CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125526Orig1s000

OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	November 4, 2015
From	Mary H. Parks, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	125526
Applicant Name	GlaxoSmithKline
Date of Submission	November 4, 2014
PDUFA Goal Date	November 4, 2015
Proprietary Name / Established (USAN) Name	Nucala (mepolizumab)
Dosage Forms / Strength	100 mg/vial, as a white lyophilized powder for reconstitution
Applicant Proposed Indication(s)/Populations	..for add-on maintenance treatment of severe eosinophilic asthma, as identified by blood eosinophils greater than or equal to 150 cells/uL at initiation of treatment or blood eosinophils greater than or equal to 300 cells/uL in the past 12 months, in patients aged 12 years and older. NUCALA has been shown to reduce exacerbations of asthma in patients with an exacerbation history.
Action:	Approval
Approved Indication(s)/Populations (if applicable)	Nucala is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Mepolizumab is a first-in-class humanized IgG1, kappa anti-IL5 monoclonal antibody that rapidly and avidly binds to soluble IL5 and prevents it from binding to the IL5α chain of the IL5 receptor on eosinophils. Nonclinical pharmacology studies demonstrate the inhibitory effect of mepolizumab on IL5-dependent eosinophil differentiation which translated into dose-dependent reductions in circulating eosinophil counts as observed in several animal and clinical studies Based on its mechanism of action, mepolizumab was investigated as a treatment for patients with severe asthma where eosinophils are considered to be a major contributor to the inflammatory process.

The efficacy and safety of mepolizumab in this subset of patients with severe asthma were evaluated in three double-blind, placebo-controlled trials. All patients in the Phase 3 trials were on high doses of inhaled corticosteroids (ICS) and 38% were taking maintenance oral corticosteroids. The majority of these patients also had a history of multiple exacerbations in the year prior to study enrollment. The primary endpoint in two of the trials was clinical exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. In both these trials, mepolizumab treatment resulted in significant reductions in exacerbation rate compared to placebo. The number xacerbations requiring hospitalization or emergency room visit was lower in the mepolizumab treated group versus placebo. The third pivotal trial evaluated the effect of mepolizumab on reducing the dose of systemic oral corticosteroids (OCS). Mepolizumab treatment resulted in greater reduction in daily maintenance OCS dose while maintaining asthma control compared with placebo. Approximately 54% of mepolizumab-treated patients had at least a 50% reduction in daily prednisone dose compared with 33% of placebo-treated patients.

Lung function as measured by FEV1 was not significantly different between mepolizumab and placebo in any of the clinical trials conducted in this program, including a population of asthma patients with less severe disease.

In this program, GSK identified patients with “eosinophilic asthma” based on several criteria. The earliest Phase 3 trial utilized blood eosinophil counts or three other criteria including sputum eosinophil counts, exhaled nitric oxide, and clinical deterioration with attempted reduction in current maintenance therapy. The latter two Phase 3 trials selected patients with severe asthma who had a screening blood eosinophil count ≥ 150 cells/mcL at Visit 1 OR ≥ 300 cells/mcL in the past 12 months. Their initial proposed Indications included this range of blood eosinophil count; however, FDA analyses of effect based on counts less than or greater than 150 cells/mcL could not justify relying solely on this biomarker to identify which patient with severe asthma may derive benefit from mepolizumab.

The safety review did not identify a signal of concern to offset the benefit. The review included a close assessment of concerns related to biologics including allergic/hypersensitivity reactions, infection, and malignancies. With exception for two cases of herpes zoster reported as serious events, there were no findings which precluded approval or could not be addressed through routine labeling.

There are currently no approved therapies within this class or for this subset of patients with severe asthma. Three independently conducted well-designed trials demonstrated a clinically meaningful effect of mepolizumab on reducing the risk of clinical exacerbations and allowed for more patients to reduce their dose or oral corticosteroids without compromising control of their asthma.

All review disciplines have recommended approval of this BLA and I concur with this recommendation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic disease that causes inflammation in the airways of the lungs. During an asthma attack, airways become narrow making it hard to breathe. Inhaled corticosteroids (ICS) are the mainstay of treatment for asthma with the addition of other controllers (e.g., long-acting beta-agonists (LABAs), leukotriene modifiers or theophylline) if ICS alone is inadequate. Asthma which requires treatment with high-dose ICS plus a second controller, with or without oral corticosteroids to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy is defined as severe asthma. Severe asthma attacks can lead to asthma-related hospitalizations because these attacks can be serious and even life-threatening.	While many patients with asthma can be adequately controlled with currently available therapies, there remains a subset of patients who require high-doses of ICS and other controllers, including systemic steroids which have their own inherent side effects. There is an unmet medical need for therapies that will prevent clinical exacerbations and/or allow patients to reduce the dose of systemic corticosteroids.
Current Treatment Options	• There are currently no approved therapies for the subset of patients with severe asthma and an eosinophilic phenotype although these patients will be on high-dose inhaled corticosteroids and additional controllers with or without oral corticosteroids. This program attempted to identify the 'eosinophilic phenotype' based on blood eosinophil counts.	This development program attempted to identify patients who should receive mepolizumab based on blood eosinophil counts. While exploratory analyses of two studies suggest a greater treatment effect of mepolizumab on exacerbations with higher baseline eosinophil counts, another exploratory analysis of a third study

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		showed numerically more patients able to reduce their oral corticosteroid dose.
Benefit	• Significant reductions in clinical exacerbations of asthma, including hospitalization and/or emergency room visits • Significant reductions in doses of oral corticosteroids, including 54% who had more than a 50% reduction • No significant effect on FEV1 was observed, including in patients with less severe asthma	Despite no treatment effect observed on lung function, as measured by FEV1, the efficacy findings in this program were on clinically meaningful endpoints.
Risk	• Safety was assessed in three double-blind, randomized, placebo controlled trials and two open-label extension studies. • Adverse events of interest included allergic/hypersensitivity reactions, infections, and malignancies.	No safety concerns that offset the efficacy findings.
Risk Management	• No REMS was proposed	Based on the safety finding, risk management through labeling is acceptable.

2. Further discussion to support regulatory action

Background
Mepolizumab is a humanized IgG1, kappa anti-IL5 monoclonal antibody that rapidly and avidly binds to soluble IL5 and prevents it from binding to the IL5α chain of the IL5 receptor on eosinophils. Nonclinical pharmacology studies demonstrate the inhibitory effect of mepolizumab on IL5-dependent eosinophil differentiation which translated into dose-dependent reductions in circulating eosinophil counts as observed in several animal and clinical studies Based on its mechanism of action, mepolizumab was investigated as a treatment for patients with severe asthma where eosinophils are considered to be a major contributor to the inflammatory process.

Inhaled corticosteroids (ICS) are the mainstay of treatment for asthma with the addition of other controllers (e.g., long-acting beta-agonists (LABAs), leukotriene modifiers or theophylline) if ICS alone is inadequate. Asthma which requires treatment with high-dose ICS plus a second controller, with or without oral corticosteroids to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy is defined as severe asthma.

The mepolizumab program specifically targeted a subset of the severe asthma patient population. As per the applicant's submission, the three pivotal studies supporting this BLA enrolled patients who were diagnosed with severe asthma as defined by the American Thoracic Society in 2000.[1,2] All patients in the 3 trials were on high doses of ICS and 38% were taking maintenance oral corticosteroids. The majority of these patients also had a history of multiple exacerbations in the year prior to study enrollment. Given the mechanism of action of mepolizumab and two studies conducted by individual investigators suggesting benefit of mepolizumab in patients characterized as having "eosinophilic inflammation of the airway"[3,4], the study population in this BLA was further selected based on biomarkers that might enrich for drug responsiveness. Selection on this latter characteristic was not constant across the Phase 2 and 3 trials with results from an earlier study informing the selection criteria for later studies. Consensus on defining patients based on an eosinophilic characteristic has been challenging. Perhaps the lack of consensus is best explained in the recent Joint Task Force Report published by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) where identification of different phenotypes is described as "speculative at best" or is acknowledged that "there are no widely accepted definitions of specific asthma phenotypes".[5,6] Despite this, there is agreement among FDA review disciplines that efficacy

---

[1] BLA 125526 Module 2.7.3, Summary of Clinical Efficacy, page 13
[2] Proceedings of the ATS Workshop on Refractory Asthma. Current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341-2351.
[3] Haldar P et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973-984.
[4] Nair P et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360:985-93.
[5] Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-373.
[6] Throughout my review I will place "quotation marks" around descriptive terms as a point that there is not yet an

and safety of mepolizumab were established in a subset of patients with severe asthma and across all review disciplines there is a final recommendation for its approval.

I concur with the Division and consulting disciplines that this BLA should be approved. I refer the reader to Dr. Chowdhury's excellent Division Director memo and also the individual discipline reviews which provide more granular detail of the program.

Clinical/Statistical – Efficacy

Please see the separate reviews of Drs. Chowdhury, Gilbert-McClain, Chaudhury, and Abugov for a full discussion of clinical efficacy. As their individual reviews go into details of the study design, conduct and results, this memo will only highlight some key findings from three clinical trials supporting efficacy in the proposed indication. These trials are summarized in the following table.

Table 1. Pivotal Trials

Study No.	Patient population	Treatments	Primary endpoint
97	Ages 12-65 yrs on ICS and additional controllers, h/o ≥2 exacerbations past yr and the had markers to identify presence of eosinophilic inflammatory airway dz	616 patient randomized 1:1:1:1 to: -M75 IV -M250 IV -M750 IV -Placebo	Exacerbation rate over 52-week study duration
88	Ages ≥ 12 yrs on ICS and additional controller, h/o ≥2 exacerbations past yr and had biomarker based on blood eosinophil counts	576 patients randomized 1:1:1 to: -M75 IV -M100 SC -Placebo	Exacerbation rate over 32-week study duration
75	Ages≥12 yrs on ICS and additional controllers and OCS, and had biomarker based on blood eosinophil counts	135 patients randomized 1:1 to: -M100 SC -Placebo	% reduction in OCS during Weeks 20-24 in this 24-week study

Exacerbation

Of the three pivotal trials, Study 97 and 88 identified clinical exacerbation as a primary efficacy endpoint. Exacerbation in both these trials was defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. In both these trials, mepolizumab treatment resulted in significant reductions in exacerbation rate compared to placebo. Study 97 was conducted before Study 88. Three IV doses of mepolizumab were evaluated and there did not appear to be any additional benefit with doses higher than mepolizumab 75 mg IV every 4 weeks. Based on the dose-ranging Study 92 (described in the Clinical Pharmacology review) and modeling based on inhibition of blood eosinophil counts, Study 88 was conducted employing the 75 mg IV dose and a 100 mg SC dose of mepolizumab. Study 88 confirmed the reduced exacerbation

established definition for "eosinophilic asthma" or asthma of an "eosinophilic phenotype"

rate associated with mepolizumab treatment observed in Study 97 and also demonstrated comparable efficacy between the 75 mg IV and 100 mg SC dosing regimen. The following table from Dr. Chowdhury's memo summarizes the primary efficacy results in both Studies 97 and 88.

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

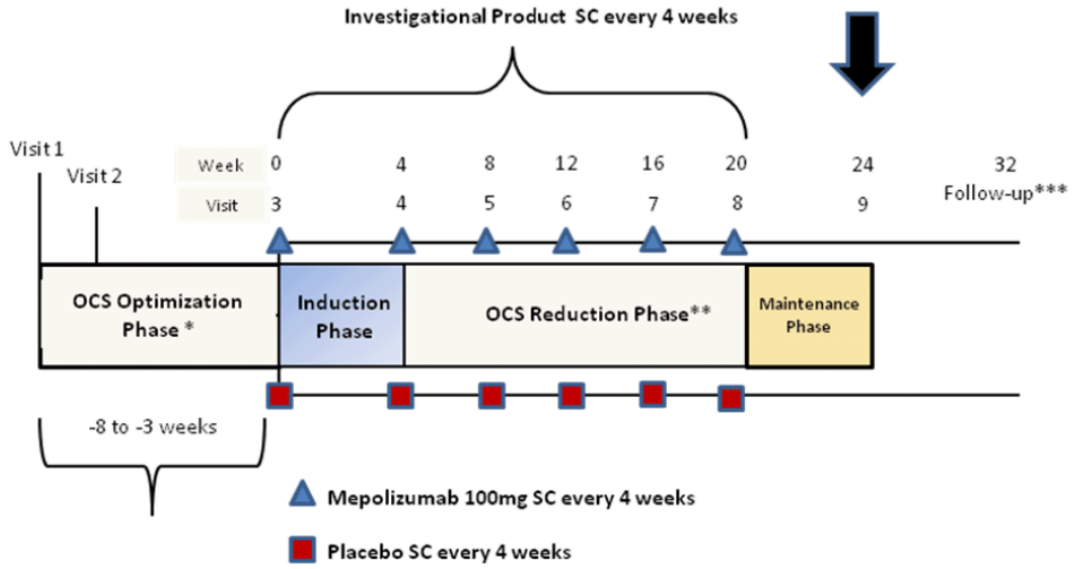
Study	Treatment	n	Annual rate of asthma exacerbation	Difference to placebo	Rate Ratio (95% CI), p-value
97	Mepolizumab 75 mg IV	153	1.24	-1.16	0.52 (0.39, 0.69), <0.001
	Mepolizumab 250 mg IV	152	1.46	-0.94	0.61 (0.46, 0.81), <0.001
	Mepolizumab 750 mg IV	156	1.15	-1.24	0.48 (0.36, 0.64), <0.001
	Placebo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

Hospitalization and ED visits were components of the combined primary endpoint of all exacerbations but the number of such events was small. However, the rate of exacerbations due to hospitalization and ED visits was lower in the mepolizumab group compared to placebo and while statistical significance could not be ascribed to lower rate ratios with these events, these are clinically meaningful events and the numerically lower numbers with mepolizumab treatment is supportive of the overall clinical benefit on this endpoint.

Oral Corticosteroid Use Reduction

Study 75 enrolled patients who, in addition to ICS and an additional controller medication, required maintenance OCS of 5.0 to 35 mg/day prednisone or equivalent. Although exacerbation history was not a required inclusion criterion, the majority of patients in this trial had at least one exacerbation in the 12 months prior to screening (85% placebo, 83% mepolizumab); 30 to 41% had ≥ 4 exacerbations in the previous year.

The study was divided into 4 phases as illustrated below:



*The OCS Optimization Phase could be extended to 10 weeks if a subject experienced an exacerbation during this phase.
** OCS dose titration occurred throughout the Optimization and Reduction Phases of the study. OCS titration did not necessarily coincide with the Visits scheduled for investigational product administration as indicated above.
*** Only subjects who did not enter the open label extension (OLE) study completed the Follow-up Visit at 12 weeks post last dose

The different phases and algorithm for OCS dose reduction have been described in Dr. Chaudhry's review (page 33-34) and will not be repeated here.

The primary endpoint was the percent reduction of OCS dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Mepolizumab treatment resulted in greater reduction in daily maintenance OCS dose while maintaining asthma control compared with placebo. Approximately 54% of mepolizumab-treated patients had at least a 50% reduction in daily prednisone dose compared with 33% of placebo-treated patients.

Rate of exacerbations was also evaluated as a secondary endpoint in Study 75. Fewer patients in the mepolizumab group experienced a clinically significant exacerbation compared to placebo. 42% of mepolizumab-treated patients experienced at least one or more exacerbation versus 68% of patients on placebo with fewer patients in the mepolizumab group in each frequency category 1 through 3. There were 2 mepolizumab patients who had 4 exacerbations compared to none in placebo.

Lung Function

Lung function as measured by FEV1was obtained in all pivotal trials. This endpoint was identified in a pre-planned hierarchical analysis in Studies 97 and 88 and not identified in a pre-planned analysis in Study 75. The following table summarizes the findings from all three trials .

Table 2. ΔFEV1 in Phase 3 Trials

	Study 97		Study 88			Study 75**	
	Pbo	75 mg IV	Pbo	75 mg IV	100 mg SC	Pbo	100 mg SC
ΔFEV1 (mL)	60	121	86	186	184	-4	110
Diff from Pbo, 95% CI p-value*	---	61(-38,161) 0.23	---	100(14,187)	98(12,184)	---	114(-44,273)

*only for Study 97 as endpoint failed in analysis hierarchy in Study 88 and not pre-specified in Study 75
**ΔFEV1 was an exploratory endpoint in Study 75

There was no statistically significant difference between mepolizumab and placebo on change from baseline in FEV1.

A fourth study (Study 6) was discussed by FDA staff in their reviews. Study 6 was a 12-week, double-blind, placebo-controlled trial evaluating two doses of mepolizumab (250 and 750 mg IV). The study enrolled patients with FEV1≥ 50% and ≤80% predicted with demonstrated reversibility≥ 12%. Prior treatment with ICS was allowed but patients did not have a history of exacerbation and were not identified by any biomarkers for eosinophilic inflammation.

The primary endpoint was change from baseline in the mean morning domiciliary peak expiratory flow rate recorded in the 7 days preceding Week 12. There was no statistically significant difference between placebo and the two doses of mepolizumab studied in this trial. Change from baseline in FEV1 was a secondary endpoint and as summarized in the following table from Dr. Abugov's review, there was no significant difference between mepolizumab doses and placebo on this endpoint.

Table 11. Exploratory Analysis, ΔFEV1 at Week 12, Study 6.

	Δ Pre-Dose FEV1 (N)		
	Pbo	**250 mg IV**	**M750 mg IV**
N =	(129)	(121)	(118)
FEV1 (mL)	138	88	89
Diff from Pbo		-51	-50
95% CI		(-162, 60)	(-160, 60)

source: reviewer program FEV S06 biomarker 2015 02 20, CSR Table 25

Other secondary endpoints were assessed in the pivotal trials, including measures of asthma control and measures of health status. Of these, the Division has recommended the changes in in the Asthma Control Questionnaire (ACQ-5) and St. Georges Respiratory Questionnaire (SGRQ) be included in labeling. I agree with this recommendation.

Role of Eosinophils

As alluded to in earlier sections of this memo, this clinical development program was designed to target a specific subset of patients with severe asthma wherein eosinophils appear to play a dominant role in the inflammatory process. Selection based on eosinophils as an enrichment biomarker was different between Study 97 and Studies 88 and 75.

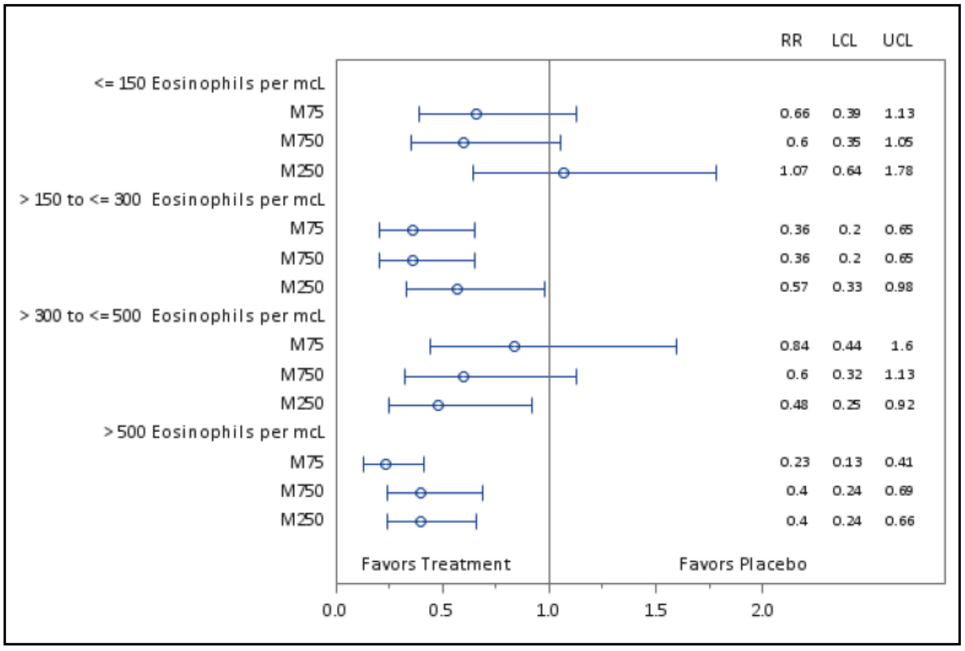
The following table summarizes the selection criteria for identifying patients with an "eosinophilic phenotype".

Table 3. Selection of Patients Based on Eosinophilic Criteria

Study 97	**Study 88**	**Study 75**
• Elevated peripheral blood eosinophil count ≥ 300 cells/uL OR • Sputum eosinophil ≥ 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 ≤ 25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in previous 12 months	• Peripheral blood value ≥ 300 cells/uL in the prior 12 months OR • An elevated peripheral blood eosinophil count ≥ 150 cells/uL at Visit 1 (screening) related to asthma	• Peripheral blood value ≥ 300 cells/uL in the prior 12 months OR • An elevated peripheral blood eosinophil count ≥ 150 cells/uL at Visit 1 (screening) related to asthma

Dr. Abugov's review dedicated a section (reader is referred to Section 4.2 of Dr. Abugov's review) to evaluating blood eosinophil count as an effect modifier – in part, as a response to GSK's originally proposed indication which specified **blood** eosinophil cutpoints of ≥ 150 cells/mcL at initiation of treatment or ≥ 300 cells/mcL in the past 12 months. Blood eosinophil counts were the only selection criteria for Studies 88 and 75 but in Study 97, blood eosinophil count was one of 4 criteria (See Table 3). Study 97 was analyzed by GSK to identify enrichment criteria for Study 88. Dr. Abugov's review provides a detailed summary of this analysis and FDA's confirmation of the applicant's findings. Figure 10 below is from Dr. Abugov's review and summarizes the treatment effect on exacerbation by screening blood eosinophil counts in Study 97.

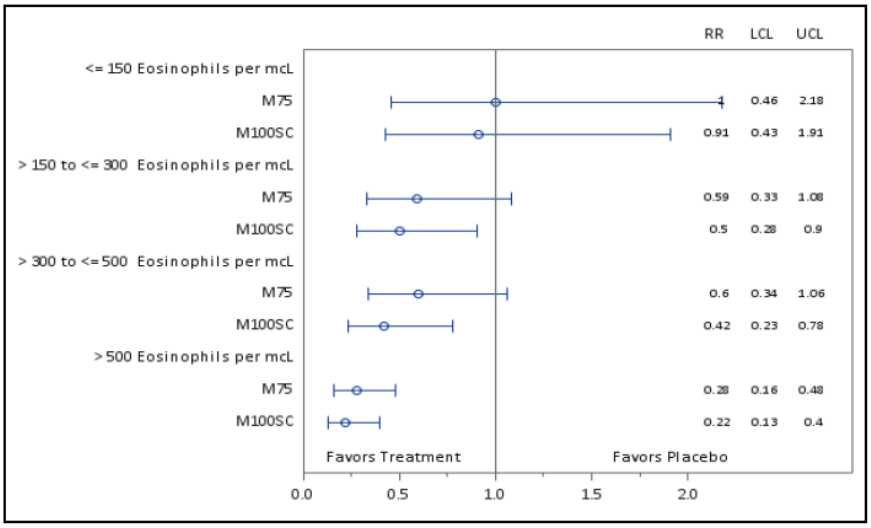
Figure 10. Exacerbation Rate Ratios, by Screening Blood Eosinophil Count, Study 97



Source: reviewer program Exac Forest Plots Subgr S97 2015 06 17.sas

Based on Study 97, blood eosinophil counts ≥ 150 and number of exacerbations in the prior year (see Figure 11 in Dr. Abugov's review) were identified as appropriate enrichment criteria for subsequent studies. Study 88 and 75 enrolled patients with blood eosinophil counts ≥ 150 at Visit 1 but also allowed patients with values ≥ 300 in the year prior to Visit 1. Figure 14 below from Dr. Abugov's review presents treatment effect of mepolizumab on exacerbation by screening blood eosinophil counts in Study 88.

Figure 14. Exacerbation Rate Ratios, by Screening Blood Eosinophil Count, Study 88



Source: reviewer program Exac Forest Plots Subgr S88 2015 04 06.sas

Exploratory analyses of Study 88 suggested a greater treatment effect of mepolizumab on exacerbation rates in patients with higher baseline eosinophil levels. This observation lends support to selecting patients with an elevated blood eosinophil levels for a therapy that inhibits eosinophilic production. However, identifying patients solely on blood eosinophil levels, in particular elevated levels, might also exclude patients who may benefit from mepolizumab but who do not have an elevated blood eosinophil level or whose level is below the cutpoint identified in exploratory analyses of Study 97 and 88 (i.e., 150).

As noted in Table 3, Study 97 selected patients on 3 other criteria unrelated to blood eosinophil level, including sputum eosinophil counts, exhaled NO, and clinical deterioration with reduction in current maintenance therapies. Having any one of these other 3 criteria may have allowed a patient with blood eosinophil counts ≤ 150 to be initiated on mepolizumab. In Study 88, patients with a history of a blood eosinophil count ≥ 300 within the year prior could also have been initiated on mepolizumab despite not having an elevated level more proximal to the start date. While the forest plots in Figures 10 and 11 do not show a statistically significant treatment effect of mepolizumab in patients with screening blood eosinophil counts ≤ 150, the lower confidence limit in all mepolizumab treatment groups crosses 1.0 and in two dose groups (75 mg and 750 mg IV) in Study 97, the point estimate is below 1.0, in favor of mepolizumab.

Study 75 evaluated the effect of treatment on ability to reduce dose of oral corticosteroids. While systemic corticosteroids are critical for the maintenance of control in some patients with severe asthma, they can have serious adverse effects from their potent anti-inflammatory actions and effects on multiple metabolic systems. The ability to reduce the dose of systemic corticosteroids without worsening control of severe asthma is clinically meaningful.

I requested Dr. Abugov to perform exploratory analyses in the subgroup of patients in Study 75 with screening blood eosinophil counts below 150 cells/mcL. These patients would have qualified for Study 75 based on a historical blood eosinophil count ≥ 300 cells/mcL within the past 12 months. The following table was created by Dr. Abugov.

Table 4. Percent OCS Reduction from Baseline for Subjects with ≤ 150 Eosinophils per mcL[a], Study 75 (courtesy of Dr. Robert Abugov)

Reduction in OCS	M100SC	Pbo	Odds Ratio (95% CI)[b]	Nominal P-Value[b]
90% - 100%	5 (29%)	0 (0%)		
75% - <90%	4 (24%)	0 (0%)		
50% - <75%	3 (18%)	2 (17%)		
>0% - <50%	1 (6%)	2 (17%)		
No change or any increase or lack of asthma control or withdrawal from treatment	4 (24%)	8 (67%)		
Statistical Analysis			6.7 (1.5, 29.0)	.008

[a] Average of values at baseline and screening.
[b] Confidence limits and nominal p-values are from asymptotic theory and should be considered approximate.

There are few patients in this subgroup and interpretation of these data should proceed with caution. From this exploratory, subgroup analysis of patients who had an average baseline and screening blood eosinophil count below 150 cells/mcL, there were 5 patients in the mepolizumab treated group who had a 90-100% reduction in their OCS dose versus none in placebo treated group. Conversely, more placebo-treated patients in this subgroup either had no change or required an increased in OCS during this trial versus the mepolizumab treatment group (67% vs 24%).

Could there be other characteristics to this subset of patients of severe asthma that should be considered in initiation of therapy other than a single screening blood eosinophil count? Could a single low blood eosinophil count reflect a recent increase in corticosteroid dose or timing of steroid dosing with blood draw[7]? Could fluctuations and variability in this biomarker result in shifts that might qualify a patient one day and disqualify on another based on a pre-defined cutpoint? On this later point, it is of interest to note that Dr. Abugov evaluated the probability of shifts in blood eosinophil counts at screening to baseline. In Table 34 from his review and referenced below, screening and baseline eosinophil counts were obtained one week apart. While 63% of patients with low screening blood eosinophil levels remained so a week later, 19% of patients also shifted upward into the next quartile, 12% shifted upwards by two quartiles and 6% to the next quartile. The converse can also happen with patients shifting from high counts at screening to low counts at baseline. The point to take away from this table is that a single blood eosinophil count may be a very tenuous biomarker to rely upon solely when determining whether a patient should be initiated on or denied mepolizumab.

[7] Beam WR et al. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Resp Dis*. 1992 Dec;146(6):1524-1530.

Table 34. Transition Matrix* for Blood Eosinophil Count, from Screening to Baseline, Study 88

	BL	BML	BMH	BH
SL	0.63	0.19	0.12	0.06
SML	0.34	0.45	0.14	0.07
SMH	0.17	0.13	0.43	0.27
SH	0.06	0.08	0.20	0.65

Source: reviewer program markov eosin count s97 2015 04 20.sas
*For study 88, L, ML, MH, H are low medium-low, medium high, and high eosinophil quartiles, bounded by 0, 205, 345, and 560 eosinophils per microliter

Despite the uncertainty on how best to define a patient population with "eosinophilic asthma" in this program, the selection of patients based on blood eosinophil levels to evaluate the effectiveness of mepolizumab was based on analyses of a well-controlled clinical investigation (Study 97). Results were analyzed and informed the selection criteria for two other pivotal studies in this program and overall, three separate trials confirm the efficacy of mepolizumab 100 mg sc every 4 weeks in patients with severe asthma who derived clinically meaningful benefit from either reduced risk of exacerbation or the ability to reduce the dose of systemic corticosteroids.

In conclusion, I agree with the Division and other review disciplines that efficacy for mepolizumab has been established in a subset of patients with severe asthma. The endpoints establishing efficacy – reduced clinical exacerbations including ER visits or hospitalizations or reduced doses of oral corticosteroids – are clinically meaningful, especially in a patients who may have exhausted all available therapeutic options or experience untoward effects of high-dose corticosteroids.

Safety

Please see the clinical reviews of Drs. Chowdhury, Gilbert-McClain, and Chaudhry. There were no safety issues identified precluding approval or necessitating a required safety study under FDAAA.

In addition to a standard assessment of safety, events of interest included immunogenicity, allergic reactions (including anaphylaxis), injection site reactions, infections (including opportunistic infections), and malignancies. Two patients on mepolizumab versus none in placebo experienced herpes zoster which were considered serious AEs. This event will be included in labeling.

Advisory Committee Meeting

This application was discussed at the Pulmonary Drugs Advisory Committee Meeting in June 10, 2015. Dr. Chowdhury has summarized the vote results and discussion surrounding the votes.

Pediatrics

There were only 28 pediatric patients (ages 12 to 17 yrs, inclusive) in this clinical development program. The majority of them were enrolled in Study 88 (n=25) and an analysis by age category revealed a point estimate favoring drug in all age cutpoints; however, the confidence interval was wide for patients 12 to 17 yrs, likely reflecting the small number of patients. Dr. Chaudhry's primary review does not recommend approval for adolescents age 12 to 17 yrs whereas Dr. Chowdhury's Division Director memo includes patients 12 yrs and older in his recommendation for approval and I agree with him.

This approval will have required pediatric studies under PREA including an assessment of safety, PK and PD parameters in the pediatric population ages 6 to 11 years of age. A waiver was granted for children under 6 yrs of age as it is unlikely to occur at a high enough number to allow clinical studies.

Other Relevant Regulatory Issues

Drs. Chowdhury and Gilbert-McClain summarized the facilities inspection for mepolizumab drug product in their separate memos. Subsequent to finalization of their memos, Office of Compliance has provided an update and is NOT recommending a withhold action.

Labeling

There were extensive discussions on the Indications and Usage section of the product label and how to describe the subset of severe asthma patients intended for mepolizumab treatment. As alluded to in the Clinical/Statistical-Efficacy section of my memo, the applicant proposed to describe the indicated population by using their eligibility criteria in two of the three pivotal studies. However, this proposal would likely require blood eosinophil levels be drawn before initiation of therapy and values falling outside this defined range *might* result in a patient not being considered for treatment because of perceived lack of benefit or denial of insurance coverage.

Subgroup analyses of all three pivotal studies suggested a greater treatment effect of mepolizumab on reducing clinical exacerbations in patients with higher blood eosinophil counts. However, subgroup analyses in Study 75 also pointed to a subset of patients whose eosinophil levels fell below the threshold of 150 cells/mcL who had marked reductions in their oral corticosteroid dose. From this observation I do not believe the Indications section should specify a blood eosinophil range nor should it single out blood eosinophil counts in defining this subset of severe asthma patients with "eosinophilic phenotype".

The Indications and Usage section should state that mepolizumab is indicated in patients with severe asthma who are 12 years and older who have an "eosinophilic phenotype" with cross reference to the Clinical Studies section which will describe further how the patients were selected for investigation in this program. While the term "eosinophilic phenotype" does not provide precision on identifying this subset of patients, analyses of this program would suggest

that we don't yet have the exact identifiers and to focus on one (i.e., blood eosinophil counts) may result in the exclusion of treatment in patients who may benefit from mepolizumab.

Risk Evaluation and Mitigation Strategies

No REMS is necessary for approval of this BLA.

Postmarketing Requirements and Commitments

Pediatric studies under PREA and PMCs as described in the quality review of this BLA will be included in the approval action.

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

/s/

MARY H PARKS
11/04/2015