Appendix - Addendum to the Clinical Pharmacology Review: Genomics and Targeted Therapy Group Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	125526
Submission Date	11/4/2014
Applicant Name	GlaxoSmithKline
Generic Name	Mepolizumab
Proposed Indication	Severe eosinophilic asthma
Primary Reviewer	Robert Schuck, Pharm.D., Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

1 Background

Mepolizumab is a humanized monoclonal antibody that binds to interleukin (IL)-5, a cytokine critical in promoting eosinophil generation, recruitment, activation, and survival. In the current original BLA submission, GlaxoSmithKline is seeking approval of mepolizumab for add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/μL in the past 12 months.

In recent decades, asthma has become recognized as a heterogeneous collection of respiratory diseases and classification of asthma into subtypes based on the underlying pathophysiological mechanism has been proposed to identify patients most likely to benefit from specific therapies (PMID: 18805339, 21281866). The role of eosinophils in the pathogenesis of asthma is well-established and sputum eosinophilia is associated with more severe asthma (PMID: 10619791). The most recent report from the Global Initiative for Asthma (GINA) "Strategy for Asthma Management and Prevention" indicates that "patients with severe asthma may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated, or eosinophilic asthma" and recognizes sputum or blood eosinophilia as a potentially modifiable risk factor for exacerbations and developing fixed airflow limitation. However, a specific definition of "eosinophilic asthma" is not provided, and various criteria have been proposed (PMID: 24748808). Moreover, while blood eosinophils are frequently elevated in these conditions, eosinophil counts display significant intra-patient variability; for example, eosinophil counts in allergic rhinitis patients may be impacted by seasonal exposure to allergens (PMID: 23334207, 9722227).

Activated eosinophils secrete four principal proteins (major basic protein, eosinophilic cation protein, eosinophilic-derived neurotoxin, and eosinophil peroxidase) and inflammatory mediators including cysteinyl leukotrienes, platelet-activating factor, and prostaglandin D_2. Collectively, these eosinophil-derived products result in recruitment and activation of inflammatory cells and contribute to the airway remodeling and airway hyperrresponsiveness that underlies asthma exacerbations (PMID: 24748808). Activation of eosinophils and recruitment into the airway is promoted via cytokines, chemokines, and cellular adhesion molecules. IL-5 is a key pathologic

mediator driving eosinophil activation and recruitment to the lung, and increased levels of IL-5 are present in bronchoalveolar lavage fluid (BAL) from asthma patients with elevated BAL eosinophil counts (PMID: 7499683). Therefore, therapeutic strategies that target IL-5 are hypothesized to be effective in severe eosinophilic asthma phenotypes (PMID: 23197041). The purpose of this review is to evaluate the impact of blood eosinophil counts on the efficacy of mepolizumab.

2 Submission Contents Related to Genomics and Targeted Therapy

Study reports with contents related to Genomics and Targeted Therapy review are listed in Table 1.

Table 1. Study reports with contents related to Genomics and Targeted Therapy review.

Study ID	Phase N	Design/Purpose	Enrichment Criteria Related to Eosinophils
MEA112997	2b/3 N=152-156 / arm	Dose Ranging Study	• An elevated peripheral blood eosinophil level of ≥300/μL that was related to asthma or • Sputum eosinophils ≥3% or • Exhaled nitric oxide ≥50 ppb (could have been performed at Visit 1 or Visit 2 pre-randomization) or • Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≥25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in the previous 12 months
MEA115588	3 N=191-194 / arm	Efficacy/Safety Trial	• An elevated peripheral blood eosinophil count of ≥300/μL that was related to asthma demonstrated in the past 12 months prior to Visit 1 (screening) or • An elevated peripheral blood eosinophil count of ≥ 150/ μL at Visit 1 that is related to asthma.
MEA115575	3a N=66-69 / arm	Oral Corticosteroid Reduction Trial	• Airway inflammation characterized by an elevated peripheral blood eosinophil level of ≥300 cells/μL that was related to asthma within the previous 12 months prior to Visit 3 or • A peripheral baseline eosinophil level ≥150 cells/μL between Visit 1 and Visit 3 that was related to asthma.

In studies MEA112997, MEA115588 and MEA115575 (b) (4) was used as the central laboratory. Blood eosinophil counts were performed as part of the complete blood count with differential on the Coulter LH750 Hematology Analyzer.

3 Key Questions and Summary of Findings

3.1 Do blood eosinophil counts impact response to mepolizumab?

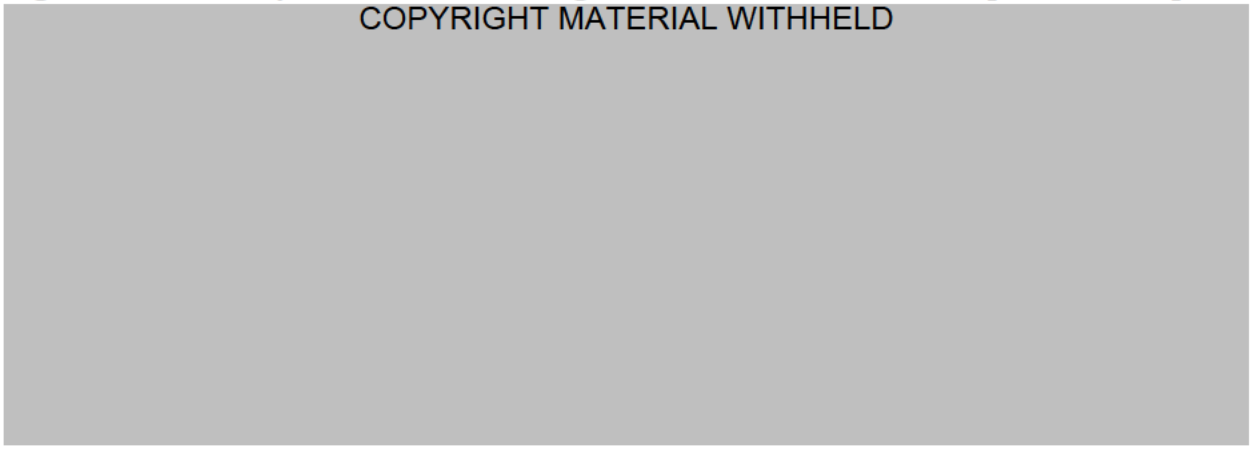
Collectively, the clinical trial data indicate that blood eosinophil counts are predictive of response to mepolizumab treatment, and patients with higher eosinophil levels derive greater treatment benefit. With respect to mepolizumab treatment, patients with eosinophilic inflammation are a distinct, identifiable, and clinically relevant subpopulation of asthmatics.

Prescribing of mepolizumab should be guided by blood eosinophil counts and restricted to patients with evidence of eosinophilic inflammation.

3.1.1 Literature review:

A large observational study (National Health and Nutrition Examination Survey) showed that elevated blood eosinophil counts are associated with higher prevalence of asthma, wheezing, asthma attacks, and asthma-related emergency department visits (PMID: 23890753). Moreover, clinical studies have demonstrated a significant correlation between peripheral blood eosinophil counts and clinical severity of asthma and pulmonary function (PMID: 2215562). In addition, a recent meta-analysis demonstrated that adult asthma patients who had treatment tailored according to sputum eosinophils had a reduced number of exacerbations compared to control subjects whose treatments were adjusted based only on clinical factors (Figure 1, PMID: 20937641).

Figure 1. Meta-analysis of studies tailoring asthma treatment based on sputum eosinophils.



Source: PMID 2093764; events = asthma exacerbations

Initial studies of anti-IL-5 therapies were conducted in patients with relatively mild disease and did not enrich based on eosinophilic phenotype or history of exacerbations. In these studies anti-IL-5 therapies significantly reduced both blood and sputum eosinophil counts; however, no significant improvements in clinical endpoints were observed (PMID: 17872493, 11191542, 12649124). Since these initial studies of anti-IL-5 therapies enrolled patients with relatively mild disease and no biomarkers of eosinophilic inflammation, later studies of mepolizumab were enriched for patients with a history of exacerbations and sputum eosinophil counts. These studies demonstrated mepolizumab use improved asthma control and allowed oral steroid reduction, in addition to lowering blood and sputum eosinophils (PMID: 19264686, 19264687).

3.1.2 Sponsor's analysis:

3.1.2.1 MEA112997

MEA112997 was a dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma. In addition to a diagnosis of severe

uncontrolled refractory asthma, patients had to meet at least one of several enrichment criteria (based on blood/sputum eosinophil levels and other factors) to be enrolled in the study (Table 1). Patients were randomized to either placebo, mepolizumab 750 mg intravenously (i.v.) every 4 weeks, mepolizumab 250 mg i.v. every 4 weeks, or mepolizumab 75 mg i.v. every 4 weeks. A significant reduction in exacerbation rate was observed for all mepolizumab arms compared to placebo (Table 2).

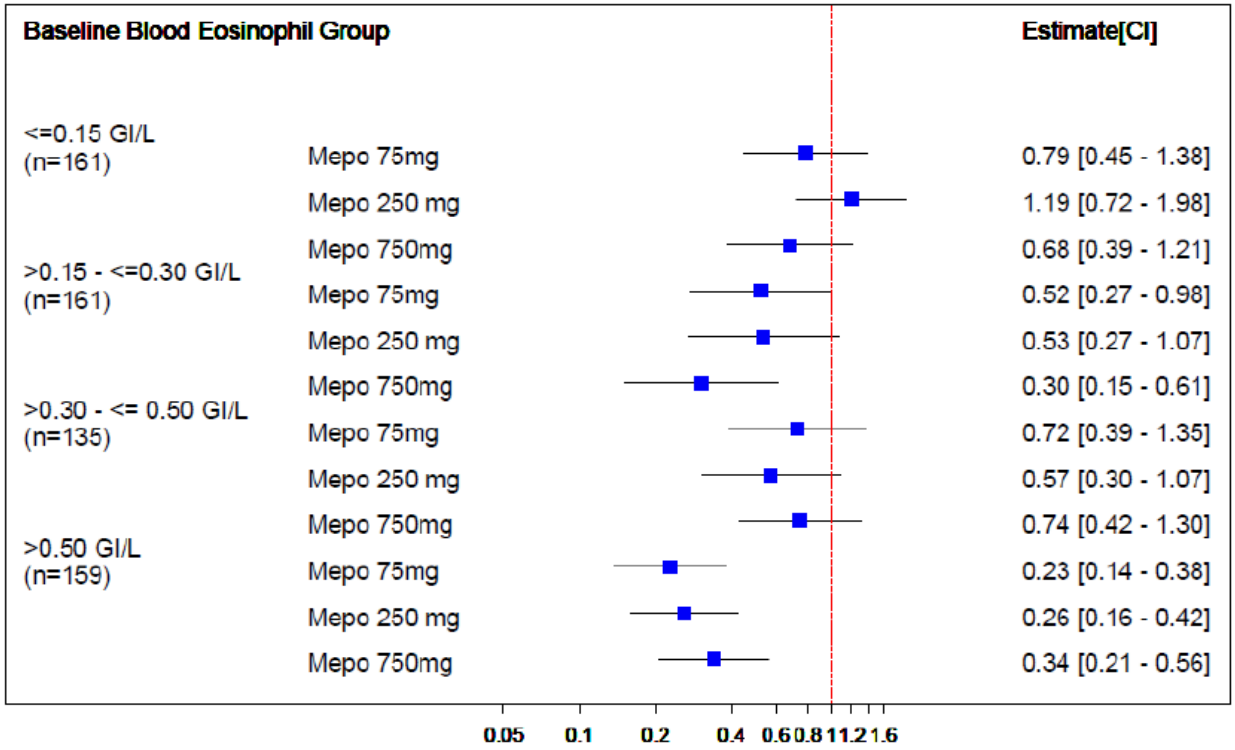
Table 2. Primary analysis of clinically significant exacerbations in MEA112997.

	Placebo N=155	Mepolizumab 75 mg N=153	Mepolizumab 250 mg N=152	Mepolizumab 750 mg N=156
n	155	153	152	156
Exacerbation rate/year	2.40	1.24	1.46	1.15
p-value for linear test for trend	<0.001			
Comparison vs. placebo				
Rate ratio (mepolizumab/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: Applicant's Table 10, study report MEA112997.

A subgroup analysis indicated that in patients with <0.15 GI/L blood eosinophils at baseline, there was a smaller decrease in the rate of clinically significant exacerbations. Analysis of interaction between baseline blood eosinophil group (≤150 cells/µL, 150-300 cells/µL, 300-500 cells/µL, >500 cells/µL) and treatment demonstrated a significant impact of blood eosinophils on treatment outcome (interaction p=0.002, Figure 2).

Figure 2. Rate of clinically significant exacerbations by baseline blood eosinophil group: ratio to placebo.



Source: Applicant's Figure 5, study report MEA112997.

Reviewer comment: The applicant's analysis demonstrates a significant interaction between baseline eosinophil group and reduction of exacerbations. These data support blood eosinophils as an important determinant of mepolizumab efficacy.

3.1.2.2 MEA115588

MEA115588 evaluated the effects of mepolizumab 75 mg i.v. every four weeks and mepolizumab 100 mg subcutaneously (s.c.) every four weeks as adjunctive therapy compared to placebo in severe asthma patients with evidence of eosinophilic inflammation (see Table 1 for eosinophil-related enrollment criteria). The rate of clinically significant exacerbations (the primary endpoint of the trial) was assessed at Week 32 (4 weeks after the last treatment dose). Treatment with mepolizumab 75 mg i.v. reduced the rate of exacerbations 47% and treatment with mepolizumab 100 mg s.c. reduced the rate of exacerbations 53% compared with placebo ($p<0.001$ for each comparison, Table 3).

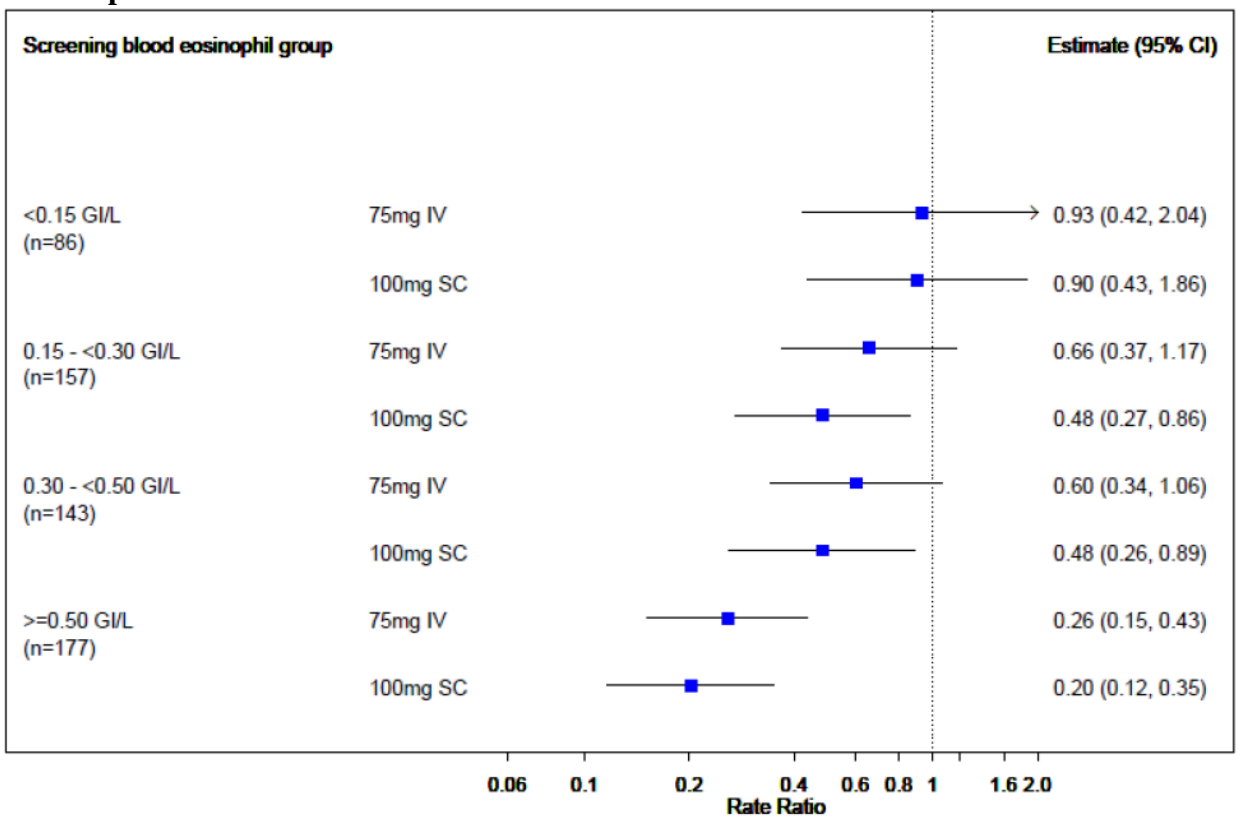
Table 3. Frequency of clinically significant exacerbations in MEA115588.

	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[1]		<0.001	<0.001

Source: Applicant's Table 13, study report MEA115588.

Analysis of the rate of clinically significant exacerbations by screening blood eosinophil levels demonstrated that patients in the highest screening blood eosinophil group had numerically greater reduction in exacerbations compared to patients with lower screening eosinophils. Overall, the subgroup analysis suggested a positive correlation between blood eosinophil count and the reduction in clinically significant exacerbations (Figure 3).

Figure 3. Rate of clinically significant exacerbations by screening blood eosinophil group: ratio to placebo.



Source: Applicant's Figure 3, study report MEA115588.

Reviewer comment: The applicant's analysis demonstrates a stepwise effect in which

mepolizumab treated patients have greater reduction of exacerbations as screening eosinophil count increases. These data are supportive of blood eosinophils as an important determinant of mepolizumab efficacy.

3.1.2.3 MEA115575

MEA115575 compared the effects of mepolizumab adjunctive therapy to placebo on reducing the use of oral corticosteroids (OCS) in systemic corticosteroid-dependent subjects with severe asthma and elevated eosinophils (see Table 1). Following an OCS Optimization Phase, all subjects who met the randomization criteria and enrolled in the study were maintained on their previous asthma therapy and randomized to receive mepolizumab 100 mg s.c. every 4 weeks (N=69) or placebo (N=66) while reducing OCS. The primary efficacy endpoint was percent reduction of OCS dose compared to baseline during Weeks 20-24 while maintaining asthma control (categorized as 90 to 100%, 75 to <90%, 50 to <75%, >0-<50%, no decrease). Mepolizumab treated subjects achieved greater categorical OCS reduction compared to placebo treated subjects (OR 2.39, 95% CI 1.25-4.52, p=0.008). When analyzed by baseline eosinophil levels (<150 cells/μL, 150 to <300 cells/μL, 300 to <500 cells/μL, and ≥500 cells/μL), the <150 cells/μL and 300 to <500 cells/μL subgroups had numerically larger OCS reduction compared with the other two categories (150 to <300 cells/μL and ≥500 cells/μL). However, subjects who met the enrollment criterion of peripheral blood eosinophil level of ≥300 cells/μL in the past 12 months had a greater OR for reduction of OCS vs. placebo (OR 4.35, 95% CI 1.86-10.17) compared to subjects who did not meet this criterion (OR 1.16, 95% CI 0.37-3.64).

Reviewer comment: The results of the MEA115575 study indicate that baseline blood eosinophil count does not have a consistent impact on the effect of mepolizumab in reducing OCS use. Mepolizumab may be more effective in reducing OCS use in patients with a history of blood eosinophil levels of ≥300 cells/μL in the past 12 months. However, the small study population makes these subgroup analyses difficult to interpret.

3.1.3 FDA analysis:

For a detailed analysis of blood eosinophils as an effect modifier please see Statistical Review by Dr. Robert Abugov.

3.2 Can patients with eosinophilic inflammation be reliably identified in order to receive mepolizumab treatment?

Intra-patient blood eosinophil counts are highly variable, and use of different hematology analyzers in different laboratories may add additional imprecision to the quantification of eosinophils. However, data from the mepolizumab clinical trials, which quantified blood eosinophil counts using standard laboratory tests, demonstrate that patients with higher blood eosinophil counts derive greater benefit from mepolizumab. Therefore, quantification of eosinophil counts using standard laboratory tests to identify patients for mepolizumab treatment appears reasonable.

Blood eosinophils counts are quantified during routine laboratory screening for complete blood

count (CBC) with differential, which is commonly assessed in asthma patients. It is anticipated that different healthcare systems will utilize different hematology analyzers, which will have varying analytical performance and reference ranges. The degree of inter-analyzer variability in eosinophil counts and reported reference ranges is not well-characterized, and the clinical trials evaluating mepolizumab utilized a central laboratory with a single analyzer to quantify eosinophil counts, which eliminates this source of variability.

Intra-patient eosinophil counts are also highly variable (PMID: 22900679), and parasitic and fungal infections, allergies, atopic dermatitis, and diurnal changes may elevate eosinophil counts. However, despite this high intra-patient variability in eosinophil counts, patients with higher eosinophils appear to derive greater benefit from mepolizumab, even when the analysis is based on a single measurement. Moreover, although efficacy of mepolizumab appears to diminish at lower blood eosinophil counts, no major safety findings were observed in the data that would limit approvability of the mepolizumab in severe asthmatics (see Clinical Review by Dr. Sofia Chaudhry). Therefore, the risk of a "false positive" finding of eosinophilic inflammation is minimal with respect to treatment with mepolizumab.

4 Summary and Conclusions

Collectively, the results of studies MEA112997, MEA115588, and MEA115575 indicate that patients with higher blood eosinophil counts derive greater benefit from mepolizumab therapy, despite the variability associated with quantification of eosinophils. Although a low number of patients with eosinophil counts <150 cells/μL were evaluated in these studies, efficacy appears limited in this population. However, given the intra-patient variability in eosinophil counts over time (see Statistical Review) and the utilization of both historical eosinophil counts and baseline eosinophil counts for study entry, determining the appropriate patient population based on eosinophil thresholds is impractical. Therefore, it may be most appropriate to indicate mepolizumab for asthma patients with evidence of eosinophilic inflammation and appropriate clinical qualifiers (e.g., exacerbations) and describe the impact of eosinophils on mepolizumab efficacy that was observed in the clinical trials in labeling, rather than specifying an eosinophil threshold above which the drug is indicated.

5 Recommendations

5.1 Post-marketing studies

None.

5.2 Labeling Recommendations

Please refer to final labeling.

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/s/

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