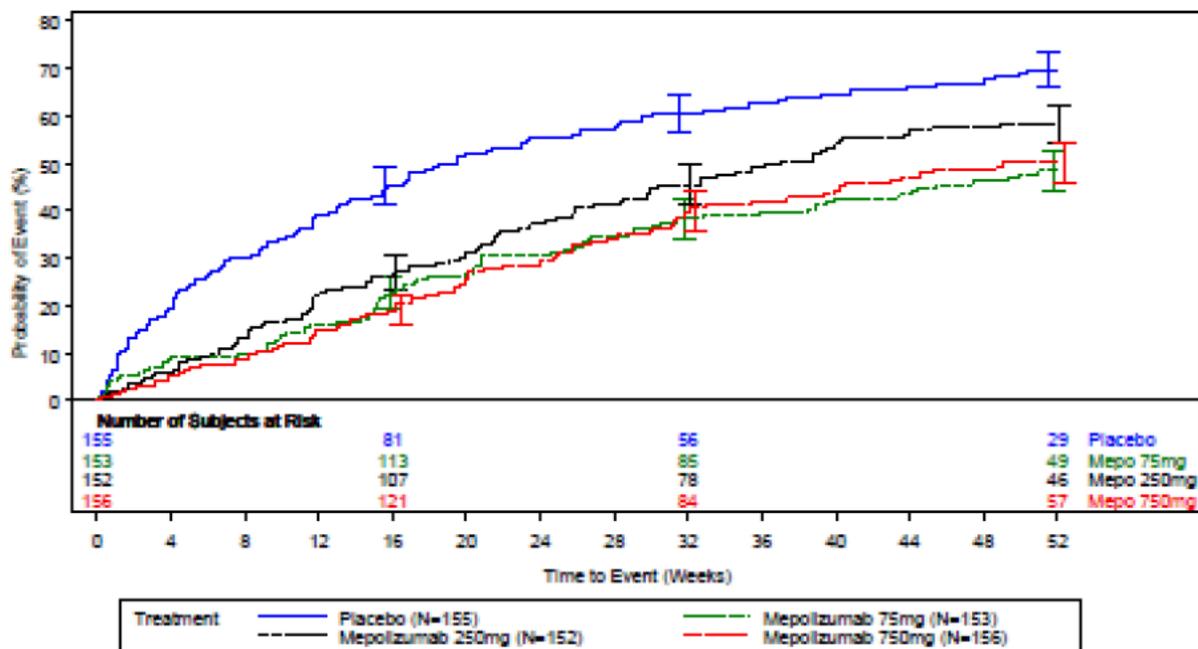
Similar trends in both studies are seen for the time to first exacerbation requiring hospitalization or ER visit and time to first exacerbation requiring hospitalization (data not shown).

Figure 11: Kaplan-Meier cumulative incidence curve for time to first clinically significant exacerbation: Study 88



Source: Study 88 CSR Figure 4

Figure 12: Kaplan-Meier cumulative incidence curve for time to first clinically significant exacerbation: Study 97



Source: Study 97 CSR Figure 6.06

Oral Corticosteroid Use Associated with an Exacerbation: Studies 97, 88

Consistent with the primary endpoint, mepolizumab treated subjects had fewer exacerbations treated with OCS than placebo treated subjects. However, the average number of days of OCS treatment per exacerbation was similar to slightly lower for placebo-treated subjects compared to those treated with mepolizumab (Table 17). Thus, while mepolizumab may decrease the number of exacerbations, it does not appear to impact the length of time clinicians used OCS to treat an exacerbation.

Table 17: Summary of number of days with oral corticosteroids associated with an exacerbation: Studies 97 and 88

	Placebo	Mepolizumab			
		100SC	75 IV	250 IV	750 IV
Study 97					
N	155	--	153	152	156
Number of exacerbations treated with OCS	276		145	177	148
Mean number of days with OCS use per exacerbation	13.1	--	14.2	11.2	14.5

Study 88					
N	191	194	191	--	--
Number of exacerbations treated with OCS	208	103	107		
Mean number of days with OCS use per exacerbation,	10.4	11.1	11.1	--	--
Source: Study 97 CSR Table 30; Study 88 CSR Table 36, Table 37					

6.1.4.2 Oral Corticosteroid (OCS) Percent Reduction from Baseline during Weeks 20-24 by Reduction Categories: Study 75

6.1.5 Analysis of Secondary Endpoints(s)

The sponsor evaluated multiple secondary endpoints in each of its pivotal efficacy and safety studies. Although statistically significant results were not shown for these secondary endpoints, the results trend in support of efficacy for mepolizumab.

Table 18: Summary of statistical hierarchal testing procedure: Studies 97, 88

Ordering of the secondary endpoints for multiplicity adjustment	
Study 97	<ul style="list-style-type: none"> • Rate of exacerbations • FEV1 pre-bronchodilator at week 52 • AQLQ at week 52 • Rate of exacerbations requiring hospitalizations or ED visit • ACQ at week 52
Study 88	<ul style="list-style-type: none"> • Rate of asthma exacerbations • Frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visit • Frequency of exacerbations requiring hospitalization • Mean change from baseline in clinic pre-bronchodilator FEV₁ • Mean change in St. George's Respiratory Questionnaire
Study 75	<ul style="list-style-type: none"> • No adjustment for multiplicity was made for the secondary endpoints. The analyses of the secondary endpoints were to be considered sensitivity analyses.
Source: Study 97 CSR page 52, study 88 CSR page 102	

While the frequency of exacerbations requiring hospitalization, or hospitalization/ED visit were officially designated as secondary endpoints in Studies 97 and 88, and the OCS use with each exacerbation were designated as “other endpoints”, these results are discussed as exploratory analyses in the discussion of the primary endpoint data of this briefing document.

Of note, no adjustments for multiplicity were made for any of the secondary endpoints evaluated in Study 75. These data were considered by the sponsor to be exploratory analyses in support of the primary endpoint.

Lung Function: Studies 97, 88 and 75

While the effect on lung function was not a primary efficacy variable for any of the pivotal efficacy studies, evaluation of a treatment effect on lung function is an important consideration in any asthma program.

The change from baseline in pre-bronchodilator FEV1 at Week 52 and Week 32 were designated as secondary endpoints in Studies 97 and 88, respectively. The evaluation of lung function data in Study 75 was designated as an “other endpoint”.

No consistent improvement over placebo in trough FEV1 is seen in Study 97. However, in Studies 88 and 75, numeric treatment benefits of approximately 100 ml in the mepolizumab 100 mg SC treatment groups compared to placebo are seen in the trough FEV1 data. Of note, the approximate 100 ml improvement is in addition to background standard of care therapy which for > 93% of the study population included ICS/LABA therapy (Figure 13, Figure 14, and Figure 15; Table 11).

For Study 97, a small, non-statistically significant, treatment difference between mepolizumab-treated subjects and placebo for trough FEV1 is seen at Week 52 (mepolizumab 75 IV: 61 ml 95%CI [-39, 161]; mepolizumab 250 mg IV 81 ml, 95%CI [-19, 180]; and mepolizumab 750mg IV: 56 ml, 95%CI [-43, 155]). However, similar differences from placebo are not seen earlier in the study. Some of this positive treatment difference may be due to a loss of FEV1 benefit seen over time in the placebo group. Conversely, the lack of mepolizumab treatment effect may be due an unanticipated FEV1 benefit seen in placebo + standard of care treatment group and may reflect the benefits of enrolment in a clinical study (Figure 13).

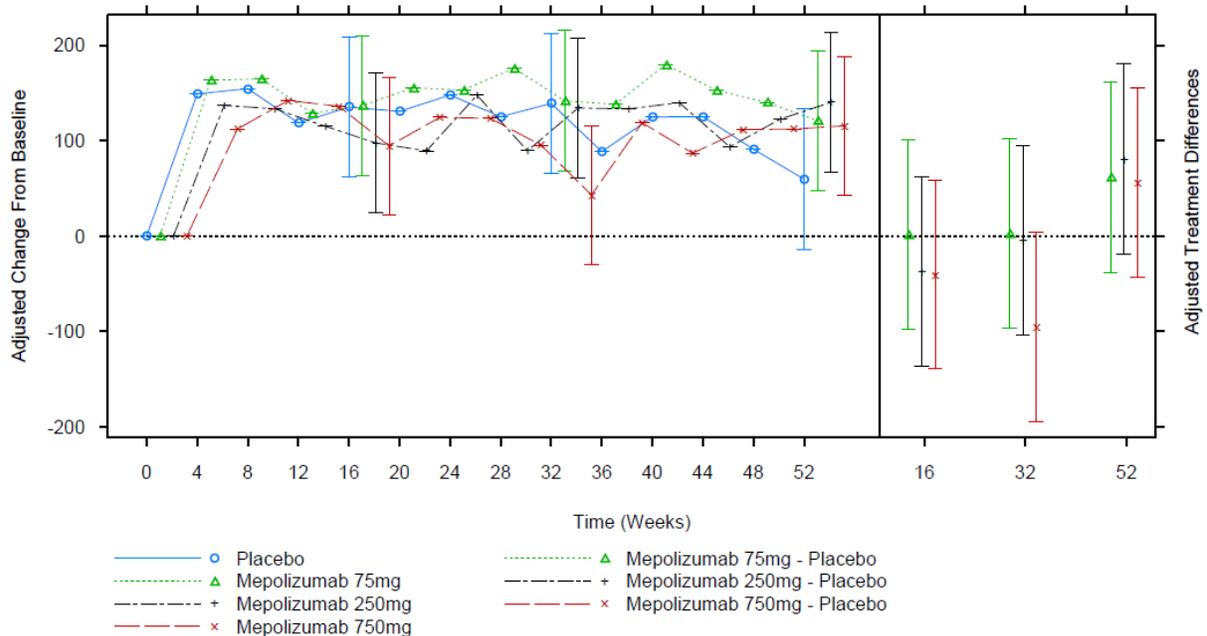
For Study 88, the point estimate at Week 32 demonstrates a 98 ml (95% CI 11, 184) and 100 ml improvement (95% CI 13, 187) in the change from baseline over placebo for the 100 mg SC and 75 mg IV treatment arms respectively. In this study, the placebo group did demonstrate some improvement from baseline in pre-bronchodilator FEV1; however, the improvement was not as profound as in Study 97, and the mepolizumab treatment arm consistently demonstrated numeric improvement compared to placebo across all timepoints.

For Study 75, numeric improvements from placebo are seen at Week 24 (114 ml improvement; 95% CI -42, 271; Figure 15). In contrast to Studies 97 and 88, the placebo group failed to demonstrate any improvement from baseline.

The difference in the placebo response between the three studies remains unclear, although the lack of placebo effect in Study 75 may be due, in part, to the OCS withdrawal built into the study design.

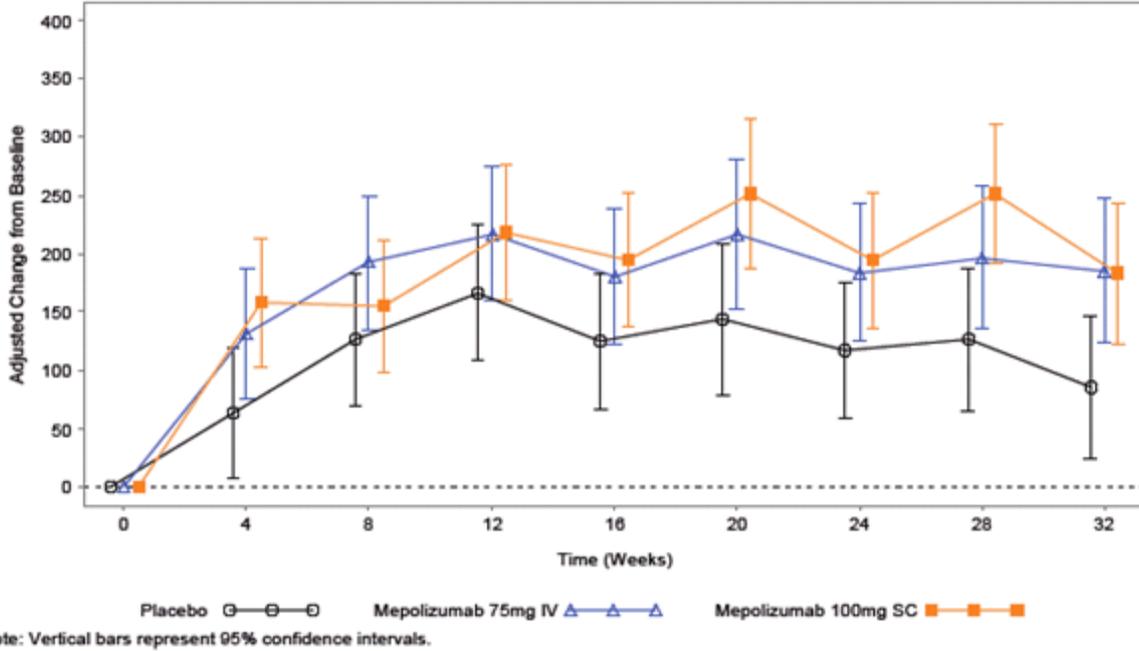
Similar data are seen for the evaluation of post-bronchodilator FEV1 (data not shown).

Figure 13: Change from baseline in pre-bronchodilator FEV1 (ml): Study 97



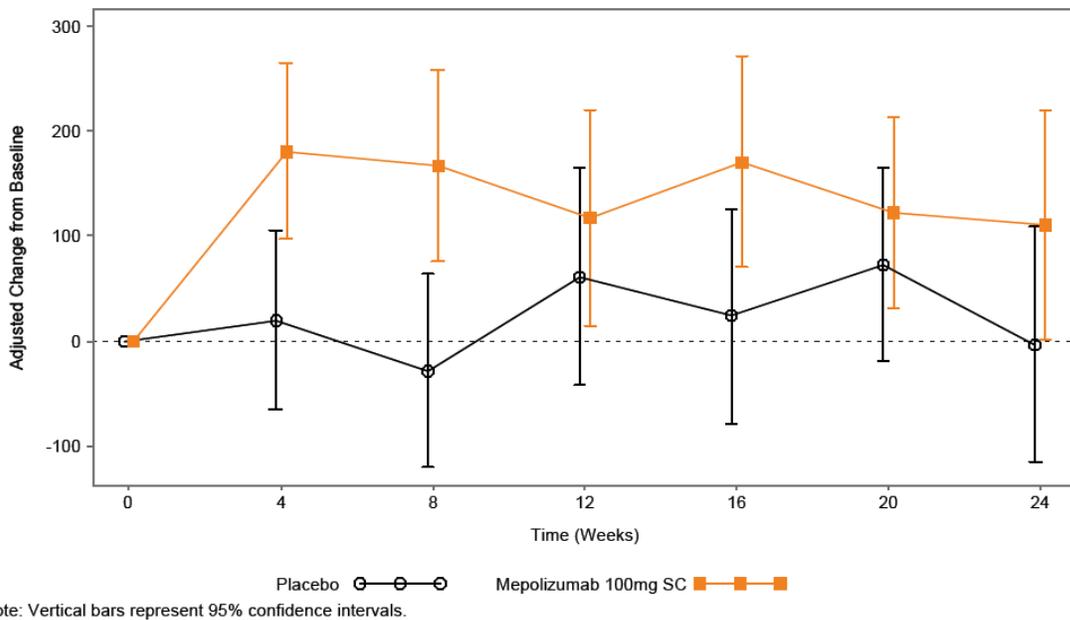
Source: Study 97 CSR Figure 7

Figure 14: Change from baseline in pre-bronchodilator FEV1: Study 88



Source: Study 88 CSR Figure 8

Figure 15: Change from baseline in pre-bronchodilator FEV1: Study 75



Source: Study 75 CSR Figure 4

SGRQ: Studies 88 and 75

SGRQ was assessed in Studies 88 and 75, but not in Study 97. In both studies, a greater decrease in SGRQ was observed for the mepolizumab treatment groups compared to placebo at the end of treatment. Differences from baseline as well as differences from placebo exceed the established minimally clinically important difference (MCID) of 4 (Table 19). Of note, results are only nominally significant due to failure within the testing hierarchy for Study 88 and failure to account for multiplicity in Study 75.

Similar to the total score, greater improvements for mepolizumab treated groups over placebo are seen for the individual domains comprising the total score (data not shown).

Given the clinical relevance of quality of life data to patients, this reviewer supports inclusion of these data into the USPI pending review by the Agency’s statistical team regarding missing data for this endpoint.

Table 19: Exploratory Analysis SGRQ mean total score: Study 88 and Study 75

	Placebo	Mepo 100	Mepo 75
Study 88			
Baseline	46.9	47.9	44.4
Week 32	38	31.5	30.2
LS mean change from baseline	-9	-16	-15
95% CI	-11, -7	-18, -14	-18, -13
Difference from placebo	--	-7.0	-6.4
95% CI	--	-10.2, -3.8	-9.7, -3.2
Study 75			
N	66	69	--
Baseline	45	49.6	--
Week 24	42.1	40.6	--
LS mean change from baseline	-3	-9	--
95% CI	-6,0	-12,-6	--
Difference from placebo	--	-5.8	--
95% CI	--	-10.6,-1.0	--
Source: Statistical Reviewer Analysis and Study 88 GSK Errata dated April 3, 2015 Module 1.11.3 and Study 75 Tables 6.32, 34			

ACQ score: Studies 97, 88, 75

Numeric improvements in ACQ were demonstrated for mepolizumab treated subjects in Studies 97, 88, and 75.

Table 20: Exploratory Analysis: Mean change from baseline in ACQ Score: Studies 97, 88, 75

	Mepolizumab
--	-------------

	Placebo	100 SC	75 IV	250 IV	750 IV
Study 97: Week 52					
LS mean Δ from baseline	-0.63	--	-0.78	-0.91	-0.85
Difference from placebo	--	--	-0.15	-0.28	-0.22
95% CI	--	--	-0.39,0.10	-0.53,-0.04	-0.46,0.02
Study 88: Week 32					
LS mean Δ from baseline	-0.50	-0.94	-0.92	--	--
Difference from placebo	--	-0.44	-0.42	--	--
95% CI	--	-0.63,-0.25	-0.61,-0.23	--	--
Study 75: Week 24					
LS mean Δ from baseline	-0.09	-0.61			
Difference from placebo	--	-0.52			
95% CI		-0.87,-0.17			
Source: Study 97 CSR Table 6.46, Study 88 CSR Table 4, Study 75 Table 32					

Similar to SGRQ, should the statistical team verify the results of the sponsor's analyses, this review finds the quality of life data to be clinically relevant and recommends inclusion into product labeling.

6.1.6 Other Endpoints

Selected endpoints from this clinical development program are discussed under 6.1.5 secondary endpoints, including "other endpoints" that were not accounted for in the statistical testing hierarchy. Additional endpoint data from the exacerbation studies are summarized below. Overall, the data are supportive of the primary endpoint.

For Study 97, the mean change from baseline in peak expiratory flow (PEF) demonstrated small numeric increases in morning PEF in the mepolizumab treatment groups compared to placebo. In addition, the mean change from baseline in daily salbutamol/albuterol use, daily asthma symptom scores, change from baseline in awakening at night due to asthma symptoms requiring rescue medication use all demonstrated small decreases from baseline in the mepolizumab treated subjects compared to placebo. While not statistically significant these data support the findings of the primary endpoint.

For Study 88, the mean change from baseline in PEF demonstrated small numeric increases in the mepolizumab treatment arms compared to placebo. In addition, small numeric decrease in rescue medication use and mean daily asthma symptoms are seen for mepolizumab treated subjects. Similar changes from baseline are seen for the number of night time awakenings between active treatment groups and placebo. In general, while none of the results are statistically significant, the trends from these data support the findings of the primary endpoint.

6.1.7 Subpopulations

The Agency’s statistical review provided a subgroup analyses of the efficacy data by gender, age, race, ethnicity and region. All mepolizumab doses were pooled in these analyses to increase the sample size. Of note the adolescent subgroup is missing from Studies 97 and 75 as only one adolescent was enrolled in Study 97 and 2 adolescents were enrolled in Study 75. Similarly, an analysis in subjects of African descent is missing from Study 75 as this study did not enroll any subjects in this subgroup.

Table 21 and Table 22 provide a breakdown of the study enrolment by race and number adolescent subjects in this clinical development program. While the proportion of enrolled African Americans from US sites is similar to what would be expected from the US population, the population is under-represented when evaluated as a proportion of the global development program. This is due to the fact that US clinical sites only enrolled about 10 to 15% of the population in this clinical development program.

Table 21: Samples sizes, actual and expected for selected subgroups: Studies 97, 88, 75

	Study		
	97	88	75
Randomized, N	616	576	135
African Descent, n (%)	24 (4)	16 (3)	0
American of African Descent, n (%)	22 (4)	14 (2)	0
Asian, n (%)	34 (6)	105 (18)	3 (2)
Hispanic, n (%)	61 (10)	51 (9)	5 (4)
12 to 17 years of age, n (%)	1 (<1)	25 (4)	2 (1)

Source: FDA Statistical Reviewer Analysis

Table 22: Sample sizes, actual and expected: Studies 97, 88 and 75

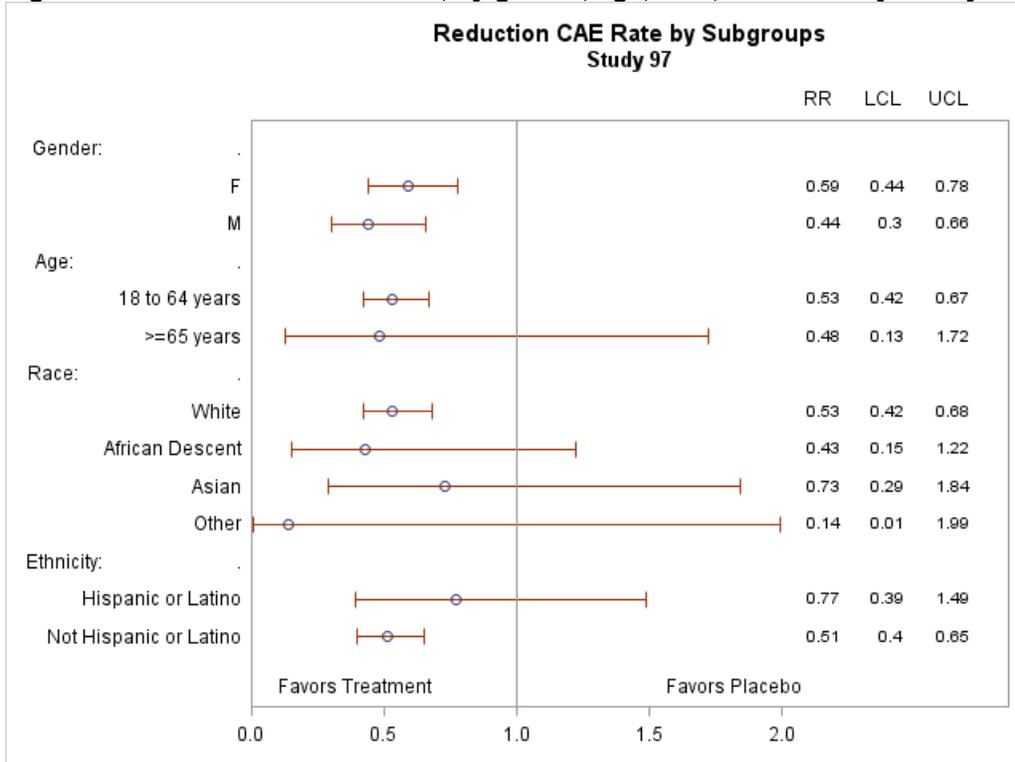
	Study		
	97	88	75
Randomized with the USA	78	67	7
American of African Descent, n (%)	22 (28)	14 (21)	0
Asian, n (%)	1 (1)	1 (1)	0
Hispanic, n (%)	6 (8)	5 (7)	0
12 to 17 years of age, n (%)	1 (1)	4 (6)	0

Source: FDA Statistical Reviewer Analysis

Figure 16 to Figure 18 provide the exacerbation rate ratios for gender, age, race, ethnicity for Studies 97, 88 and 75, Figure 19 and Figure 20 provide the rate ratios by region for Studies 97 and 88. Overall, no effect is seen for the subgroup analysis

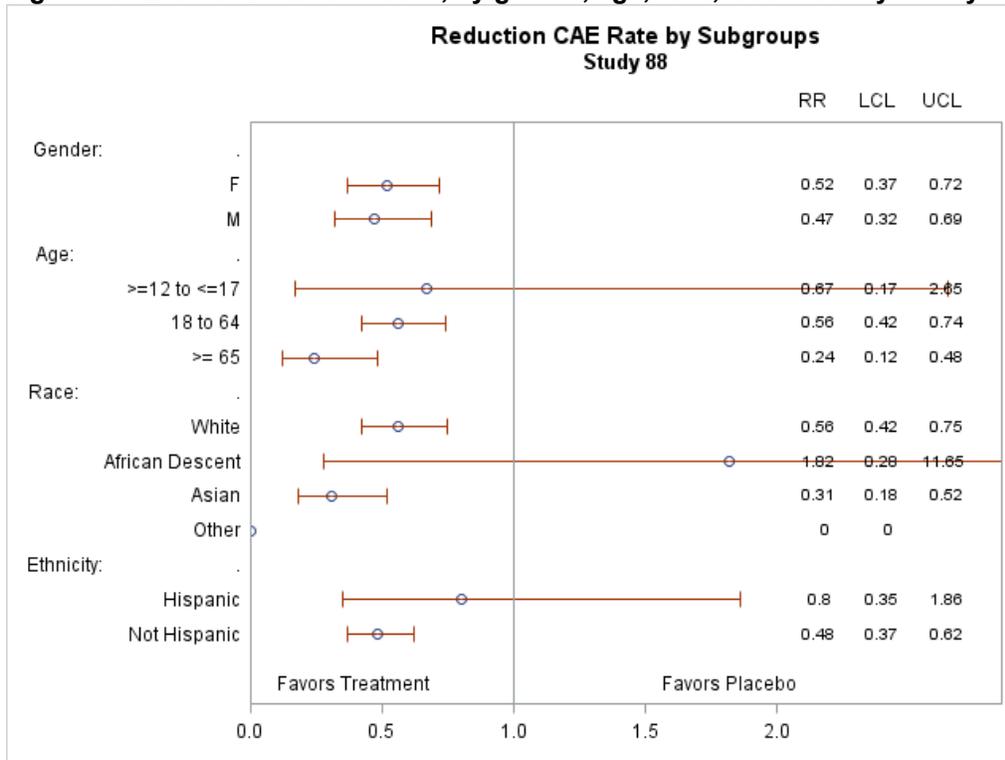
by gender or region, the data for the adolescent and African American populations is found to be too limited to draw conclusions as is discussed in additional detail below.

Figure 16: Exacerbation rate ratios, by gender, age, race, and ethnicity: Study 97



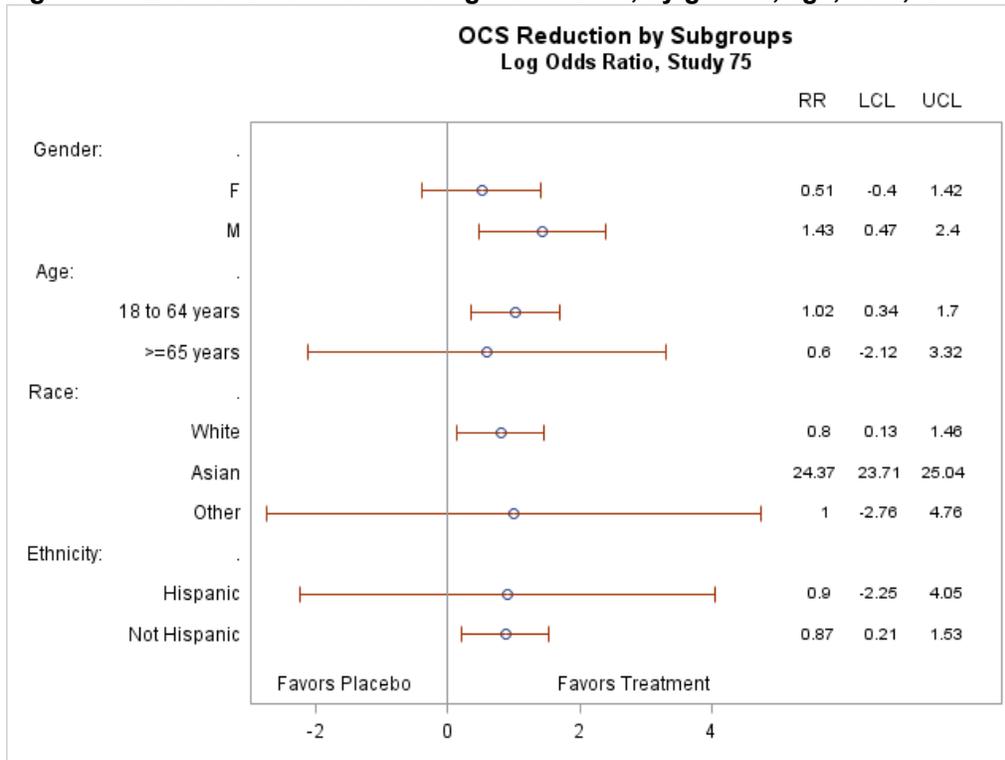
Source: FDA Statistical reviewer Analysis

Figure 17. Exacerbation rate ratios, by gender, age, race, and ethnicity: Study 88



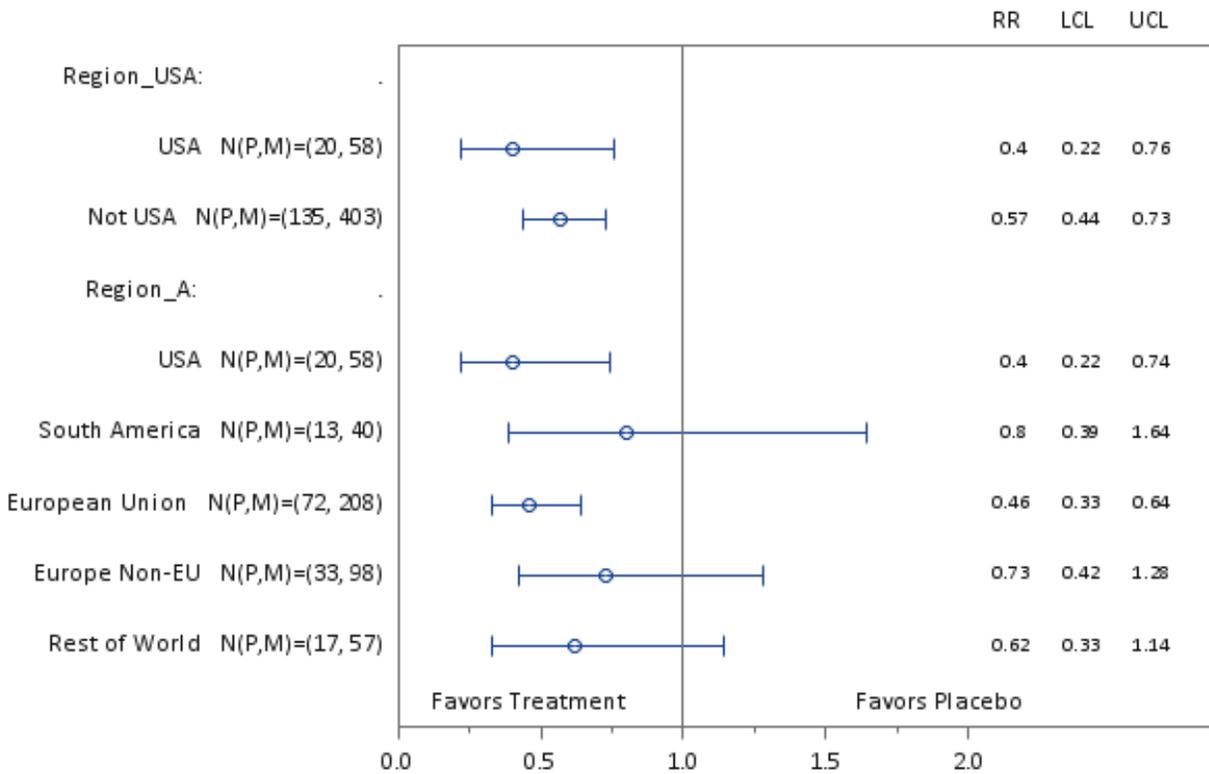
Source: FDA Statistical reviewer Analysis

Figure 18. Exacerbation reduction log odds ratios, by gender, age, race, and ethnicity: Study 75



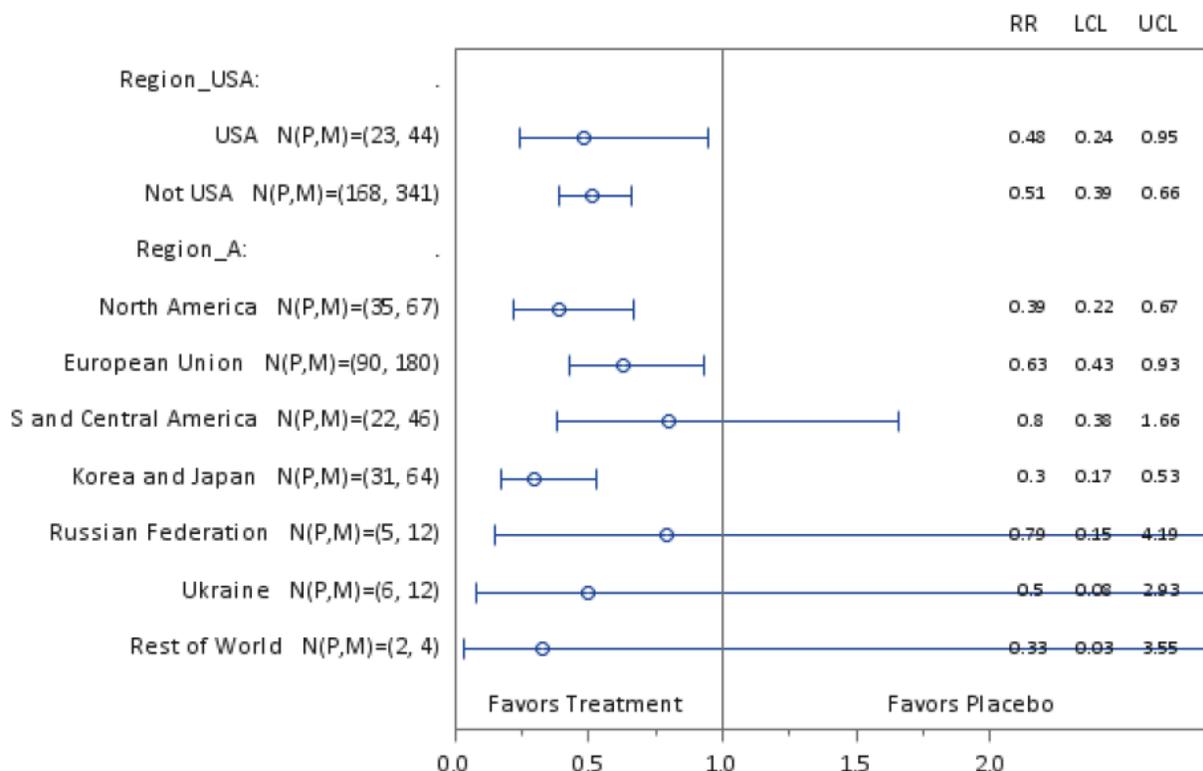
Source: FDA Statistical Reviewer Analysis

Figure 19: Exacerbation rate reduction by region: Study 97



Source: Statistical Reviewer Analysis

Figure 20: Exacerbation rate reduction by region: Study 88



Source: Statistical Reviewer Analysis

Adolescents

While, the rate ratio for adolescent subjects trend in a favorable direction in Study 88, the overall quantity of data is too limited to draw firm conclusions regarding the efficacy of mepolizumab in this population. As this program targets a new phenotype of severe asthma, the relevance of this phenotype to the pediatric population remains unclear and

(b) (4)
 . Thus this review is recommending Approval for the indication in subjects ≥ 18 years of age and a Complete Response for patients 12 to 17 years of age. Additional evaluation as PMRs in the pediatric population are recommended. This pediatric issues was raised and discussed at a meeting of the Pulmonary Allergy Drugs Advisory Committee and these recommendations reflect the discussion and vote at the meeting (See Section 9.3).

Race and Ethnicity

Given the increased asthma morbidity and mortality seen in African American patients with asthma²⁴, the subgroup analysis and the adequacy of the available data for this patient population is also of particular interest to the Agency.

Efficacy trends in the appropriate direction for Hispanic and Asian subjects in all three studies. As can be seen in Figure 16 and Figure 17 the efficacy data for patients of African Descent trends in the appropriate direction for Study 97 but not for Study 88; wide confidence intervals are noted for both. When the data are pooled the overall trend is in support of a positive treatment, although again wide confidence intervals are seen. While the data supporting efficacy and safety of this population are limited, there is no reason to surmise that mepolizumab would behave differently in this patient population. Given the unmet medical need in severe asthmatics of all ethnicities including African Americans, this review does not recommend any the inclusion of any restrictions regarding use at this time.

This issue was discussed at a meeting of the Pulmonary Allergy Drugs Advisory committee held on June 11, 2015 and these recommendations are made taking into account the committee discussion of these issues.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Doses ranging from 75 mg IV up to 750 mg IV were evaluated in the mepolizumab severe asthma program. A single subcutaneous dose, 100 mg SC (the dose proposed for marketing) was evaluated in the development program.

No additional treatment effect seen from doses higher than the 75 mg IV dose evaluated in study 87. The PK/PK study 92 demonstrates a similar systemic exposure and PD profile for the 75 mg IV dose and 100 mg SC, the dose and route being evaluated for marketing. In addition, the similar treatment effect compared to placebo between 75 mg IV and 100 mg SC in study 88, coupled with the a positive treatment effect demonstrated for the 100 mg SC over placebo in Study 75 provide support for the dose and route proposed for marketing.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

A review of the treatment benefit over the course of each study does not reveal a loss of treatment benefit with time. Prolonged post-study efficacy evaluations were not conducted after cessation of treatment. However, within weeks following drug cessation,

²⁴ SilverS, Stacy K., and David M. Lang. "Asthma in African Americans: What can we do about the higher rates of disease?." *Cleveland Clinic journal of medicine* 79.3 (2012): 193-201.

peripheral blood eosinophil counts, a PD marker for the drug, increase as would be expected.

6.1.10 Additional Efficacy Issues/Analyses

To demonstrate the lack of treatment benefit in subjects with less severe asthma, the sponsor provided the results of Study 06.

Study 06 was a Phase 2, randomized, parallel-group, double-blind, placebo-controlled, multinational, 12-week study. Of note, this study used an earlier pilot formulation of mepolizumab for which there is no PK bridge to the current proposed product. The impact of this change and any differences between the products are unknown.

A total of 362 asthmatic subjects were enrolled. No adolescent subjects were enrolled in this study. Subjects were required to have a FEV1 \geq 50% and \leq 80% predicted with demonstrated reversibility \geq 12%. Prior treatment with an inhaled corticosteroid dose up to a maximum of 1000 mcg/day of beclomethasone or equivalent was allowed.

After a 4-week run-in, eligible subjects were randomized 1:1:1 to receive mepolizumab 250 mg IV, mepolizumab 750 mg IV or placebo. The 12-week treatment period was followed by an 8-week follow-up period. The primary endpoint was the change from baseline of the mean morning domiciliary peak expiratory flow rate recorded in the seven days preceding Week 12. Change from baseline in trough FEV1, asthma symptom score and rescue medication use were evaluated as secondary endpoints.

A total of 362 subjects were randomized with 94% completing the study (97%, 92% and 94% for mepolizumab 750 mg IV, 250 mg IV and placebo respectively). Subjects were predominantly Caucasian (81-89%) with a mean age ranging from 36-37 years of age per treatment group.

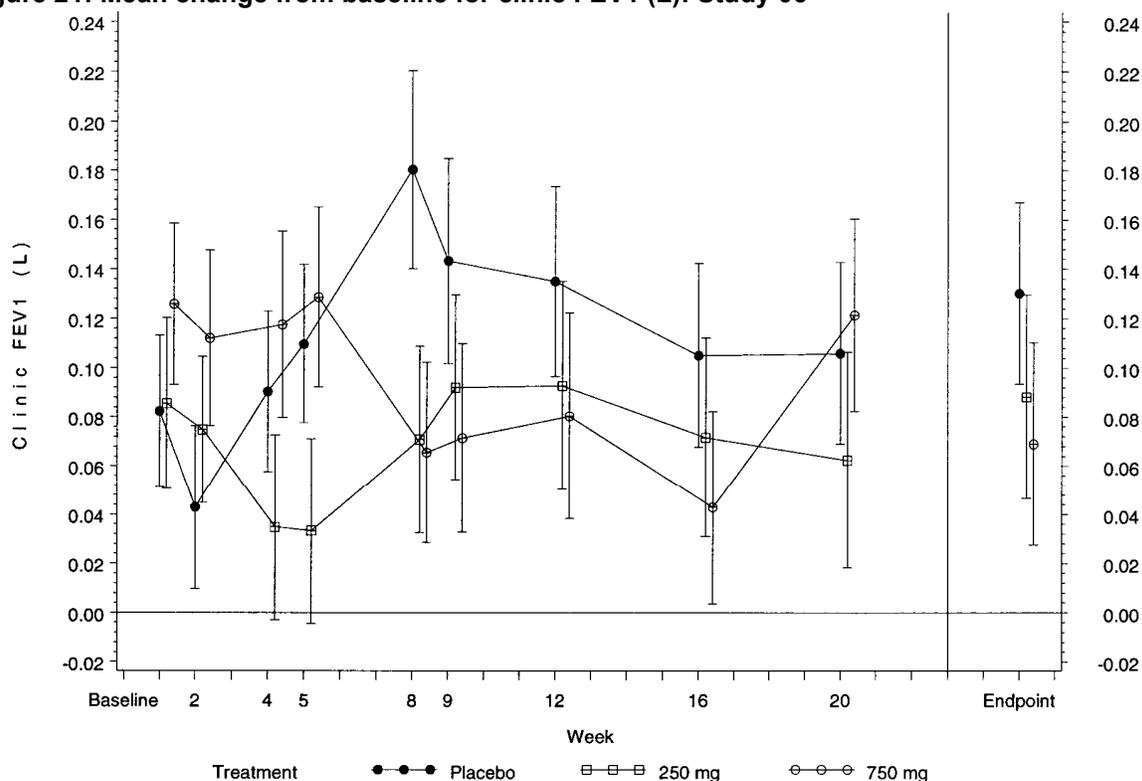
No statistically significant differences between placebo and mepolizumab treatment groups were seen for the primary endpoint. The results of the secondary endpoints, demonstrated a similar lack of treatment effect (Table 23; Figure 21). However, among the few exacerbations recorded in this study, a numeric reduction was seen for the highest evaluated dose group (750 mg IV) compared to placebo.

Table 23: Summary of efficacy data: Study 06

	Placebo N = 126	Mepo 250 IV N = 120	Mepo 750 IV N = 116
Domiciliary AM PEFr, (L/min)			
Mean change from baseline	11.32	19.03	13.08
Mean difference from placebo	--	7.83	1.70
95% CI	--	-2.89, 18.55	-9.06, 12.47

	Placebo N = 126	Mepo 250 IV N = 120	Mepo 750 IV N = 116
Clinic pre-dose FEV1 (L)			
Mean change from baseline	0.13	0.09	0.07
Mean difference from placebo	--	-0.04	-0.05
95% CI		-0.15, 0.07	-0.16, 0.05
Asthma summary symptom score¹			
Mean change from baseline	-1.50	-1.33	-1.02
Mean difference from placebo	--	0.19	0.48
95% CI	--	-0.31, 0.70	-0.03, 0.98
Rescue medication use (puffs/day)			
Mean change from baseline	-0.72	-0.57	-0.59
Mean difference from placebo	--	0.15	0.14
95% CI	--	-0.34, 0.64	-0.36, 0.63
¹ Asthma Symptom Summary Score = composite score of asthma symptoms during night, morning and daytime ranked on a 0 – 4 scale. Symptoms were recorded twice daily in the daily diary, in the am nighttime and morning scores were recorded, and evening scores were recorded in the pm. Source: CSR Study 06 Tables 23, 25, 28 29			

Figure 21: Mean change from baseline for clinic FEV1 (L): Study 06



Source: CSR Study 06 Figure 3

7 Review of Safety

Safety Summary

The safety database from this clinical development program includes data from the three pivotal efficacy and safety studies (Studies 97, 88 and 75) as well as longer-term safety data from two open-label extension studies (Studies 61 and 66) which were ongoing at the time of BLA submission.

There were three (3) respiratory-related deaths in the clinical development program. However, the deaths are balanced across treatment arms (including placebo), and there is no corresponding increase in respiratory or asthma SAEs. Rather, review of the asthma SAE data reveals a consistent imbalance in favor of mepolizumab treatment which supports the positive exacerbation treatment effect demonstrated in the clinical development program. The number of respiratory-related deaths in the program may be indicative of the underlying severity of the studied population; however, no firm conclusions can be drawn from these limited data.

An imbalance in cardiac-related SAEs is seen from evaluation of the safety data from Study 97. However, when the data are grouped into ischemic versus arrhythmogenic events, the imbalance decreases. Furthermore, no imbalance is seen in Studies 88 and 75, although these studies were of shorter treatment duration than Study 97.

While lingering concerns remain of the risk of mepolizumab use and parasitic disease, no major safety findings were observed in the data that would limit approvability of the product for use in a severe asthmatic population. Routine post marketing pharmacovigilance and a parasitic PMR, as well as PREA PMRs are recommended.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review primarily relies on data from three placebo-controlled studies in a severe asthma population: MEA112997 (Study 97), MEA115588 (Study 88) and MEA115575 (Study 75) as these studies most closely approximate the patient population to receive mepolizumab in the clinical practice. Within this review, the pooled database for these studies is referred to as the Placebo-Controlled Severe Asthma Studies (PCSA).

Longer term safety data are provided by two open-label studies, MEA115666 (Study 66), MEA115661 (Study 61). These studies were ongoing at the time of the BLA submission with updated data provided to the Division in a 120-day safety update. The data from this safety update used a cutoff date of October 27, 2014 and provides cumulative review of the data for the studies ongoing at the time of BLA submission²⁵.

Additional information on the sponsor's pooled analyses may be found in Section 7.1.3 of this review.

7.1.2 Categorization of Adverse Events

In the mepolizumab clinical development program an adverse event (AE) was defined as any untoward medical occurrence in a subject temporally associated with use of mepolizumab regardless of relatedness to mepolizumab. Adverse events were coded

²⁵ Data from the ongoing compassionate use program in Hypereosinophilic Syndrome provides additional deaths and non-fatal SAEs from September 2013 through October 27, 2014 as opposed to cumulative results from the study.

and grouped using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In addition to the PCSA database, the applicant provided multiple additional pooled safety analyses in this BLA application. The data groupings are summarized in Table 24.

Table 24: Pooled safety databases

Data Grouping	Included Indications	Number of Studies	Number of subjects
All Studies	All indications	19	2,331
Placebo-controlled Multi-dose Studies (PC)	All indications	9	1,876
Placebo-controlled Multi-dose Asthma Studies (PCMDA)	Asthma	6	1,737
Placebo-controlled Severe Asthma Studies (PCSA) ¹	Asthma	3	1,327
Open-label Extension Studies (OLE) ²	Asthma	2	998
¹ includes data from Studies 97, 88, and 75			
² includes data from Studies 61 and 66			
Source: Modified from ISS Table 1			

As noted in Section 7.1.1, this review focuses on the PCSA database as these data most closely approximate the patient population to receive this product in clinical practice. Additional long-term safety data are provided by the open-label extension (OLE) studies in severe asthma. To supplement its database, the sponsor also provided safety data from completed studies in other patient populations. These data are presented throughout this safety review where relevant.

For the review of adverse event data, many areas of this safety review focus on the exposure-adjusted analysis as opposed to frequency tables. Use of the exposure-adjusted data allows for a comparison of all active treatment arms while adjusting for the different treatment durations evaluated in each pivotal severe asthma study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The size of the database and duration of exposure are adequate for review. A total of 2,331 patients are included in the sponsor's overall safety database, of whom 2,022 received at least one dose of mepolizumab. Of these, a total of 1,327 patients with severe asthma were evaluated in the PCSA database with 915 receiving at least one dose of mepolizumab.

Table 25: Extent of Exposure: PCSA

	Placebo N = 412	Mepolizumab				
		100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156	All doses
Total # of subjects, n	412	263	344	152	156	915
Total subject years	284	147	254	142	144	687
Exposure (months)						
Mean	8.3	6.7	8.9	11.2	11.0	9.0
Median	7.5	7.4	7.6	12.0	12.0	7.6
Min, Max	1, 13	1, 8	1, 13	1, 13	1, 14	1, 14
Range of Exposure (months)						
< 12, n (%)	288 (70)	263 (100)	217 (63)	22 (14)	26 (17)	528 (58)
≥ 12, n (%)	124 (30)	0	127 (37)	130 (86)	130 (83)	387 (42)

Source: Modified from ISS Tables 3, 6

No differences in baseline demographics are seen between treatment groups. Demographic data for Studies 97, 88, and 75 are summarized in Table 8, Table 9, Table 10 respectively in Section 5.1.2.

The safety data contained in the 120-day safety update provide open-label data for mepolizumab 100 mg SC for greater than one year in 836 subjects with a median exposure of 20 months in Study 66 and 12 months in Study 61²⁶. Study 66 enrolled subjects from Study 97 with a minimum 12 month break in therapy between the two studies, while Study 61 directly enrolled subjects from Studies 88 and 75.

7.2.2 Explorations for Dose Response

Doses ranging from 75 mg IV up to 750 mg IV were evaluated in the mepolizumab severe asthma program. A single subcutaneous dose, 100 mg SC (the dose proposed for marketing) was evaluated in the development program. Based on PK/PD bridging data from Study 92, the systemic exposure from this dose is within the evaluated

²⁶ The duration of exposure from the start of the parent study into the extension study was calculated as above when there was *no break* in treatment between the two studies.

intravenous dosing. The safety data from all evaluated doses are presented and analyzed throughout the safety review to provide contextual information for the 100 mg SC dose.

7.2.3 Special Animal and/or In Vitro Testing

There were no specific animal and/or in vitro testing conducted for this clinical development program.

7.2.4 Routine Clinical Testing

See Section 5.3 for a list of the specific safety assessments included in the clinical trials. The results of the laboratory data are discussed in Section 7.4.2, vital sign data in 7.4.3, ECG data in 7.4.4 and immunogenicity data in 7.4.6.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific studies evaluating metabolic, clearance, or drug interactions were included in this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no monoclonal antibodies targeting IL-5 approved for use in the United States or other foreign countries. However, based on targeted pathway and preliminary safety data from Study 97, the following Adverse Events of Special Interest were pre-specified for analysis and review in this program. Because mepolizumab is a monoclonal antibody, the sponsor included evaluations of systemic and local site reactions, neoplasms, and opportunistic infections. Cardiac disorders were also specified as AESI based on preliminary safety information obtained from Study 97. Each of these AESI is discussed further in Section 6.3.4.

- Systemic reactions
- Local site reactions
- All infections including opportunistic infections
- Neoplasms
- Cardiac disorders.

7.3 Major Safety Results

7.3.1 Deaths

A total of 8 deaths have been reported in the severe asthma studies: 5 in the PCSA database and three in the open label extension study. The deaths are balanced across treatment arms with 2 in placebo treated subjects, 1 in the 100 mg SC dose group, 2 in the 250 mg IV dose group, and 1 in the 750 mg dose group. Additional details of these deaths are provided in Table 26.

Table 26: Details of on-treatment deaths

Treatment	Study (Country)	Age/Sex	Cause of death Preferred Term	Additional notes
Placebo	88 (Korea)	51 yo/M	Road traffic accident	--
Placebo	75 (Germany)	38 yo/F	GI hemorrhage and aspiration	Hospitalized for a severe asthma exacerbation and was found to have pulmonary mycoides that was treated with voriconazole. Subject then developed GI hemorrhage and aspiration leading to death
250 mg IV	97 (Chile)	60 yo/F	Acute pancreatitis Septic shock	Subject had biliary microlithiasis and mesenteric thrombosis. Subject then developed acute pancreatitis with an abscess followed by septic shock and death.
250 mg IV	97 (France)	56 yo/F	Asthma	Rapid evolution of asthma symptoms occurring over minutes. Symptoms began hours after last injection of mepolizumab. Subject was in cardiac arrest upon arrival to ER.
750 mg IV	97 (Chile)	54 yo/M	Asphyxia	Completed suicide No prior history of depression but also taking cyclobenzaprine
100 mg SC	OLE (Australia)	29 yo/M	Respiratory Arrest	Severe asthma exacerbation
100 mg	OLE		Complications	Sudden death

Treatment	Study (Country)	Age/Sex	Cause of death Preferred Term	Additional notes
SC	(NA)		from morbid obesity	

The number of potential respiratory-related deaths (3 patients) in this relatively small database is notable given that deaths are not frequently seen in asthma clinical development programs. To place these data in context, GSK recently reported blinded results from its ongoing large LABA safety study in 11,724 adult and adolescent subjects with asthma. Per GSK's reports, there have been no deaths independently adjudicated as related to asthma in this large database²⁷. However, it should be noted that the patient population enrolled in the large LABA safety trial differs in severity from the population evaluated in this program.

While the number of respiratory-related deaths in this program is unexpected, the data do not strongly suggest a treatment-related effect as the events are balanced across treatment arms. Reassuringly, similar concerns are not seen from a review of the non-fatal SAE data which favored treatment and demonstrated a reduction in asthma SAEs in mepolizumab treated subjects compared to placebo. The frequency of death in this clinical development program may be due to the underlying severity of the patient population evaluated in this program, although this cannot be confirmed.

In addition to the respiratory-related deaths, the death due to suicide is also of interest, particularly as the subject did not have a history of depression or prior suicide attempts. However, no conclusions for causality to mepolizumab can be drawn from this single case which is further confounded by the concomitant use of cyclobenzaprine. The post marketing section of the U.S. prescribing information for cyclobenzaprine notes that cases of depressed mood have been reported with cyclobenzaprine use as well as additional neuropsychiatric events including: abnormal sensations, anxiety, agitation, psychosis, abnormal thinking and dreaming²⁸. Reassuringly, no additional non-fatal SAEs concerning for depression or neuropsychiatric events are seen from a review of the PCSA database.

7.3.2 Nonfatal Serious Adverse Events

In the PCSA database, a total of 155 subjects reported SAEs.

²⁷ Joint Meeting of the Pulmonary Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, March 19, 2015. Slide A-12 GSK slide set and Slide 14 FDA Introductory Remarks.

²⁸ Flexeril (cyclobenzaprine) US Prescribing information website http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017821s051lbl.pdf accessed on January 22, 2015

An imbalance in respiratory SOC favoring active treatment is seen. This imbalance is primarily driven by events of asthma, which are not unexpected in an asthma development program. The imbalance in favor of treatment is consistent with the positive treatment effect on exacerbations that mepolizumab demonstrates in this clinical development program (Table 27, Table 28).

Treatment related imbalances are seen in the Cardiac Disorders and Vascular Disorders SOC. These imbalances are discussed in greater detail in Section 6.3.5 of this review. No other consistent treatment related imbalances are seen from a review of the data.

Table 27: Exposure-adjusted¹ non-fatal SAEs by System Organ Class: PCSA

	Mepolizumab				
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
Respiratory, thoracic, mediastinal d/o	200.7	61.0	98.3	112.5	76.7
Infections & Infestations	49.3	54.2	31.5	21.1	48.8
Injury Poisoning Procedural Complication	17.6	6.8	15.7	14.1	7.0
Renal and Urinary d/o	24.6	13.6	0	14.1	0
Cardiac d/o	3.5	6.8	11.8	7.0	27.9
Gastrointestinal d/o	7.0	6.8	3.9	14.1	7.0
Nervous System d/o	14.1	0	3.9	0	7.0
Vascular d/o	0	0	11.8	7.0	7.0
Musculoskeletal and connective tissue d/o	7.0	13.6	0	0	0
Immune system d/o	3.5	6.8	3.9	0	0
Metabolism and nutrition	0	6.8	7.9	0	0
Neoplasms benign, malignant, and unspecified	7.0	0	0	7.0	0
Reproductive system and breast d/o	3.5	0	0	7.0	7.0
Skin and subcutaneous tissue d/o	0	6.8	3.9	7.0	0
General d/o and administration site conditions	0	0	3.9	7.0	0
Hepatobiliary disorders	0	6.8	3.9	0	0
Investigations	3.5	0	0	7.0	0
Blood and lymphatic system d/o	0	0	0	7.0	0
Congenital, familial, and genetic d/o	3.5	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	3.9	0	0
Psychiatric d/o	3.5	0	0	0	0

	Mepolizumab				
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
¹ reported as frequency per 1000 subject years SY = subject years Source: ISS Table 2.057					

Table 28: Exposure-adjusted¹ non-fatal SAEs by Preferred Term occurring in more than one subject: PCSA

	Mepolizumab				
	Placebo 284 SY	100 SC 147 SY	75 IV 254 SY	250 IV 142 SY	750 IV 144 SY
Any SAE	348.6	189.9	204.5	232.1	188.1
Asthma	193.7	61.0	94.4	112.5	76.7
Pneumonia	10.6	6.8	3.9	0	13.9
Nephrolithiasis	10.6	6.8	0	0	0
Bronchitis	7.0	0	3.9	0	0
Lobar pneumonia	3.5	0	7.9	0	0
Tendon rupture	3.5	0	3.9	0	7.0
Atrial flutter	3.5	6.8	0	0	0
Cerebrovascular accident	7.0	0	0	0	0
Herpes zoster	0	13.6	0	0	0
Hypersensitivity	3.5	6.8	0	0	0
Hypertension	0	0	3.9	0	7.0
Myocardial ischemia	0	0	3.9	0	7.0
Viral upper respiratory tract infection	3.5	0	3.9	0	0
¹ reported as frequency per 1000 patient years SY = subject years Source: ISS Table 17					

No new safety signals are seen from a review of the cumulative data from the OLE studies provided in the 120-day safety update. Data for the AESI from the OLE are provided in Section 6.3.4.

7.3.3 Dropouts and/or Discontinuations

In the PCSA database there were a total of 35 subjects who reported an AE that led to withdrawal. No new safety concerns are seen from a review of these data. Asthma was the most frequently reported PT which is not unexpected given the underlying patient population. This occurred with greatest exposure-adjusted incidence in the 750 mg IV and placebo arms (Table 29).

Table 29: Adverse events occurring in ≥ 1 subject leading to discontinuation of mepolizumab or study withdrawal: PCSA database

	Mepolizumab				
	Placebo	100 SC	75 IV	250 IV	750 IV
Preferred term, n (%)					
N	412	263	344	152	156
Any event	12 (3)	3(1)	4(1)	8(5)	8(5)
Asthma	3 (<1)	0	1(<1)	1(<1)	2(1)
Hypersensitivity	2 (<1)	0	0	1 (<1)	2 (1)
Arthralgia	0	0	1 (<1)	1(<1)	0
Liver function test abnormal	1 (<1)	0	1 (<1)	0	0
Exposure-adjusted rates¹					
Subject years	284	147	254	142	144
Any	45.8	20.3	19.7	70.3	55.7
Asthma	10.6	0	3.9	7.0	13.9
Hypersensitivity	7.0	0	0	7.0	13.9
Arthralgia	0	0	3.9	7.0	0
Liver function test abnormal	3.5	0	3.9	0	0
¹ frequency of event per 1000 subject-years of exposure SY = subject years					
Source: ISS Table 19					

7.3.4 Significant Adverse Events

Deaths are discussed in Section 7.3.1, non-fatal SAEs in Section 7.3.2, dropouts and discontinuations for adverse events in Section 7.3.3 and submission specific primary safety concerns are discussed in Section 7.3.5. No additional significant adverse events have been identified for this application.

7.3.5 Submission Specific Primary Safety Concerns

Cardiovascular Safety

The sponsor's review of the safety data from Study 97 identified an increase in cardiac, thromboembolic, and ischemic SAEs (Placebo = 3[2]; 75 mg IV = 4 [3]; 250 mg IV = 2[1]; 750 mg IV (4 [3])²⁹

²⁹ Study 97 CSR Table 47

Given this potential signal, GSK implemented a prospective cardiovascular (CV) monitoring strategy for the remainder of its mepolizumab clinical development program. This included:

- Baseline collection of CV risk factors/functional status
- Base evaluation of clinical symptoms of ischemic heart disease (if clinically indicated)
- Additional ECG monitoring
- Use of CV-specific data collection forms to collect additional data on CV events of interest
- Use of an Independent Data Monitoring Committee (IDMC) and external adjudication panel to review CV safety. The committee adjudicated pre-specified CV events and all cause events that occurred during Phase 3 studies.

The charter for the IDMC specified that the committee would meet for the first time after 8 subjects experienced an adjudicated CV event in Studies 75 and 88. At the time of the BLA submission, this threshold was not met. A total of three events from Study 88 were adjudicated as CV or all-cause deaths (placebo: case of DVT/PE and an all-cause death from road traffic accident; mepolizumab 75 mg IV: myocardial infarction/unstable angina). No events from Study 75 met criteria for adjudication. The committee concluded at the end of the two double-blind studies that there were too few overall CV events for a meaningful assessment and recommended continuation of the open label extension studies.

In addition to the individual study results from Study 97, it is useful to consider pooled data from the placebo-controlled safety database. The SAE data were retrospectively reviewed by GSK to identify SAEs of Cardiac, Vascular, and Thromboembolic origin. This reviewer performed a similar analysis of all SAE PTs, the results of which were consistent with that reported by GSK. The exposure-adjusted data for the PCSA database are presented in Table 30. No major differences are observed when evaluating the data in subjects with or at risk for cardiovascular disease (data not shown). While decreased, a dose-dependent trend for cardiovascular events is still seen with the intravenous dosing, particularly for the high dose 750 mg IV group in the total population as well as in those with a CV history. This imbalance compared to placebo is not seen with the dose proposed for marketing. These data should be interpreted cautiously given the infrequency with which the events occurred.

Table 30: Exposure-adjusted on-treatment serious cardiac, vascular and thromboembolic events: PCSA database

	Mepolizumab									
	Placebo 284 SY		100 SC 147 SY		75 IV 254 SY		250 IV 142 SY		750 IV 144 SY	
	#	rate	#	rate	#	Rate	#	Rate	#	rate
Any event	3	10.6	1	6.8	6	23.6	3	21.1	5	34.8

	Mepolizumab									
	Placebo 284 SY		100 SC 147 SY		75 IV 254 SY		250 IV 142 SY		750 IV 144 SY	
Cardiac d/o										
Any event	1	3.5	1	6.8	3	11.8	1	7.0	4	27.9
Atrial flutter	1	3.5	1	6.8	0	0	0	0	0	0
Myocardial ischemia	0	0	0	0	1	3.9	0	0	1	7.0
Acute myocardial infarction	0	0	0	0	1	3.9	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0	1	7.0
Coronary artery insufficiency	0	0	0	0	0	0	1	7.0	0	0
Coronary artery thrombosis	0	0	0	0	1	3.9	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	1	7.0
SVT	0	0	0	0	0	0	0	0	1	7.0
Vascular d/o										
Any event	0	0	0	0	3	11.8	1	7.0	1	7.0
Hypertension	0	0	0	0	1	3.9	0	0	1	7.0
Distributive shock	0	0	0	0	0	0	1	7.0	0	0
Malignant hypertension	0	0	0	0	1	3.9	0	0	0	0
Venous thrombosis limb	0	0	0	0	1	3.9	0	0	0	0
Nervous system d/o										
Any event	2	7.0	0	0	0	0	0	0	0	0
Cerebrovascular accident	2	7.0	0	0	0	0	0	0	0	0
Gastrointestinal d/o										
Any event	0	0	0	0	0	0	1	7.0	0	0
Thrombosis mesenteric vessel	0	0	0	0	0	0	1	7.0	0	0
¹ frequency of event per 1000 subject-years of exposure SY = subject year Source: Response to information request dated February 2, 2015 Table 2.203										

When the data are categorized into ischemic events vs. arrhythmic events, the imbalance decreases further (Table 31) making it difficult to conclude that the data demonstrate a treatment-related cardiovascular effect.

Table 31: Serious ischemic and arrhythmic adverse events: PCSA database

	Mepolizumab				
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Serious ischemic events* [†]	2 (<1)	0	2 (<1)	2 (1)	2 (1)
Serious arrhythmic events [‡]	1 (<1)	1 (<1)	0	0	2 (1)

* PTs include: myocardial ischemia, acute myocardial infarction, coronary artery insufficiency, coronary artery thrombosis, myocardial infarction, cerebrovascular accident, thrombosis mesenteric vessel
[‡] PTs include: atrial flutter, atrial fibrillation, supraventricular tachycardia
Source: Response to information request dated February 2, 2015 reviewer modifications of Table 2.204 and reviewer modifications of Table 2.203
[†] Source: Integrated Summary of Safety Table 2.105, values represent number of subjects with an event rather than number of events

A total of 14 events of Serious Cardiac, Vascular, Thromboembolic and Ischemic AEs were reported from the OLE studies through October 27, 2014 (Table 32). The lack of a placebo comparator arm makes interpretation of these data difficult; however, an increased frequency of events compared to the placebo-controlled database is not seen. Of these 14 events, six events were sent to the CEC for adjudication. A total of 4 events were confirmed as CV events (Table 32). The fatal event was adjudicated by the charter but was not CV-related (respiratory arrest, see Section 6.3.1 Table 26).

Table 32: Serious Cardiac, Vascular, Thromboembolic, and Ischemic Adverse Events: OLE Studies 61 and 66¹

	Mepo 100 SC		
	Study 66 N = 347	Study 61 N = 651	Total N = 998
Any Event, n (%)	5 (1)	9 (1)	14 (1)
Atrial fibrillation	1 (<1)	3 (<1)	4 (<1)
Acute myocardial infarction ²	1 (<1)	0	1 (<1)
Angina pectoris ²	0	1 (<1)	1 (<1)
Cardio-respiratory arrest	0	1 (<1)	1 (<1)
Cerebral hemorrhage	0	1 (<1)	1 (<1)
DVT	0	1 (<1)	1 (<1)
Hypertension	1 (<1)	0	1 (<1)
Hypertensive heart disease	0	1 (<1)	1 (<1)
Hypotension	0	1 (<1)	1 (<1)
Mitral Valve incompetence	0	1 (<1)	1 (<1)
Myocardial infarction ²	0	1 (<1)	1 (<1)
Pulmonary embolism ²	0	1 (<1)	1 (<1)
Subarachnoid hemorrhage	1 (<1)	0	1 (<1)
Thrombophlebitis superficial	1 (<1)	0	1 (<1)
Serious ischemic events	1 (<1)	3 (<1)	4 (<1)

Source: 120 day safety update March 3 2015 Modified from Tables 17, 18, Table 2.044
¹ cumulative data through October 27, 2014
² classified as serious ischemic events

Table 33: Adjudication committee interpretation of cardiac events

Adjudication Category	Mepo 100 SC		
	Preferred Term	Study 66 N = 651	Study 61 N = 998
Myocardial infarction/unstable angina requiring hospitalization	Acute myocardial infarction	1	0
	Myocardial infarction	0	1
Stroke	Subarachnoid hemorrhage	1	0
	Deep vein thrombosis/pulmonary embolism	0	1
All cause death	Respiratory arrest	1	0

Source: 120 day safety update March 3, 2015 Tables 19

Of note, subsequent to the October 27, 2014 safety cutoff of for the 120-day safety update, GSK reported 2 additional deaths occurring in the open-label extension studies. These included death due to acute cardiac failure in a 64 year old patient receiving 100 mg SC mepolizumab.

Hypersensitivity reactions, anaphylaxis and local injection site reactions

A treatment-related imbalance in local injection site reactions is seen from a review of the data in the PCSA database (Table 34). The data from the OLE studies did not reveal an increased frequency of hypersensitivity events in patients receiving mepolizumab 100 mg SC.

Table 34: On-treatment systemic and local injection site reactions: PCSA

	Mepolizumab				
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Systemic Hypersensitivity Reaction	7(2)	3(1)	4(1)	3(2)	2(1)
Local Site Reactions	14(3)	21(8)	11(3)	0	0
Source: ISS Table 2.086, 2.179					

This mepolizumab development program used the NIAID/FAAN anaphylaxis criteria³⁰ to evaluate potential cases of systemic hypersensitivity reactions to determine if the cases were anaphylaxis. In addition, the applicant conducted a retrospective manual review of the associated symptoms outlined in the anaphylaxis criteria, a retrospective standard MedDRA Query (SMQ) for anaphylactic reactions, and a review of AEs associated with eczema/rash, dyspnea, and nasal congestion to determine if reporting of these events was associated with unrecognized hypersensitivity reactions.

A review of the line listings for hypersensitivity events was also conducted by this reviewer. No cases meeting the NIAID/FAAN criteria were identified by this review of the PCSA database or OLE Studies 97 or 88. However, one potential anaphylactic case from the ongoing open-label Study 201312 was identified. Study 201312 is an open-label extension of Study 61, enrolling subjects with a history of life-threatening/seriously debilitating asthma. Details of this case are outlined below.

- Study 201312: 42-year-old female with a history of sulfite allergy (previous reactions to red wine) developed itching, angioedema and bronchospasm 30 min after ingestion of 100 g of raisins and 14 hours after her most recent dose of mepolizumab. Examination at the ER revealed oxygen saturation of 94% (baseline value), normal blood pressure, and no evidence of soft tissue swelling or urticaria although wheezing was audible. The subject was treated with clemastine, bronchodilator nebulizers and prednisone. The case narrative notes that no changes were made to the mepolizumab dosing. Follow-up information provided by the sponsor in May 2015 indicates that this individual has

³⁰ Sampson et al., "Second symposium on the definition and management of: a summary report." J Allergy Clin Immunol 2006; 117:391-7.

successfully rechallenge with mepolizumab 8 times with no further symptomatology.

Thus, this reviewer concurs with the investigator’s assessment that the comorbid condition of a sulfite allergy is the more likely cause for this event.

Infections including opportunistic Infections

Herpes zoster is the only opportunistic infection to occur in more than one subject in the PCSA database. The PT of Herpes Zoster occurred in 4 subjects treated with mepolizumab 75 mg IV, 2 subjects each in the placebo and mepo100 mg SC treatment groups, and a case of ophthalmic herpes zoster in the 750 mg IV dose group (Table 35). The OLE studies include an additional 5 reports of herpes zoster through the October 27, 2014 safety cutoff date in patients treated with mepolizumab 100 mg SC and review of the data from the Hypereosinophilic development program reveals additional cases. While chronic corticosteroid use may be a confounder, the imbalance between treatment and placebo arms in the PCSA database is potentially suggestive of a treatment-related effect. GSK has a current statement outlining that herpes zoster was the only on-treatment SAE to occur in more than 1 individual treated with mepolizumab and more commonly with placebo. Given the AE data seen in the program and these SAE data, inclusion of the proposed statement into product labeling is supported.

The OLE studies also include 3 reports of esophageal candidiasis through the October 27, 2014 safety cutoff date. Interpretation of these data is limited by the lack of a placebo comparator arms for these studies, and further confounded by background inhaled corticosteroid use which is a known risk factor for the development of esophageal candidiasis.

Of note, the clinical development program excluded enrollment of patients with parasitic disease. However, there was one report of parasitic gastroenteritis that was treated with albendazole in a subject receiving mepolizumab 100 mg SC in Study 88 (no confirmatory diagnostic testing was performed). There were no reports of parasitic infection from the OLE studies. Conclusions regarding the use of mepolizumab in parasitic disease cannot be drawn from the data provided in the clinical development program, and further evaluation of this issue is warranted given the mechanism of action of this biologic.

Table 35: Opportunistic infections: PCSA database

	Mepolizumab				
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Any event	4 (<1)	3 (1)	4 (1)	0	2(1)
Herpes zoster	2 (<1)	2 (<1)	4 (1)	0	0

	Mepolizumab				
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Blastomycosis	1 (<1)	0	0	0	0
Gastrointestinal fungal infection	0	1(<1)	0	0	0
Ophthalmic herpes zoster	0	0	0	0	1 (<1)
Ophthalmic herpes simplex	1 (<1)	0	0	0	1 (<1)
Respiratory moniliasis	0	0	0	0	1 (<1)

Source: ISS Table 2.123

Besides the slight imbalance in herpes zoster SAEs, no additional imbalance in infectious SAEs are noted in this clinical development program; see Section 6.3.2, Table 27 and Table 28 for additional information.

Malignancies

There are no treatment-related imbalances in the malignancy data from the PCSA database. A total of 3 malignancies were reported in the placebo-treated subjects, 1 subject in the mepolizumab 75 mg IV group and 1 subject in the 250 mg IV dose group (Table 36).

In the OLE studies, there were 9 reports of malignancies through the October 27, 2014 safety cutoff date. These included 2 reports of breast cancer, 2 reports of prostate cancer, 1 basal cell carcinoma, 1 endometrial cancer, 1 gastric cancer, 1 skin cancer, and 1 squamous cell carcinoma.

The reported malignancies from this development program are not uncommon in the general population. Continue routine pharmacovigilance for malignancies is recommended.

Table 36: On- treatment malignancy: PCSA

	Mepolizumab				
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156
Any event	3 (<1)	0	1 (<1)	1(<1)	0
Basal cell carcinoma	0	0	1 (<1)	0	0
Basosquamous carcinoma	1 (<1)	0	0	0	0
Prostate cancer	1 (<1)	0	0	0	0
Squamous cell carcinoma	1 (<1)	0	0	0	0
Uterine cancer	0	0	0	1 (<1)	0

Source: ISS Table 2.116

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the section of this review, common adverse events are defined as events occurring in $\geq 3\%$ of subjects in a given treatment group. On-treatment adverse events occurring more frequently in the 100 mg SC dose and route proposed for marketing than placebo are provided in Table 37.

Table 37: Common on-treatment Adverse Events reported by 3% of more of subjects in any treatment group and more frequent in the mepolizumab 100 mg SC arm: Study MEA115575 and first 24 weeks of MEA115588

	Placebo N = 257	Mepo 100 SC N = 263
Preferred Term, n %		
Headache	46 (18)	51 (19)
Injection site reaction	8 (3)	20 (8)
Back pain	9 (4)	14 (5)
Fatigue	11 (4)	12 (5)
Influenza	6 (2)	7 (3)
Urinary tract infection	4 (2)	9 (3)
Abdominal pain upper	5 (2)	7 (3)
Pruritus	5 (2)	7 (3)
Eczema	1 (<1)	9 (3)
Muscle spasms	1 (<1)	7 (3)

Source: Response to IR dated February 2, 2015 Table 2.202

No major differences are seen from a review of the common adverse events from all the doses included in the PCSA database or the OLE studies through the October 27, 2014 safety cutoff date.

7.4.2 Laboratory Findings

No clinically meaningful differences in chemistry parameters are noted for the mepolizumab 100 mg SC compared to placebo (data not shown). A dose dependent trend for increased transaminases is seen with the intravenous dosing, particularly for the high dose 750 mg IV group (Table 38). Of note, no associated trend in increased bilirubin is seen from these data and review of the AE data does not reveal an imbalance in liver adverse events. In addition, no imbalance is seen with the dose proposed for marketing. One additional subject with elevated transaminases and an

SAE of cholestatic jaundice was reported in the 120-day safety update; however, the subject continued on mepolizumab treatment and the event resolved.

Decreased eosinophil counts are seen in the mepolizumab treated groups; however, this is an expected effect of the biologic. No additional clinically meaningful differences in hematologic parameters are seen from a review of the data (data not shown).

Table 38: Summary of LFTs above upper limit normal: PCSA

	Mepolizumab				
	Placebo N = 412	Mepo 100 SC N = 263	Mepo 75 IV N = 344	Mepo 250 IV N = 152	Mepo 750 IV N = 156
ALT					
> 2x ULN	6 (1)	4 (2)	4 (1)	0	4 (3)
> 3x ULN	3 (<1)	0	3 (<1)	1 (<1)	2 (1)
AST					
> 2x ULN	4 (<1)	2 (<1)	2 (<1)	1 (<1)	3 (2)
> 3x ULN	2 (<1)	1 (<1)	3 (<1)	0	3 (2)
AP					
> 2x ULN	0	0	0	0	0
> 3x ULN	0	0	0	0	0
Bilirubin¹					
> 2xULN	0	0	0	0	0
> 3x ULN	0	0	0	0	0
GGT					
> 2x ULN	14 (3)	9 (3)	16 (5)	6 (4)	7 (4)
> 3x ULN	17 (4)	6 (2)	15 (4)	6 (4)	9 (6)

¹ if direct bilirubin is available, then it must be > 35% total bilirubin to satisfy criteria
Source: ISS Table 2.145

7.4.3 Vital Signs

Vital sign data, including the absolute change and mean change from baseline data for Study 97 and absolute change data from Studies 88 and 75 were reviewed. No clinically significant differences between treatment groups are seen for sitting pulse, systolic, or diastolic blood pressures.

7.4.4 Electrocardiograms (ECGs)

ECGs were assessed at Week 20 and Week 56 (or early withdrawal visit) in Study 97. They were assessed at Week 8, 16, 24, and 4 weeks post-dose for subjects entering

the OLE studies and 12 weeks post-last dose for subjects not continuing into the OLE studies for Studies 88 and 75.

In general, monoclonal antibodies are not associated with QTc prolongation and thorough QTc studies are generally not required for these clinical development programs. For the mepolizumab programs, a few outlier subjects had maximum post-baseline QTc(F) values > 480 and ≤ 500 msec; however, causality to the investigational product cannot be given the limited number of outlier subjects. The effects on heart rate are discussed in Section 6.4.3.

The ECGs in this program were evaluated by licensed cardiologists and categorized as abnormal or normal for the three efficacy studies. For Studies 75 and 88, the findings were further classified as “abnormal, clinically significant” or abnormal, “not clinically significant”. No major treatment-related imbalances are seen from a review of these data.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted for this development program.

7.4.6 Immunogenicity

As mepolizumab is a monoclonal antibody, anti-mepolizumab antibodies with an assessment of neutralizing antibody status for positive values, was assessed throughout this clinical development program. No immunogenicity concerns from a clinical perspective are raised from a review of the immunogenicity data.

Immunogenicity was assessed throughout its clinical development program using a screening assay followed by a confirmation assay. Anti-drug antibodies (ADA) and drug neutralizing titers were assessed following a positive confirmation assay.

Overall, 6% of patients receiving mepolizumab 100 mg SC were ADA positive in the PCSA database and 5% in the OLE studies. The majority of mepolizumab treated patients developed initial antibodies by the first treatment assessment at Week 16 (68%; 19/28 patients). Of the positive subjects in the PCSA studies, a single patient developed neutralizing antibodies in the OCS reduction study, Study 75 (Table 39). As the patient had a low peripheral blood eosinophil count at baseline (on chronic oral corticosteroids), the impact of the neutralizing antibodies on the drug’s pharmacodynamic eosinophil response remains unclear. Clinically, the subject did experience loss of asthma control with OCS reduction. There were no SAEs in this patient; however the subject developed an injection site reaction leading to treatment and study withdrawal.

A total of 21 subjects (5%) in Study 66 and 31 subjects in Study 61 (5%) developed antidrug antibodies in the OLE studies through a safety cutoff date of October 27, 2014. Rates were similar between subjects receiving MDP1 (4%) and MDP2 (4%). All subjects tested negative for neutralizing antibodies.

The enrollment of patients from trial 97 into the OLE following a cessation in drug therapy (mean drug holiday 18 months) allowed for an assessment of immunogenicity after drug holiday as well as a switch from IV to SC dosing. Based on data at the time of BLA submission, a total of 18 subjects had a positive ADA sample for at least one visit after baseline, 13 of whom had transient post-dose values. None of these were positive for a neutralizing antibody.

Table 39: Summary of ADA and NAb assay: PCSA

	Mepolizumab					
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156	All doses N = 915
ADA assay						
N	402	260	334	149	150	893
Negative	397(99)	245(94)	324(98)	147(99)	149(99)	865 (97)
Positive	5(1)	15(6)	10(3)	2(1)	1(<1)	28(3)
Nab assay						
n	5	15	8	2	1	28
Negative	4	14	8	2	1	27(96)
Positive	0	1(7)	0	0	0	1 (<1)
Source: Immunogenicity report Table 24						
Tabulation does not include results from 3 patients who were positive at baseline						

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A review of the dose dependence for adverse events is presented where relevant throughout this safety review.

7.5.2 Time Dependency for Adverse Events

GSK provided summary tables for time to onset to an adverse event for its placebo controlled multi-dose asthma studies (0 - < 12 weeks, 12-< 24 weeks, 24 - < 36 weeks, 36 - < 48 weeks, and > 48 weeks). An analysis of these data reveals no major differences in the safety profile based on time.

7.5.3 Drug-Demographic Interactions

No new safety signals are identified by evaluating the safety data by gender, age, race, ethnicity, and region. However, many of the subgroup analyses are limited by small sample sizes. The overall event rates are summarized below.

Table 40: On-treatment adverse events by subgroups: PCSA database

	Mepolizumab					
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156	All doses N = 915
Gender						
Female, n	234	160	209	93	93	555
Any event,n(%)	195 (83)	132 (83)	180 (86)	79 (85)	77 (83)	468 (84)
Male, n	178	103	135	59	63	360
Any event,n(%)	143 (80)	77 (75)	107 (79)	45 (76)	45 (71)	274 (76)
Age						
12-17, n	9	9	9	1	0	28
Any event,n(%)	6 (67)	7 (78)	9 (100)	1 (100)	17 (89)	23 (82)
18 – 64, n	366	216	302	143	153	814
Any event n(%)	298 (81)	172 (80)	249 (82)	116 (81)	119 (78)	656 (81)
≥ 65, n	37	38	33	8	3	82
Any event n(%)	34 (92)	30 (79)	29 (88)	7 (88)	3 (100)	69 (84)
Race						
Af. Heritage, n	9	7	11	7	5	30
Any event n(%)	7 (78)	6 (86)	11 (100)	7 (100)	4 (80)	28 (93)
White, n	349	219	288	136	140	783
Any event n(%)	281 (81)	173 (79)	237 (82)	108 (79)	107 (76)	625 (80)
Asian, n	49	35	43	7	10	95
Any event n(%)	45 (92)	29 (83)	37 (86)	7 (100)	10 (100)	83 (87)
Other, n	5	2	2	2	1	7
Any event n(%)	5 (100)	1 (50)	2 (100)	2 (100)	1 (100)	6 (86)
Region						
US, n	46	26	41	19	20	106
Any event,n(%)	39 (85)	24 (92)	39 (95)	17 (89)	16 (80)	96 (91)
EU, n	210	141	158	70	69	438

	Mepolizumab					
	Placebo N = 412	100 SC N = 263	75 IV N = 344	250 IV N = 152	750 IV N = 156	All doses N = 915
Any event, n(%)	166 (79)	108 (77)	125 (79)	50 (71)	50 (72)	333 (76)
Rest of world, n	156	96	145	63	67	371
Any event n(%)	133 (85)	77 (80)	123 (85)	57 (90)	56 (84)	313 (84)

Source: ISS Table 2.130, 2.132, 2.134, 2.136

Table 41 provides the total SAE data by age, race and gender.

Table 41: SAE events by demographic subgroup

	Mepolizumab			
	Placebo N = 412	100 SC N = 263	75 IV N = 344	All doses N = 915
Gender,				
Female, n	234	160	209	555
Any event, n(%)	38 (16)	12 (8)	25 (12)	65 (12)
Male, n	178	103	135	360
Any event. n (%)	25 (14)	5 (5)	9 (7)	27 (8)
Age				
12-17, n	9	9	9	28
Any event, n (%)	2 (22)	1 (11)	0	2 (11)
18 – 64, n	366	216	302	814
Any event, n (%)	55 (15)	13 (6)	32 (11)	84 (10)
≥ 65, n	37	38	33	82
Any event	6 (16)	3 (8)	2 (6)	6 (7)
Race				
Af. Heritage, n	9	7	11	30
Any event, n (%)	3 (33)	3 (43)	2 (18)	8 (27)
White, n	349	219	288	783
Any event, n (%)	49 (14)	8 (4)	28 (10)	72 (9)
Asian, n	49	35	43	95
Any event, n (%)	11 (22)	6 (17)	4 (9)	12 (13)
Other, n	5	2	2	7
Any event, n (%)	0	0	0	0

Source: Table 30 from GSK Briefing Document for June 11, 2015 Pulmonary Drugs Advisory Committee Meeting

7.5.4 Drug-Disease Interactions

Mepolizumab was evaluated in subjects with less severe asthma in Study 06. Additional details of this study design and the efficacy data can be found in Section 5.1.7 of this document. While the study was relatively small, the safety data from this study allow for estimation of mepolizumab's safety profile in a less severe asthmatic population.

No major differences in the safety profile are demonstrated by a review of the safety data from Study 06; although, the analysis is limited by the small sample size.

Rates of adverse events were comparable between placebo and mepolizumab treatment groups with a slight numeric imbalance in favor of treatment (placebo 76%; mepolizumab 250 and 750 68% and 69% respectively). The most common AE preferred term was URTI (18-20%) followed by asthma. For the AE term of asthma a small numeric imbalance in favor of treatment (placebo 24%; mepolizumab 250 mg IV 21% and mepolizumab 750 mg IV 17%) was seen. There were no deaths during the study. Non-fatal SAEs were reported in the 4 subjects in the placebo group (vertigo, bladder carcinoma, unintended pregnancy, asthma), in three subjects in the mepolizumab 250 mg dose group (hydrocephalous, constipation, and GI disorder NOS) and in two subjects in the mepolizumab 750 mg dose group (2 reports of asthma).

7.5.5 Drug-Drug Interactions

No specific drug-drug interaction studies were performed for this development program. As noted throughout the review, the safety data obtained from the severe asthma program were obtained in subjects on background standard of care therapy for severe asthma. Thus the safety data obtained from this program reflects current clinical use of the product should the product be approved.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific non clinical carcinogenicity studies were conducted for this supplemental BLA.

7.6.2 Human Reproduction and Pregnancy Data

As of October 27, 2014, 18 pregnancies were reported in 17 female subjects receiving mepolizumab in the completed and ongoing mepolizumab studies (all indications). Of the 16 known outcomes, 10 resulted in live births (1 placebo, 2 mepo 100 SC, 3 mepo 75 mg IV, 4 mepo 750 IV), 4 resulted in spontaneous abortions (1 each in placebo, mepo 100 SC, mepo 75 mg IV, and mepo 750 mg IV) and 2 were electively terminated. A total of 2 pregnancies were ongoing at the time of database lock.

For product labeling, the sponsor notes that (b) (4)
(b) (4). Labeling further notes that (b) (4)
In addition, the sponsor has indicated in its proposed labeling that it will establish a pregnancy registry to monitor (b) (4) outcomes of pregnant women exposed to mepolizumab.

The Agency's Pediatric Maternal Health Staff have reviewed the mepolizumab pregnancy data and the proposed label and have recommended modifications and clarifications to Section 8.1 of the of the USPI which are acceptable from a clinical standpoint. In addition, the consult recommended that the pregnancy registry be made a post marketing commitment to ensure the Agency has access to updates and the completed study report.

7.6.3 Pediatrics and Assessment of Effects on Growth

As discussed in Section 5.7.3 of this review, there were a limited number of adolescents enrolled in the development program. While the small number enrolled limits the interpretation of the safety data, no major differences in safety are observed when adverse events are evaluated. Given the mechanism of action for of mepolizumab, there are no anticipated effects on pediatric growth. See Section 7.5.3 for overall rates of AEs in the adolescent subgroup compared to other ages.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Single intravenous doses up to 1,500 mg of mepolizumab have been administered to subjects with eosinophilic disease without dose related toxicities. Mepolizumab is not anticipated to be a drug with abuse potential. Review of the adverse event data during the post-treatment follow-up period does not indicate any evidence of withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

Alteration in commercial drug product during phase 3 program

The sponsor altered its manufacturing processes during the phase 3 development program. The primary change was to decrease the amount of lyophilized product in the vial to correspond with the proposed dose of marketing with other minor manufacturing changes outlined in the product quality review.

Because this change was made during the phase 3 program, the sponsor was able to provide AE data from the manufactured drug product 1 (MPDP 1) collected from the pivotal phase 3 efficacy trials and MPDP2 (commercial product) from the ongoing open label extension studies. Review of these AE tabulations do not reveal any new safety concerns for the proposed commercial product. In addition MPDP2 does not appear to be any more immunogenic than MPDP1.

There are no identified issues with the proposed commercial product from a clinical perspective.

8 Postmarket Experience

At the time of this review, mepolizumab is not approved for marketing in any country.

9 Appendices

9.1 Literature Review/References

Literature references, including publications regarding mepolizumab use in asthma, are cited throughout this review where relevant.

9.2 Labeling Recommendations

The specific labeling language remains a review issue at the time of finalization of this review.

However, as discussed in the Efficacy Summary, this review favors inclusion of more general statements in the indication statement regarding the targeted patient population. To that end, the indication should specify that the therapy is indicated as add-on maintenance therapy in patients with asthma with exacerbations despite therapy with high-dose inhaled corticosteroids plus an additional controller therapy with or without additional oral corticosteroids with initiation of treatment guided by peripheral blood eosinophil levels. The statement outlines that that therapy should be reserved for patients with severe asthma and should be used as add-on therapy to current standard of care. However, the specific peripheral blood eosinophil thresholds used to enrich this study population are described in Section 14 of the USPI rather than the indication statement. This is a similar approach to handling enrichment criteria for exacerbations where the number of prior exacerbations are not enumerated in the indication statement but reserved for description in Section 14 of the USPI. To further assist clinicians in identifying appropriate patients for treatment, Section 14 should outline the specific enrichment criteria used in the development program as well as include a discussion of the treatment modification effect by eosinophils that has been demonstrated for this treatment. Ultimately this approach allows for the judgment and discretion of the treating clinician which is prudent given the lack of clinical consensus guidelines in identifying and defining a severe eosinophilic asthma population.

This review also recommends inclusion of study results from the failed lung function study, Study 06 into the product label as a means to help guide clinicians on appropriate patient population for use of the product. To that end, Section 14 should also present the lung function data that were obtained from each of the pivotal studies.

9.3 Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee Meeting was held on June 11, 2015. The committee was asked to discuss the following topics:

- Asthma severity most likely to benefit from mepolizumab
- Role of eosinophils in initiating treatment
- Adequacy of the efficacy and safety data in children 12 to 17 years of age
- Ethnicity of the study population.

Overall the committee felt use should be limited to a severe asthma population, with eosinophil counts guiding who should initiate treatment. No specific eosinophil cutoff values were endorsed by then panel, but general concern regarding the utility of the historical threshold value ≥ 300 cells/ μL was raised. In general, the committee noted the lack of data in the adolescent and African American population. However, some members voiced concern regarding restricting use in either of these populations given the unmet medical need in both.

The committee was asked to vote individually on the efficacy and safety of mepolizumab as well as whether the risk benefit supports approval. Each voting question was subdivided by age with a vote in adults ≥ 18 years of age and in adolescents 12 to 17 years of age. Overall, the committee voted strongly in favor of the demonstration of efficacy and safety with a favorable risk benefit in the adult population; however the majority of the panel felt that the data were too limited to demonstrate efficacy and safety in the adolescent population. Further evaluation in adolescent population was recommended.

To summarize the committee voted 14 “Yes” and 0 “No” that efficacy had been demonstrated in the adult population, with 5 voting “Yes” and 9 voting “No” for the demonstration of efficacy in the adolescent population. For Question 4, there were 13 “Yes” votes and 1 “No” vote that safety had been demonstrated in the adult population, with only 2 “Yes votes” for the adolescent population and 12 “No” votes. For the final question asking if the risk benefit supported approval, there were 14 “Yes” votes for the adult population and 0 “No” votes, and 4 “Yes” votes for the adolescent population and 10 “No” votes.

9.4 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure Review Template

Application Number: BLA 122-526

Submission Date(s): November 4, 2014

Applicant: GlaxoSmithKline

Product: Mepolizumab 100 mg SC

Reviewer: Sofia Chaudhry, MD

Date of Review: November 18, 2015

Covered Clinical Study (Name and/or Number): MEA112997, MEA115588,
MEA115661, MEA115666

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: MEA112997: 81 principle investigators MEA115588: 119 principle investigators MEA115661: 139 principle investigators MEA115666: 65 principle investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: <u>0</u>		

Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

From trials MEA112997, MEA115588, MEA115661, MEA115666, GSK certified the absence of financial arrangement for 10 investigators (all sub investigators) 9 investigators (8 sub investigators, 1 principle), 11 investigators (10 sub investigators, 1 principle) and 13 investigators (all sub investigators) respectively. Of note the information could not be obtained from the principle investigator for trials MEA115588 and MEA115661. Dr. Matteo Sofia was deceased at the time of the collection. Notably, his center enrolled 7 subjects (out of 580) from trial MEA115588 and 6 subjects in MEA115661 (out of 649 subjects). It is unlikely that enrollment of < 2% of the study populations are likely to impact the study results.

From these same trials there were 4 investigators with significant payments to reports. These are summarized below:

- (b) (6) reported \$60,000 in Honoraria for trial MEA112997, \$400,000 in grants, \$4,000 in retainers, and \$30,000 in Honoraria for trials MEA115588 and MEA115666. In addition, (b) (6) while trials MEA115588, MEA115661, and MEA115666 were still ongoing. (b) (6) study site enrolled (b) (6) for MEA112997, (b) (6)
- (b) (6) reported \$54,250 in Honoraria for trial MEA112997. His study site recruited (b) (6)
- (b) (6) reported \$100,000 in grants and \$2,000 Honoraria for study MEA112997. His study site recruited (b) (6)
- (b) (6) reported \$78,764.40 in other payments for Study MEA115661. His study site recruited (b) (6)

All of the investigators with disclosable information and those for whom follow up information could not be obtained recruited a small sample of the total study populations. Given the small proportion of the study totals involved, it is unlikely that any misconduct could impact study results. Therefore no further action is recommended at this time.

APPEARS THIS WAY ON ORIGINAL

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

/s/

SOFIA S CHAUDHRY
06/30/2015

LYDIA I GILBERT MCCLAIN
06/30/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			No separate QTc study was performed. ECGs were evaluated throughout development.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			See comment for item 21 above
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MeDRA v 16.1 used for ISS
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Located within CSRs
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			CSR and datasets for trial 006 and XX included
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Agreed PSP provided
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow	X			+ statistical reviewer

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	Defer to statistical reviewer
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	Defer to statistical reviewer
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	None requested
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

This is a medical officer filing checklist and review for BLA 125526 for mepolizumab, an anti-IL-5 monoclonal antibody. The sponsor is proposing mepolizumab as a treatment for a severe asthmatic population which the sponsor believes has evidence of eosinophilic inflammation. The proposed dose for marketing is 100 mg SC q 4 weeks.

Clinical Development Program

The asthma clinical development program primarily relies on two, randomized, placebo-controlled, parallel-group, exacerbation trials (trials 97 and 88). It is notable that the sponsor's two pivotal exacerbation trials used different enrichment criteria to define a severe asthmatic population with evidence of eosinophilic inflammation. Both trials define severe asthma based on a background therapy requirement for high dose inhaled corticosteroids plus an additional controller therapy and a history of ≥ 2 exacerbations in the previous year. Trial 97 defined eosinophilic inflammation as the presence of peripheral blood eosinophils ≥ 300 cells/mcl or sputum eosinophilia $> 3\%$ in the past 12 months, a FENO ≥ 50 ppb, or deterioration of asthma control after 25% reduction in ICS or oral corticosteroids. Trial 88 simplified these criteria and relied on a peripheral blood eosinophil count ≥ 300 cells/mcl in the past 12 months or a count ≥ 150 cells/mcl at the time of screening

Additional efficacy support is drawn from a single steroid sparing trial, trial 75. To further support refinement of the patient population, the sponsor cites negative efficacy data from Trial 06 which evaluated uncontrolled moderate asthmatics without any additional enrichment criteria to identify patients with evidence of eosinophilic inflammation. While this trial failed to demonstrate efficacy of mepolizumab in this patient population, it is notable that the trial used a different primary endpoint (peak expiratory flow) and the collection of exacerbation data was limited by the relatively short 12 week treatment period. It is unlikely that this trial will be able to

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

provide conclusive evidence that the drug fails to work in non-severe asthmatic patients with or without evidence of eosinophilic inflammation. However, the data does provide some clinical guidance to treating clinicians on who mepolizumab may not work for. Whether the data are appropriate to include in product labeling will be a review issue.

Safety data is primarily provided by the sponsor's efficacy trials with additional longer term safety data provided by two ongoing open label extension trials. These data are further supplemented by safety data obtained from other mepolizumab clinical development programs including Hypereosinophilic Syndrome (HES), nasal polyposis, and eosinophilic esophagitis.

The sponsor's clinical development program for mepolizumab in severe eosinophilic asthma is summarized in Table 1 below.

Table 1: Severe Asthma Clinical Development Program

Trial	Design	Population	Tx Arms: N	Endpoints
Exacerbation Trials				
97	MC, R, DB, PC, PG dose ranging trial 52 week treatment period	- ≥ 12 yo - uncontrolled severe asthma - ≥ 2 exac/12 months Eosinophil enrichment criteria (within 12 months) - eos ≥ 300 or sputum eos >3% - FENO ≥ 50 ppb - deterioration of asthma control after 25% reduction in ICS/OCC	Mepo 75 IV: 153 Mepo 250 IV: 152 Mepo 750 IV: 156 Placebo IV: 155	1: Clinically significant exacerbation 2: FEV1 3: AQLQ 4: exac with hosp/ED 5. ACQ
88	MC, R, DB, DD, PC, PG 32 week treatment period	- ≥ 12 yo - uncontrolled severe asthma - ≥ 2 exac/ 12 months - on ICS + controller ±OCS Eosinophil enrichment criteria - ≥ 150 eos at screening or hx of ≥ 300 during past 12 months	Mepo 100 SC:191 Mepo 75 IV: 194 Placebo: 191	Clinically significant exacerbation 2. exac with hosp/ED 3. exac with hosp 4. FEV1 5.SGRQ
Supplemental efficacy trial				
75	MC, R, DB, PC, PG, 24-week treatment steroid reduction trial	- ≥ 18 years of age - ≥ 150 eos at screening or hx of ≥ 300 during past 12 months - No asthma exacerbation requirement	Mepo 100 SC: 69 Placebo SC: 66	Reduction in steroid dose while maintaining asthma control
Safety extension trials				

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Trial	Design	Population	Tx Arms: N	Endpoints
66	OLE safety trial Approx. duration 3.5 <i>Ongoing</i>	From trial 97, 12 month break between trials Modified drug product (TBM) introduced (100 mg/vial strength)	IV only	
61	OLE safety trial approx. duration 52 weeks from 88 and 75 <i>Ongoing</i>	From trials 88 and 75 (no break in tx) Modified drug product (TBM) introduced	SC	
Supplemental trials				
92	OL, dose-ranging PK/PD bridging trial for IV to SC administration	Moderate/severe asthma		
06	MC, R, DB, PC, PG with 12 week treatment period	- ≥ 18 years old - uncontrolled moderate asthma - FEV1 $\geq 50\%$ and $\leq 80\%$ - On ICS controller therapy - No exacerbation requirement - No eosinophil inflammation requirement	Mepo 250 IV Mepo 750 IV Placebo	1: PEF 2: FEV1

Efficacy

Trial 97 was a 52 week exacerbation trial that evaluated three intravenous doses (75 mg, 250 mg and 750 mg) of mepolizumab providing for reasonable dose ranging of the product. All three doses provided for a reduction in clinically significant exacerbations without evidence of a dose response (see Table 2). While trial 97 demonstrated an exacerbation treatment effect, a consistent, clinically meaningful improvement in FEV1 was not demonstrated (see Figure 1 for representative sample).

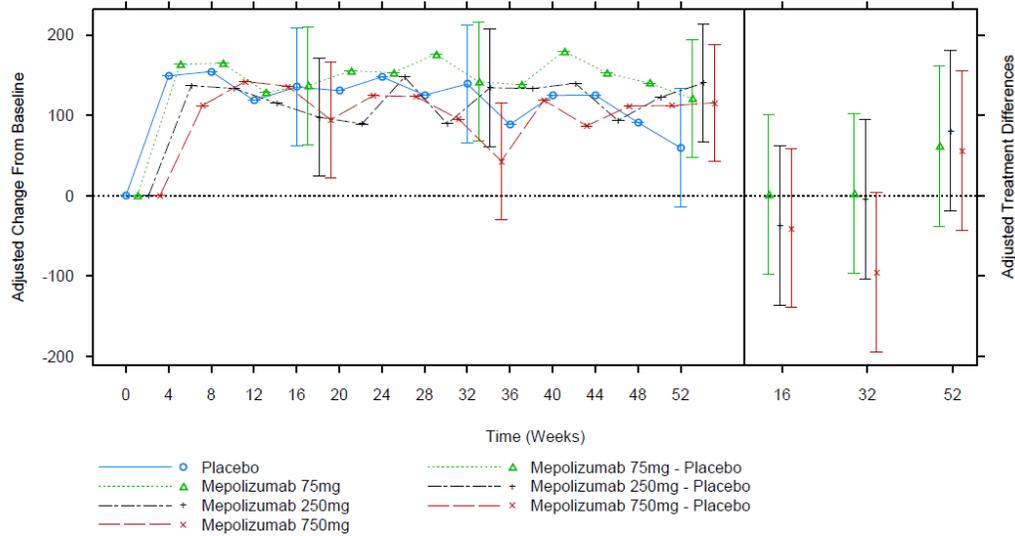
Table 2: Clinically significant exacerbations: Trial 97

	Placebo N=155	Mepo 75 mg IV N=153	Mepo 250 mg IV N=152	Mepo 750 mg IV N=156
n	155	153	152	156
Exacerbation rate/year	2.40	1.24	1.46	1.15
Comparison vs Placebo				
Rate ratio (mepo/placebo)	-	0.52	0.61	0.48
95% CI	-	(0.39, 0.69)	(0.46, 0.81)	(0.36, 0.64)
p-value	-	<0.001	<0.001	<0.001
Source: CSR 12977 Table 10				

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Figure 1: Pre-bronchodilator FEV1: Trial 97



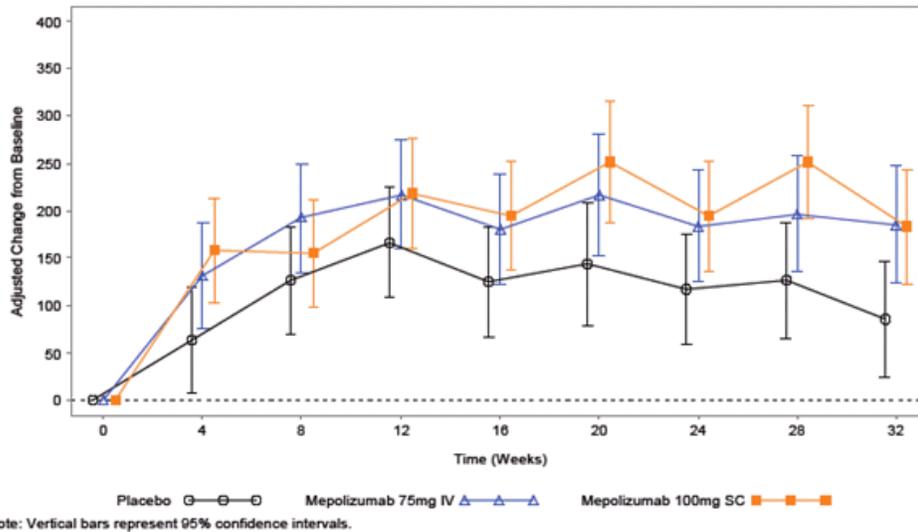
Trial 88 was a 32-week exacerbation trial evaluating 100 mg SC and 75 mg IV. It replicated the exacerbation treatment effect of the 75 mg IV dose and importantly, demonstrated a similar treatment response for to be marketed dose/route of mepolizumab, 100 mg SC q4weeks (see Table 3). These data, in conjunction with data from the IV/SC PK/PD bridging trial, provide reasonable bridging data to support approval of the 100 mg SC dose. Trial 88 demonstrated a positive effect on both pre- and post-bronchodilator FEV1 throughout the study duration (see Figure 2 for representative figure), although statistically significant p values were only reached for mepolizumab 75 mg IV at week 32 ($p < 0.05$) and at weeks 4, 20, 28 and 32 for the 100 mg SC arm ($p \leq 0.28$). Given that the treatment effect was demonstrated while all patients were on background standard of care therapy, this reviewer believes that the approximate 100 ml improvement in FEV1 is clinically meaningful, although this review acknowledges the lack of consistent statistical significance at each timepoint.

Table 3: Clinically Significant exacerbations: Trial 88

	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
n	191	191	194
Exacerbation rate/year	1.75	0.93	0.81
Comparison vs Placebo			
Rate ratio (mepolizumab/placebo)	--	0.53	0.47
95% CI	--	0.39,0.71	0.35,0.63
Unadjusted p-value	--	<0.001	<0.001
Adjusted p-value	--	<0.001	<0.001
Source: CSR 115588 table 13			

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Figure 2: Pre-bronchodilator FEV1: Trial 88



Additional efficacy support is provided by a single steroid sparing trial (trial 75). This trial was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating the effect of mepolizumab on reducing oral corticosteroid use. The trial included a 3-10 week steroid dose optimization phase followed by a 16 week treatment phase during a patient’s steroid dose was titrated followed by a 4 week maintenance phase. Per the sponsor’s analysis, mepolizumab allowed for a reduction of in oral corticosteroid dosing while maintaining asthma control compared to placebo (see Table 4). The sponsor proposes to include data from trial 75 into Section 14 of the product label. Typically, replicate data is needed to support product labeling; whether data from this single trial will be sufficient will be a review issue. Notably, this trial demonstrated a similar effect size for improvement in pre- and post-bronchodilator FEV1 as Trial 88.

Table 4: Primary Efficacy Endpoint: Trial 75

% OCS Reduction from Baseline Weeks 20-24	Number (%) subjects	
	Placebo n 66	Mepo 100 mg SC n 69
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 asthma control, or withdrawal from treatment	37 (56)	25 (36)
Odds ratio to placebo	--	2.39
95% CI	--	1.25,4.56
p-value	--	0.008

The sponsor is also proposing to include SGRQ data into Section 14 of the product label. Regulatory precedent does exist for including these data into product labels; however no precedent exists for use in asthma. It is further notable that the sponsor’s replicate evidence is drawn from trial 88, a pivotal exacerbation trial, and trial 75, the supplemental steroid sparing trial. In addition, SGRQ was evaluated as an “other endpoint” in trial 75 and was not included within the statistical testing hierarchy.

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Whether replicate evidence can be drawn from these data for inclusion into product labeling will be a review issue.

Safety

A total of 1,327 patients were evaluated in the sponsor's severe asthma program. Its database is primarily comprised of data from the three efficacy trials 24 to 52 weeks in duration (Trial 97, 88 and 75). Trial 97 provides 52-weeks of placebo-controlled safety data for 461 patients given 75 mg IV to 750 mg IV of mepolizumab. In addition, the program has two open-label safety extensions trials that are currently ongoing to provide longer term safety data. The scope of the sponsor's safety database is of reasonable size and duration to allow for review.

Conclusion:

The application is adequately indexed, organized and substantially complete to allow for review. This application is recommended as fileable from a clinical perspective. The sponsor will be advised in the 74-day letter that the specific language of the indication statement and the inclusion of the steroid-sparing data and the SGRQ data into Section 14 will be review issues.

Comments to Convey to Sponsor:

1. The concerns outlined in the EOP2 meeting held on May 4, 2012 and pre-BLA meeting held on January 15, 2014 regarding identifying and labeling the targeted patient population remain. The adequacy of the data, including data from negative trials, and the wording of the proposed indication statement will be review issues. These will likely be subjects for discussion at an advisory committee meeting.
2. We note that the proposed indication is for patients 12 years of age and older. The limited number of adolescents in your development program may not be sufficient to support an indication in adolescents and will be a review issue.
3. The limited representation of minority groups, specifically African-Americans, and Hispanics, in your development program is a concern. The adequacy of your program to be generalizable to the population without racial limitation will be a review issue and likely a subject for discussion at an advisory committee meeting.
4. We note the lack of data supporting your recommendations for handling parasitic disease. This issue may require a PMR.
5. The use of the SGRQ in asthma trials is without regulatory precedent and inclusion of the SGRQ data into product labeling will be a review issue.

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Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

SOFIA S CHAUDHRY
12/29/2014

LYDIA I GILBERT MCCLAIN
12/29/2014

I concur that the application is fileable and with the comments to be conveyed to the applicant