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APPLICATION NUMBER:

125526Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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?

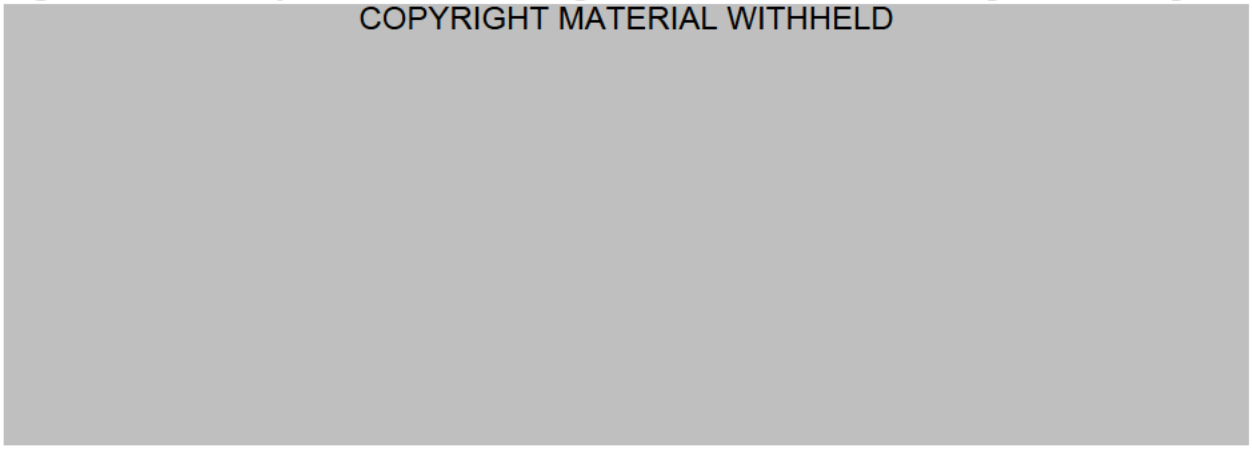
Collectively, the clinical trial data indicate that blood eosinophil counts are predictive of response to mepolizumab treatment, and patients with higher eosinophil levels derive greater treatment benefit. With respect to mepolizumab treatment, patients with eosinophilic inflammation are a distinct,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

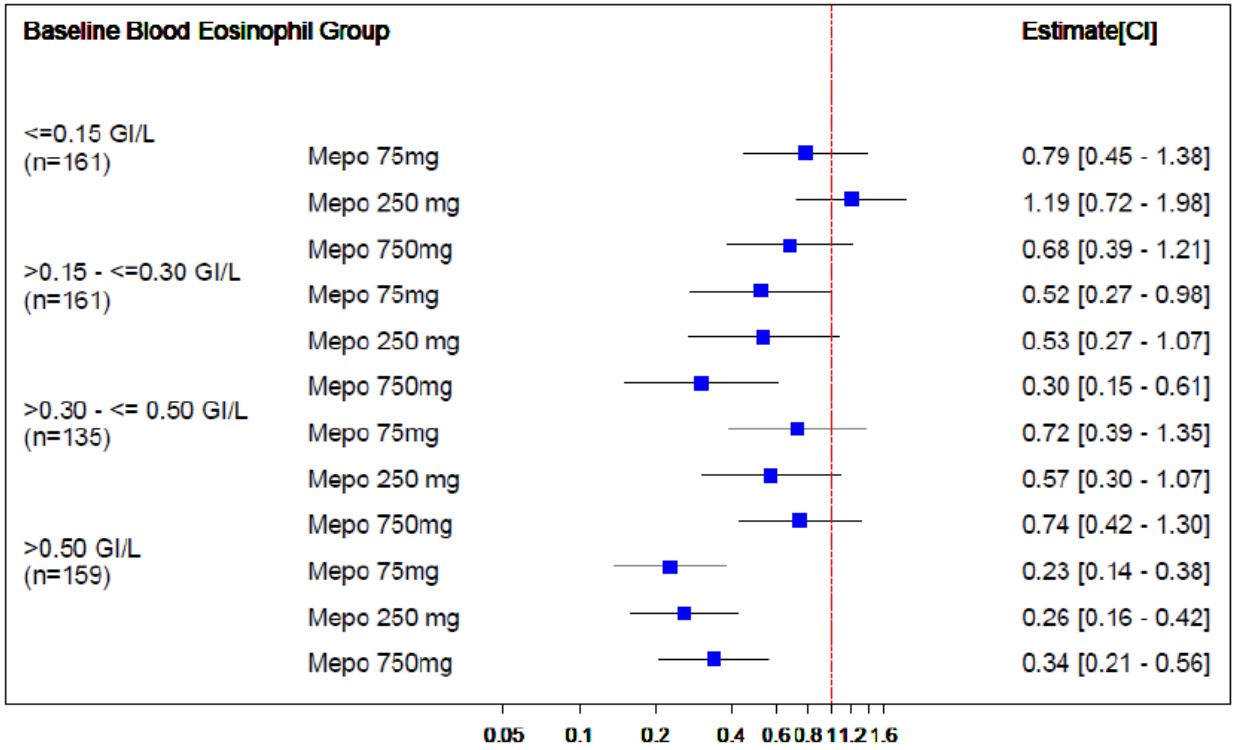
Table 2. Primary analysis of clinically significant exacerbations in MEA112997.

	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).

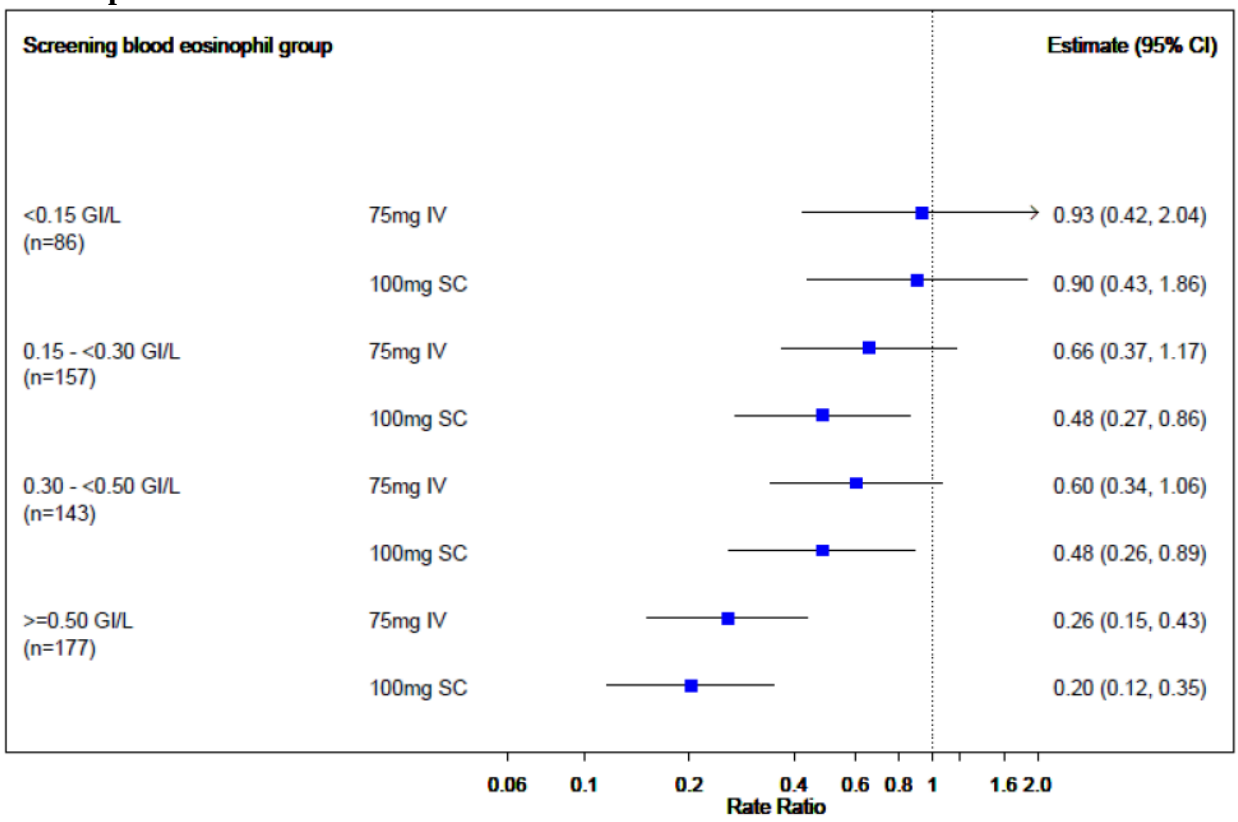
Table 3. Frequency of clinically significant exacerbations in MEA115588.

	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/

ROBERT N SCHUCK
07/10/2015

CHRISTIAN GRIMSTEIN
07/10/2015

CLINICAL PHARMACOLOGY REVIEW	
BLA Number:	125526 (related IND 006971)
Submissions Date:	11/04/2014
Submission Type:	351(a)
Proposed Brand Name:	NUCALA
Generic Name:	Mepolizumab
Sponsor:	GlaxoSmithKline LLC
Route of Administration:	Subcutaneous Injection
Dosage Form:	Lyophilized powder
Dosage Strength:	100 mg/vial
Proposed Dosing Regimen:	100 mg once every 4 weeks
Proposed Indication(s):	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
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Suresh Doddapaneni Ph.D.
Pharmacometrics Reviewer:	Jingyu Yu, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.

Note –

In this review, early development name SB-240563 sometimes was used to refer to the FDA-granted proprietary name Nucala.

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1. EXECUTIVE SUMMARY

GlaxoSmithKline LLC has submitted BLA 125526 under 351 (a) pathway seeking the marketing approval for mepolizumab (Nucala®) for the indication of "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". The proposed dosing regimen is 100 mg for subcutaneous injection once every 4 weeks. The dosage form is lyophilized powder for injection (100 mg of mepolizumab per vial).

The clinical development program of this submission includes two Phase 1 studies in healthy subjects and nine Phase II-II studies in eosinophilic asthma patients.

The following are the major clinical pharmacology findings of the current review:

1. Three mepolizumab drug product (DP) presentations have been used throughout the clinical development program. The pilot product (50 mg/vial and 250 mg/vial) was used in the pre-clinical and early Phase 1/2 clinical studies. Mepolizumab drug product 1 (MDP1, 250 mg/vial) was used in a Phase IIa Clinical Pharmacology study (MEA114092), three pivotal Phase III clinical studies (MEA112997, MEA115588, MEA115575) as well as for initiation of the open-label (OLE) studies (MEA115666, and MEA115661). Mepolizumab drug product 2 (MDP2, 100 mg/vial) is used in all ongoing clinical studies, including the two OLE safety studies (MEA115661 and MEA115666).

MDP2 is the proposed commercial presentation of the product. Excipient quantities and manufacturing process were different between the pilot product and the MDP1/2. However, no clinical PK/PD bridging study was conducted between the pilot product and the MDP1/2. Between MDP1 and MDP2, the DP composition was the same.

2. The absolute bioavailability of the 100 mg mepolizumab via SC route in the upper arm was estimated to be 80% (90% CI: 76%–84%).

3. No dose-response or exposure-response relationship was observed for asthma exacerbation in Phase 3 dose ranging study MEA112997 following 75 mg IV to 750 mg IV administration for 48 weeks.

4. A dose-response relationship for blood eosinophil counts was observed in Phase 2 dose-ranging Study 114092. Reduction of blood eosinophils counts from baseline was less in 12.5 mg SC group than other three groups (250 mg SC, 125 mg SC, and IV 75 mg groups). The estimated IC_{50} and IC_{90} of the maximum reduction of blood eosinophil count at Week 12 following SC route was 11 (95% CI= 5, 17) mg and 99 (95% CI= 47, 152) mg, respectively. However, the PD-efficacy (blood eosinophil counts-asthma exacerbation or -FEV1 change from baseline) relationship has not been established from literature reports or clinical studies. The relationship between blood eosinophil counts at baseline and asthma exacerbation rate following mepolizumab treatment was explored by Biometrics Reviewer Dr. Robert Abugov in a post-hoc manor. A trend of greater blood eosinophil count values at baseline with reduction of asthma exacerbation following mepolizumab treatment was observed.

5. Data from 3 Phase 3 studies (MEA112997, MEA115588, and MEA115575) that utilized 6th generation anti-drug antibody (ADA) assay demonstrated that 15/260 (6%) of subjects treated with 100 mg SC and 13/633 (2%) of subjects treated IV had ADA identified positive in at least one sample after having received at least one dose. Among those 28 ADA-positive asthmatic patients, only one subject was positive on neutralizing antibody. There was slight increase (22.4%) of apparent clearance (CL/F) in ADA-positive patients compared to ADA-negative patients following 100 mg SC treatment.

6. A total of 28 children 12-17 years received mepolizumab treatment in Phase 3 trials, 9 of whom had sparse PK data. Population PK analysis estimated that the exposure in these children could be 35% higher than that in adults. The clinical benefit of mepolizumab 100 mg SC once every 4 weeks for the treatment of severe asthma in children 12-17 years of age was unknown because of the limited data and unknown relevance of this severe asthma phenotype associated with eosinophilic inflammation in the pediatric population. These issues were raised and discussed during the June 11, 2015 Pulmonary Allergy Drugs Advisory Committee Meeting. Consistent with the panel's discussion and recommendation, further PREA required post marketing studies in adolescents and younger pediatric patients are needed. For details, refer to primary review by medical officer Dr. Sofia Chaudhry.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the BLA 125526 submitted on August 15, 2014 and has found the application acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Nucala (mepolizumab) is a humanized monoclonal anti-IL5 antibody. IL-5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. Mepolizumab is proposed 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. Mepolizumab is supplied as 100 mg lyophilized powder per vial to be reconstituted with 1.2 mL sterile water for Injection. The proposed dosing regimen is 100 mg subcutaneous injection once every 4 weeks.

1.3.2 Biopharmaceutics

Three mepolizumab drug product (DP) presentations have been used throughout the clinical development program. The pilot product (50 mg/vial and 250 mg/vial) was used in the pre-clinical and Phase I clinical studies. Mepolizumab drug product 1 (MDP1, 250 mg/vial) was used in a Phase IIa Clinical Pharmacology study (MEA114092), three pivotal Phase III clinical studies (MEA112997, MEA115588, MEA115575) as well as for initiation of the open-label (OLE) studies (MEA115666, and MEA115661). Mepolizumab drug product 2 (MDP2, 100 mg/vial) is used in all ongoing clinical studies, including the two OLE safety studies (MEA115661 and MEA115666). MDP2 is the proposed commercial presentation of the product. Excipient quantities and manufacturing process were different between the pilot product and the MDP1/2. However, no clinical PK/PD bridging study was conducted between the pilot product and the MDP1/2. Between MDP1 and MDP2, the DP composition was the same.

1.3.3 Pharmacokinetics

Pharmacokinetics in Healthy Subjects

The PK of MDP1 in healthy subjects was evaluated in Study MEA115705. Four groups of eight subjects were randomized 3:1 to receive mepolizumab IV (10, 75, 250 and 750 mg) or placebo. Following a 30-minute IV infusion, mepolizumab plasma concentrations declined in a bi-exponential manner. Over the dose range 10–750 mg, mepolizumab showed linear and dose-proportional PK. The mean elimination half-life was 20 to 36 days.

Pharmacokinetics in Patients

Four studies were conducted to evaluate the PK of MDP1 in patients with asthma (MEA114092, MEA112997, MEA115588, and MEA115575). Sparse pharmacokinetic samples were collected throughout, and analyzed using population PK methods.

In Study MEA115588, the systemic exposure of mepolizumab was comparable between 75 mg IV and 100 mg SC every 4 weeks, and the estimated bioavailability was 80% for 100 mg SC injection in subjects with severe asthma. Following SC administration of 100 mg mepolizumab in asthmatic subjects, the mean volume of distribution was 63 to 82 mL/kg, the mean clearance ranged from 4.0 to 4.7 mL/day/kg, and the mean elimination half-life (t1/2) was 3 to 4 weeks.

Pharmacokinetics in Special Populations

The effect of sex, age, race, and body weight on the PK of mepolizumab was assessed using the population approach, in which Study MEA115588 was included for the population PK analysis.

Race, Gender, Age, and Weight
Race, ethnicity, age and gender did not significantly impact the PK of mepolizumab. Mepolizumab clearance increased with body weight.

Immunogenicity
In the two Phase 3 studies MEA115588 and MEA115575, a total of 15 (6%) subjects treated with 100 mg mepolizumab SC were positive for post-baseline anti-mepolizumab antibodies. Antibodies were mostly transient, with 50% of antibody positive subjects demonstrating only one positive test results. Antibody titers were generally low. One subject developed neutralizing antibodies after mepolizumab exposure; no SAEs were associated with this case. There was about 29% numerical increase of mepolizumab clearance in post-baseline antibody-positive patients following 100 mg mepolizumab SC administration.

1.3.4 Pharmacodynamics

Study 114092 was a Phase 2 study that evaluated the PK/PD relationship between the exposure of subcutaneously administered mepolizumab (12.5 mg, 125 mg and 250 mg SC) and different PD markers of response. The study also compared PK/PD profiles between three SC treatments and one IV treatment (75 mg IV). In general, 75 mg IV and 125/100 mg SC mepolizumab had similar reduction effect on blood eosinophil counts.

1.3.5 Exposure-Response Relationship

Dose-response and exposure-response relationships were observed for reduction of blood eosinophil counts. The estimated dose required for 50% of maximal percentage reduction of blood eosinophil counts was 11 mg. No dose-response or exposure-response relationships were observed for FEV1 response and exacerbation rate based on combined data from MEA112997 (once every 4 weeks: 75 mg IV, 150 mg IV and 750 IV) and MEA115588 (once every 4 weeks: 75 mg IV and 100 mg SC). Exposure-response analysis for other endpoints including time to first exacerbation and frequency of exacerbations dichotomized as >= 1 to 6 exacerbations (yes or no) also exhibited the flat exposure-response relationship.

1.3.6 Dose-Response and Dose Selection

The proposed dose for marketing of 100 mg SC was supported with two dose ranging studies (MEA112997 and MEA114092) and one pivotal phase 3 exacerbation study (MEA115588). Studies MEA112997 and MEA114092 has provided evidence to support the selection of the 100 mg SC dose for further evaluation in the pivotal efficacy studies. In study MEA112997, subjects received mepolizumab 75, 250, or 750 mg or placebo IV once every four weeks to Week 48 for a 52-week treatment period. In study 92, subjects received 12.5, 125, or 250 mg of mepolizumab SC, or 75 mg IV once every 4 weeks for a total of 3 doses. Results of study MEA112997 showed that treatment with all 3 doses of mepolizumab resulted in a statistically significant reduction in exacerbations compared to placebo and there was no significant treatment difference among the three doses. In study MEA114092, a dose-dependent decrease in blood eosinophil levels was observed in all treatment groups by the third day post-treatment with similar reductions seen for 125 mg SC exposure and 75 mg IV exposure. These data, along with model-estimated inhibition of blood eosinophils provided support for evaluating both 100 mg SC and 75 mg IV in the pivotal phase 3 exacerbation study, Study MEA115588. Importantly, similar treatment effects were seen in Study MEA115588 providing evidence that the data from the 75 mg IV dose can be applied to the 100 mg SC dose. The data from these three studies support the conclusion that mepolizumab 75 mg IV and 100 mg SC would provide similar efficacy.

2. QUESTION BASED REVIEW

2.1 Regulatory History

Mepolizumab is a fully humanized monoclonal antibody (IgG1) targeted against human IL-5. It is the first anti-IL5 antibody submitted as BLA. All the asthma clinical trials of mepolizumab were developed under IND 006971, which was opened by GSK on 12/20/1996. (b) (4)

Eosinophilic asthma, the indication proposed by GSK under BLA 125526, does not have a clear disease definition, as it is not listed as an independent or sub-categorical disease under asthma in the international classification diseases (ICD, latest version 10) by WHO.

An EOP2 meeting with FDA was held on 05/04/2009. The summary of clinical pharmacology-related discussions and comments are listed as following:

1) Dose selection and dosing regimen in Phase 3 trials
   The Sponsor proposed 75 mg iv and 100 mg sc every 4 weeks in Phase 3 pivotal trails. The 100 mg sc dosing regimen was never tested in Phase 2 trials.
   FDA Response: We are unable to agree at this time. While the 75 mg IV dose appears reasonable for further study, the overall dose selection for Phase 3 is risky from several perspectives:
   - *Based on the results of MEA112997, we note that lower doses of mepolizumab may also be efficacious. Should a safety signal be identified in the clinical program, the adequacy of the dose-ranging will be a review issue.*
   - *We generally recommend that pivotal dose-ranging be conducted with the to-be-marketed formulation. There are no efficacy data to support selection of the 100 mg SC dose. The clinical relevance of serum eosinophilia, the pharmacodynamic parameter used to relate the 100 mg SC dose to the 75 mg IV dose, is unknown.*
   - *Likewise, we expect replicate trials of efficacy with the to-be-marketed product. The proposed bridging between the 75 mg IV and 100 mg SC dose may be adequate to support the SC dose; however, any differences in efficacy or safety that are observed in MEA115588 between the two formulations will jeopardize this approach. If the proposed bridging strategy fails, then the clinical program will lack replication for the to-be-marketed formulation.*

2) Sponsor proposed not to identify the isotype of the neutralizing antibody
   FDA Response: We concur with your plan to not determine the isotype of neutralizing antibodies unless there is a correlation with clinically relevant findings.

3) Sponsor proposed not to further evaluate the hepatocyte induction (CYP3A4)
   FDA Response: Agency is unable to concur at this time that no further evaluation is needed prior to BLA submission. This is an evolving area and we suggest that you follow developments in this area and make an appropriate decision regarding further DDI assessment. We suggest that you refer to the revised draft drug-drug interaction guidance published on February 18, 2012 for current thinking at this time;
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

EOP2 CMC meeting with FDA was held on 11/07/2012. The Sponsor proposed that based on the demonstrated biochemical comparability between MDP1 and MDP2, no pre-clinical pharmacology, PK or toxicology studies were deemed necessary and no formal human bioequivalence studies were conducted.

Question 4: Provided that results from manufacturing process experience and extended biophysical and biochemical analysis demonstrate comparability of the manufacturing processes and of (b) (4) drug product (MDP2 with MDP1), GSK proposes that no additional non-clinical or clinical studies are required in support of commercial registration of the (b) (4) processes. Does the Agency concur with this proposal?

FDA Response: With respect to (b) (4) please see our response to question 3. Provided we concur that (b) (4) MDP2 are comparable with (b) (4) MDP1, we agree that no additional nonclinical or clinical studies will be required in support of commercial registration of the (b) (4) and MDP2 processes. However, the pharmacology/toxicology and clinical reviewers will determine if the non-clinical and clinical studies are sufficient for filing a BLA for mepolizumab.

Pre-BLA meeting with FDA was held on 01/15/2014. The summary of clinical pharmacology-related discussions and comments are listed as following:

Question 8: The data which will be available to characterize Immunogenicity of mepolizumab administered IV and SC at the time of BLA submission is described in the briefing document. Does the Agency agree this characterization is sufficient to support registration of mepolizumab dosed SC?

FDA Response: The proposed clinical assessment of immunogenicity appears reasonable. We also request that you submit analyses of any association between immunogenicity and efficacy and adverse event rates.

Question 9: Based on available guidance (including: Revised Draft Guidance: Drug Interaction Studies UCM292362, February 18, 2012), GSK believe that the clinical pharmacology package for mepolizumab outlined in this briefing document is complete and no additional clinical pharmacology studies are needed for registration.

FDA Response: Yes, we agree that no additional clinical pharmacology studies are needed to support registration of mepolizumab. The adequacy of the data will be a review issue.

The Agency agreed Sponsor's initial pediatric study plan (iPSP) on 06/12/2014. The Sponsor proposed a Phase 2 PK/PD study in pediatric population aged 6 to 11 years old with severe eosinophilic asthma. Mepolizumab will be administered SC every 4 weeks for 12 weeks. The study initiation date will be no later than June 2015.

2.2 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

One *in vitro* and eleven *in vivo* clinical pharmacology-related studies conducted in either healthy or asthmatic subjects have been submitted in this submission. *In vitro* Study 10DMW042 was conducted between 12/06/2010 and 05/23/2011. The *in vivo* Clinical Pharmacology studies in healthy subjects and asthmatic patients are listed in Table 2.1.

Table 2.1 List of Clinical Studies Conducted in Healthy or Asthmatic Subjects Containing PK/PD Evaluation

Study ID	Study Date	Phase	Study Objective(s)	Study Design	Subjects	Treatment Groups
001[1]	05/06/1997 – 04/20/1998	2	Safety, PK, PD	R, DB, PC, DR, PG, SD	38 male with mild asthma	0.05 mg/kg, IV 0.5 mg/kg, IV 2.5 mg/kg, IV 10 mg/kg, IV Placebo, IV
006[1]	02/16/1999 – 10/05/1999	2	Safety, efficacy, PK, PD	R, DB, PC, DR, PG, RD (3-dose, Q4W)	362 patients with asthma	250 mg IV 750 mg IV placebo IV
017[1]	05/28/1999 – 01/11/2000	2	Safety, PK, PD	R, DB, PC, PG, RD (3-dose, W1, 6,8)	16 patients with asthma	250 mg SC placebo SC
018[1]	02/16/2001 – 06/22/2001	1	Safety, BA following IV, SC and IM	R, OL, PG, SD	60 Healthy subjects	250 mg SC, 3 different sites 250 mg IM 250 mg IV
035[1]	07/21/1997 – 01/08/1998	1	Safety, PK, PD	R, DB, PC, DR, PG, SD	18 males with mild asthma	0.5 mg/kg, IV 2.5 mg/kg, IV 10 mg/kg, IV Placebo, IV
036[1]	01/21/2000 – 08/15/2001	2	PD, safety	R, DB, PC, PG, RD (3-dose, Q4W)	24 patients with atopic asthma	750 mg, IV Placebo, IV
MEA112997[2]	11/09/2009 – 12/05/2011	2b/3	Efficacy, safety, PK, PD	R, DB, PC, DR, PG, RD (Q4W for 48 weeks)	616 patients with severe eosinophilic asthma	75 mg, IV 250 mg, IV 750 mg, IV Placebo, IV
MEA114092[2]	02/21/2011 – 03/07/2012	2	PD, PK, safety	R, OL, DR, PG, RD (3-dose, Q4W)	70 asthmatic patients with eosinophilia	12.5 mg, SC 125 mg, SC 250 mg SC 75 mg, IV
MEA115705[2]	08/09/2011 – 04/27/2012	1	Safety, PK, PD	R, SB, PC, PG, SD	35 healthy Japanese male	10 mg, IV 75 mg, IV 250 mg, IV 750 mg, IV Placebo, IV
MEA115588[2]	10/08/2012 – 01/18/2014	3	Efficacy, safety, PK, PD	R, DB, PC, PG, RD (8-dose, Q4W)	576 patients with severe eosinophilic asthma	75 mg IV 100 mg SC Placebo
MEA115575[2]	10/29/2012 – 12/12/2014	3	Efficacy, safety, PK, PD	R, DB, PC, PG, RD (Q4W for 24 weeks)	135 patients with severe refractory asthma	100 mg SC Placebo SC

(Source: adapted from section 5.2 Tabular Listing of all Clinical Studies.pdf, Table 1)

2.3 General Attributes of the Drug

2.3.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Mepolizumab is a fully humanized monoclonal antibody (IgG1) targeted against human IL-5. Mepolizumab consists of (b) (4)

(b) (4)

. Mepolizumab was produced (b) (4) recombinant CHO cells.

The to-be marketed drug product Mepolizumab for Injection, 100 mg/vial, is a white lyophilized cake, manufactured (b) (4) containing (b) (4) mg/mL mepolizumab, (b) (4) sodium phosphate dibasic heptahydrate, (b) (4) sucrose (b) (4) and (b) (4) polysorbate 80 (b) (4), at pH 7.0.

During clinical development, three different drug products were used: a product with pilot manufacturing process (PPMP) mostly with dosing strength of 50 mg/vial, mepolizumab drug product-1 (MDP1) with dosing strength of 250 mg/vial, and mepolizumab drug product-2 (MDP2) 100 mg/vial. Refer to Table 2.11 for the list of studies used these products. The compositions of these 3 products were listed in Table 2.2. The (b) (4)) of mepolizumab and the excipients compositions were the same between MDP1 and MDP2. The (b) (4) and excipients compositions were different between PPMP and MDP1/2. The formulation used to manufacture PPMP was optimized (b) (4) to manufacture MDP1/2.

Table 2.2 Composition of Mepolizumab throughout Clinical Development

Component	Function	Quality Standard	PPMP*	MDP1#	MDP2@
Phase			Pre-clinical, Phase1 and 2	Phase1, 2 and 3	Phase 3 and Commercial
Mepolizumab	Drug Substance	GlaxoSmithKline, Non-compendial[1]	(b) (4)		
Sucrose		United States Pharmacopeia/National Formulary (USP/NF), European Pharmacopeia (EP), and Japanese Pharmacopeia (JP)			
Sodium Phosphate Dibasic, heptahydrate		United States Pharmacopeia (USP)			
PS80		USP/NF, EP, and JP			
		(b) (4)			
WFI[5]		USP/NF, EP, and JP			

* The strength of PPMP was 50 mg/vial in early Phase 1/2 studies except Study 018 (250 mg/vial).
# The strength MDP1 was 250 mg/vial with (b) (4) overfill.
@ The strength MDP1 was 100 mg/vial with (b) (4) overfill.
The amount of mepolizumab and all the excipients per vial in MDP1 were approximately (b) (4) as the amount per vial in MDP2. The amount of mepolizumab and excipients per vial in PPMP (b) (4) as the amount per vial in MDP2.
(Source: adapted from section 3.2.P.2 pharmaceutical-development-p22.pdf, page 2, Table 1)

2.3.2 What are the proposed mechanism of action and therapeutic indications?

Multiple cell types, including eosinophils, have been shown involved in airway inflammation in asthma. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) that competitively binds to human IL-5 with a K_d ranging from 0.1 to 0.26 nM. The binding of mepolizumab with IL-5 blocks the interaction between IL-5 and the alpha chain of the IL-5 receptor present on cell surface (IC50 < 1 nM), thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils.

The proposed therapeutic indication of mepolizumab is "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".

2.3.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 100 mg administered once every 4 weeks. The route of administration is subcutaneous injection.

2.3.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

Eosinophilic asthma is a condition that does not have a clear disease definition. Mepolizumab is the first drug product indicated for eosinophilic asthma.

2.4 General Clinical Pharmacology

2.4.1 What is the basis for selecting the response endpoints?

In the pivotal clinical studies MEA115588 and MEA112997, the primary efficacy endpoint was the frequency of clinically significant exacerbations of asthma (Table 2.3) as defined by: worsening of asthma which required use of systemic corticosteroid and/or hospitalization and/or Emergency Department (ED) visits. Use of corticosteroid was defined as IV or oral steroid (e.g., prednisone) use for at least 3 days or a single intramuscular (IM) dose. For subjects on maintenance systemic CS, at least double the existing maintenance dose for at least 3 days was required.

In the pivotal clinical studies MEA115575, the primary efficacy endpoint was percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose (Table 2.3), while maintaining asthma control, categorized as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%

- >0% to <50%
- No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment

The exacerbation of asthma and reduction of OCS dose are long-term clinical endpoints and they were not measured in Phase 1/2 clinical pharmacology studies.

Table 2.3 Design of Pivotal Phase 3 Studies Supporting Mepolizumab Efficacy

Study	Design	Study Period (Weeks)			Mepolizumab Treatment (mg) and Regimen[1]	Subjects Randomized[2]
		Run-in	Treatment	Follow-up		
Exacerbation Studies						
MEA112997	Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging	2	52	4[3]	75 IV 250 IV 750 IV Placebo IV	153 152 156 155
MEA115588	Randomized, Double-blind Double-dummy Placebo-controlled, Parallel-group	1 to 6	32	8[4]	75 IV+Placebo SC 100 SC+Placebo IV Placebo SC & IV	191 194 191
OCS Reduction Study						
MEA115575	Randomized, Double-blind Placebo-controlled Parallel-group	3 to 10[5]	24	8[4]	100 SC Placebo SC	69 66

(Source: section 2.7.3 Summary of Clinical Efficacy.pdf, page 18, Table 3)

2.4.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma concentration of mepolizumab was measured to assess its pharmacokinetic parameters and exposure response relationships.

2.5 Exposure Response

2.5.1 What are the characteristics of the exposure-response relationship for effectiveness?

The exposure-response (E-R) relationship for primary efficacy endpoint (exacerbation rate) is flat based on analysis of combined data from two Phase 3 studies (MEA112997 and MEA115588 (once every 4 weeks: 75 mg IV and 100 mg SC) as shown in Figure 2.1. A series of E-R analysis for other endpoints of clinical interest, including time to first exacerbation and frequency of exacerbations dichotomized as >= 1 to 6 exacerbations (yes or no), consistently revealed the flatness of E-R relationship for efficacy. This is consistent with the flatness of dose-response observed in dose-ranging Study MEA112997 (Table 2.4).

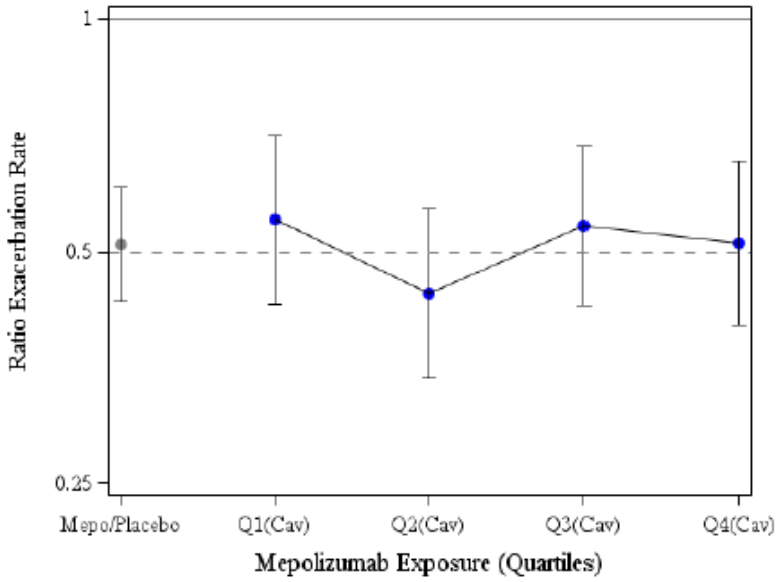

Figure 2.1 Exacerbation rate ratios following mepolizumab treatment compared with placebo by average exposure quartile (Source: from Pharmacometrics Review by Dr. Jingyu, Yu)

Table 2.4 Primary Analysis of Rate of Clinically Significant Exacerbations in Study 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: CSR MEA112997, Table 10)

In addition, PK/PD data from Study MEA114092 suggested the proposed 100 mg SC dose (comparable to 75 mg IV in exposure) has reached EC_{90} of the dose/exposure- PD response curve for reduction in blood eosinophil count, although it should be noted the correlation between blood eosinophil count and endpoints of clinical interest has not be established in the targeted patient population.

2.5.2 What are the characteristics of the exposure-response relationship for safety?

No formal exposure-response relationship of safety was evaluated. No apparent dose-response relationship was observed for drug-related adverse events from pooled safety data from Three Phase 3 studies (MEA112997, MEA115588, and MEA115575) other than increase of infusion-related reaction incidence from 75 mg IV to 750 mg IV (Table 2.5). However, the incidence of infusion-related reaction was comparable between placebo group and 75 mg IV, 250 mg IV group.

Table 2.5 Most Frequent (>=5 Subjects across Treatment Groups) Drug- Related[1] Adverse Events

Drug-Related Adverse Event (Preferred Term)	Number (%) of Subjects					
		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 Drug-related AE	67 (16)	60 (23)	61 (18)	29 (19)	33 (21)	183 (20)
Infusion-related reaction[2]	11 (3)	0	8 (2)	12 (8)	19 (12)	39 (4)
Headache	10 (2)	13 (5)	11 (3)	6 (4)	5 (3)	35 (4)
Injection site reaction	12 (3)	17 (6)	8 (2)	0	0	25 (3)
Fatigue	5 (1)	5 (2)	4 (1)	2 (1)	0	11 (1)
Hypersensitivity	6 (1)	3 (1)	2 (<1)	1 (<1)	2 (1)	8 (<1)
Nausea	7 (2)	3 (1)	0	2 (1)	0	5 (<1)
Arthralgia	2 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (1)	7 (<1)
Dizziness	1 (<1)	4 (2)	0	1 (<1)	1 (<1)	6 (<1)
Myalgia	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	5 (<1)
Edema peripheral	3 (<1)	0	3 (<1)	0	0	3 (<1)
Hypertension	3 (<1)	0	1 (<1)	2 (1)	0	3 (<1)
Injection-related reaction	3 (<1)	3 (1)	0	0	0	3 (<1)
Migraine	1 (<1)	2 (<1)	0	0	2 (1)	4 (<1)
Vomiting	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)

1 As assessed by the investigator
2 Preferred Term was only reported from studies where an IV formulation was used
(Source: section 2.7.4, summary-clin-safet.pdf, page 35, Table 11)

2.5.3 Does this drug prolong the QT or QTc interval?

No thorough QTc study was conducted in for mepolizumab. No major treatment-related imbalances were seen from a review of the efficacy studies.

Mepolizumab is a monoclonal antibody with molecular weight approximately (b) (4) KD, which restricts its ability to cross the plasma membrane and access the inner pore of hERG or other ion channels that are required for functional block. In immunohistochemistry tissue cross-reactivity study (Report RSD-100KGT), mepolizumab binding was restricted to human lymphoid tissues, and there was no binding to cardiac tissue, indicating limited opportunity for interaction with cardiac ion channels, particularly hERG. There were no acute effects on cardiovascular function observed in monkeys following IV doses up to 100 mg/kg.

As of 09/03/2007, approximately 571 subjects have been exposed to mepolizumab in GSK-sponsored clinical trials, some for a period of up to three years, totaling approximately 2520 exposures. No reports of QTc prolongation ≥500ms have been observed, except one as a consequence of right bundle branch block. In addition, no events of Torsade de Pointes have been reported. Two cases of sudden death have been reported; one from a subject on placebo and one from a subject on mepolizumab who had multiple pre-existing cardiovascular complications. Additional retrospective analyses performed, incorporating some of the standards applied in E14 also indicate that there was no effect of mepolizumab on the QT interval when compared to placebo.

2.5.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Yes, the proposed dosing regimen of 100 mg SC is consistent with the known E-R relationship.

The proposed dose for marketing of 100 mg SC was supported with two dose ranging studies (MEA112997 and MEA11409) and one pivotal phase 3 exacerbation study (MEA115588). Studies MEA112997 and MEA114092 provided evidence to support the selection of the 100 mg SC dose of mepolizumab for further evaluation in pivotal efficacy studies. In study MEA112997, subjects received mepolizumab 75, 250, or 750 mg or placebo IV once every four weeks to Week 48 for a 52-week treatment period. In study 92, subjects received 12.5, 125, or 250 mg of mepolizumab SC, or 75 mg IV once every 4 weeks for a total of 3 doses. Results of study MEA112997 showed that treatment with all 3 doses of mepolizumab resulted in a statistically significant reduction in exacerbations compared to placebo and there was no significant treatment difference among the three doses. In study MEA114092, a dose-dependent decrease in blood eosinophil levels was observed in all treatment groups by the third day post-treatment with similar reductions seen for 125 mg SC exposure and 75 mg IV exposure. These data, along with model-estimated inhibition of blood eosinophils provided support for evaluating both 100 mg SC and 75 mg IV in the pivotal phase 3 exacerbation study, Study MEA115588. Importantly, similar treatment effects were seen in Study MEA115588 providing evidence that the data from the 75 mg IV dose can be applied to the 100 mg SC dose. The data from these three studies support the conclusion that mepolizumab 75 mg IV and 100 mg SC would provide similar efficacy.

2.6 PK Characteristics of the Drug

2.6.1 What are the single and multiple dose PK parameters of drug in healthy adults?

Drug product MDP1 was only administered as single IV dose in healthy Japanese males in Study MEA115705. No multiple dose study of MDP1was conducted in heathy adults.

Following a 30 minute continuous infusion, mepolizumab concentrations declined in a bi-exponential manner (Fig. 2.2). C_{max} and $AUC_{0\text{-}inf}$ generally increased dose proportionally from 75 mg to 750 mg (Table 2.6). Mean CL ranged from 6.19 to 7.87 mL/hr (0.149 to 0.189 L/day) across different dosing groups. Mean volume of distribution (V_{ss}) ranged from 4.40 to 6.52 L across different dosing groups. Mean terminal half-life ranged from 19.8 to 36.1 days across different dosing groups.

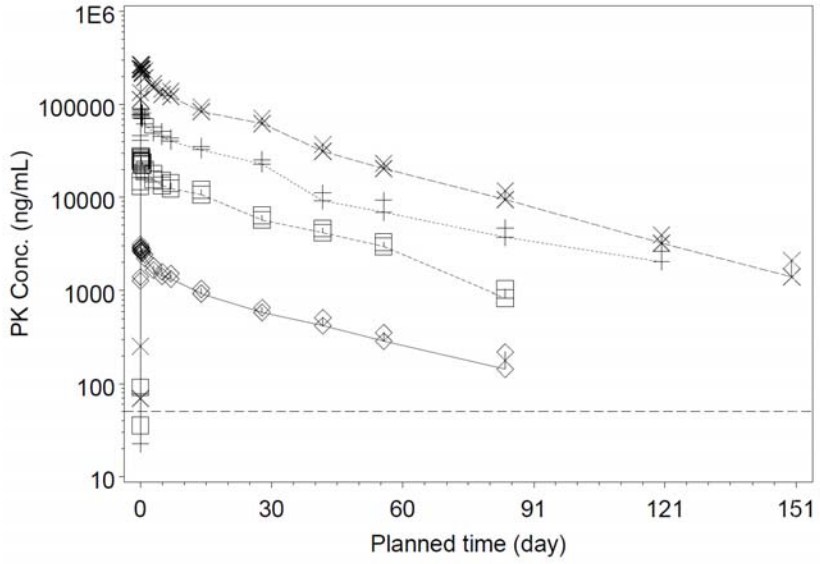

Figure 2.2 Mean (SD) mepolizumab plasma concentration-time profiles (semi-log scale) following single dose IV administration of 10 mg (n=6), 75 mg (n=6), 250 mg (n=7), and 750 mg (n=7) mepolizumab in Japanese males. (Source: CSR 115705, page 424, Figure 3.01)

Table 2.6 Mean (SD) PK Parameters for Mepolizumab Following Single Intravenous Administration in Japanese Healthy Males from Study MEA115705

Parameter (unit)	SB-240563			
	10 mg (N=6)	75 mg (N=6)	250 mg (N=7)	750 mg (N=7)
AUC(0-∞) (day*ug/mL)	54.63 (12.27)	493.36 (41.07)	1698.66 (172.17)	4495.64 (413.79)
AUC(0-t) (day*ug/mL)	47.99 (6.47)	469.14 (42.77)	1460.74 (270.47)	4448.41 (400.21)
Cmax (ug/mL)	2.87 (0.27)	26.46 (1.81)	79.26 (11.60)	253.65 (28.28)
tmax (day)	0.042 (1*) (0.02- 0.04)	0.104 (2.5*) (0.04- 0.17)	0.042 (1*) (0.02- 0.08)	0.021 (0.5*) (0.02- 0.33)
t1/2 (day)	27.43 (10.36)	19.80 (2.42)	36.14 (11.30)	22.65 (2.32)
Vss (L)	6.52 (0.77)	4.40 (0.69)	5.65 (1.35)	4.98 (0.54)
CL (mL/hr)	7.87 (1.68)	6.37 (0.55)	6.19 (0.63)	7.01 (0.74)

All parameters reported as arithmetic mean (SD) except for Tmax which is median (range).
The parameters were derived from non-compartmental analysis.
(Source: CSR 115705, page 34, Table 11)

2.6.2 How does the PK of the drug in healthy adults compare to that in patients with the target disease?

Crosss-tudy comparison showed that mepolizumab clearance appeared lower in Japanese healthy subjects, however, the confounding factor of body weight cannot be ruled out.

Inter-study comparison of mepolizumab CL following IV single-dose in Japanese males and multiple-dose in asthma patients are listed in Table 2.7. The CL appeared lower in Japanese males; however, this result might be confounded with the body weight effect (Figure 2.3).

Table 2.7 Inter-Study Comparison of Mepolizumab Clearance between Subjects following IV Route

	Study 114092*	**Study 12997***	**Study 115588***	**Study 115705[#]**
Subjects	Asthma Patients	Asthma Patients	Asthma Patients	Healthy Subjects
IV Dose Range	75 mg	75 mg – 750 mg	75 mg	10 mg – 750 mg
N	11	460	191	26
CL (L/day)*	0.210 (0.189, 0.232)	0.232 (0.226, 0.240)	0.220 (0.210, 0.232)	0.162 (0.152, 0.173)*

*Estimated typical value (95% CI) in asthmatic patient weighing 70 kg, via popPK analysis
[#] geometric mean (95% CI) in Japanese healthy males, via non-compartmental analysis
(Source: Table 4.25 and Table 2.6)

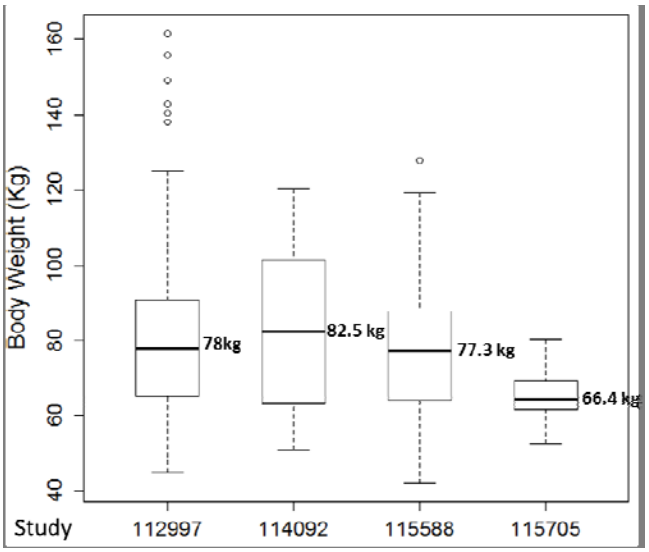

Figure 2.3 Box plot of body weight of subjects who received mepolizumab via IV route in 4 studies. The median body weight in Japanese healthy males was about 16 – 20% lower than subjects in other 3 studies. (Source: reviewer's analysis)

2.6.3 What are the characteristics of drug absorption?

By popPK analysis, the estimated CL and CL/F in a typical asthmatic patient weighing 70 Kg following 75 mg IV and 100 mg SC mepolizumab to be 0.220 (SE=0.0255) L/day (Table 4.22) and 0.280 (SE=0.00269) L/Day (Table 4.23), respectively in Phase 3 Study MEA115588. The geometric mean of post-hoc individual CL and CL/F was 0.225 (CV=32%) L/day and 0.293 (CV=36%) L/day, respectively. As the doses studied were within the linear PK range and the similar average body weight between the IV (77 ± 17 Kg) and SC (75 ± 19 Kg) groups, an ANOVA analysis was used to assess the absolute bioavailability of mepolizumab (Table 2.8). The absolute bioavailability of the 100 mg mepolizumab via SC route in the upper arm was estimated to be 80% (90% CI: 76%–84%). The result was similar to the results estimated from study MEA114092, in which the estimated absolute bioavailability for 12.5, 125 and 250 mg SC groups was 74% (90% CI: 54%–102%), 81% (90% CI: 57%– 116%), 82% (90% CI: 56%–120%) and 64% (90% CI: 45%–91%), respectively.

Table 2.8 Absolute bioavailability of Mepolizumab Following 100 mg SC Administration

Parameter	F (%)	90% CI Lower	90% CI Upper
CL	79.6	75.5	83.9

Log-transformed CL values following IV and SC administrations were analysed using an analysis of variance (ANOVA) model in Pharsight Phoenix Build 6.2.1.51.
(Source: CSR MEA115588, Table 10.13)

2.6.4 What are the characteristics of drug distribution?

By popPK analysis, the estimated apparent volume of distribution of the central compartment (V_2/F) in a typical asthmatic patient weighing 70 Kg following 100 mg SC administration was 4.44 L (95% CI =4.14, 4.76) (Table 4.23) and 5.75 L (95%CI = 4.85, 6.82) (Table 4.26), from Study MEA115588 and MEA115575, respectively. When divided by body weight, the value of estimated V_2 was 63 mL/kg and 82 mL/kg from Study MEA115588 and MEA115575, respectively.

2.6.5 What are the characteristics of drug metabolism?

Mepolizumab is a humanized IgG1 monoclonal antibody that is catabolized by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. Since the target for mepolizumab is a soluble cytokine (not a membrane-bound receptor), mepolizumab does not undergo target-mediated degradation.

2.6.6 What are the characteristics of drug elimination?

Mepolizumab is a mAb with a large molecular weight (149.2 kDa) precluding renal elimination, which is catabolized by ubiquitous proteolytic enzymes not restricted to hepatic tissue. Mepolizumab does not undergo target-mediated clearance and changes in target concentration do not influence exposure. The clearance mechanism is non-specific, with large capacity and no overlapping clearance mechanism with small molecule drugs.

By popPK analysis, the estimated CL/F in a typical asthmatic patient weighing 70 Kg following 100 mg SC administration was 0.280 L/day (95% CI =0.267, 0.295) (Table 4.23) and 0.326 L/day (95%CI = 0.267, 0.398) (Table 4.26), from Study MEA115588 and MEA115575, respectively. When divided by body weight, the value of estimated CL/F was 4 mL/day/kg and 4.65 mL/day/kg from Study MEA115588 and MEA115575, respectively. The effective half-life estimated from accumulation ratio (1.65 to 1.98) ranged from 21 to 28 days.

2.6.7 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

PK linearity was assessed in Study MEA 115705. Four groups of eight subjects were randomized 3:1 to receive mepolizumab single-dose IV (10, 75, 250 and 750 mg) or placebo. Following a 30-minute IV infusion, C_{max} and $AUC_{0\text{-}inf}$ generally increased dose proportionally from 10 mg to 750 mg. The slope for loge transformed $AUC_{0\text{-}inf}$ and C_{max} (90% confidence interval) was 1.0284 (0.9970, 1.0599) and 1.0279 (1.0014, 1.0543), respectively (Table 2.9)

Table 2.9 Dose-proportionality Analysis for $AUC_{0\text{-}inf}$ and C_{max} following Single-Dose IV Administration of Mepolizumab from 10 mg to 750 mg in Healthy Subjects

	Point estimated	90% CI (Lower, Upper)
AUC(0-∞) (day*ug/mL)	1.0284	(0.9970, 1.0599)
Cmax (ug/mL)	1.0279	(1.0014, 1.0543)

(Source: CSR MEA115588, Page 34, Table 12)

2.6.8 How do the PK parameters change with time following chronic dosing?

Following Q4w SC administration of 100 mg mepolizumab, the model predicted C_{trough} values demonstrated an accumulation ratio ranged from 1.65 to 1.72 in Study 115588 and 1.94 to 1.98 in Study 115575. The steady state appeared reached at Week 16.

2.6.9 Is there evidence for a circadian rhythm of the PK?

There was no evidence for a circadian rhythm of mepolizumab in asthma patients.

2.7 Intrinsic Factors

2.7.1 What are the major intrinsic factors responsible for the inter-subject variability exposure in patients with the target disease and how much of the variability is explained by the identified covariates?

In a popPK analysis (report 2014N210473) that included PK data via IV route from 6 studies (Study 01, 06, 18, 35, 185, and 226), twelve covariates (weight, height, age, sex, race, country of study site, disease state, creatinine clearance, and liver function [alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin]) were investigated. Body weight was the only statistically significant covariate for clearance and volume, although the magnitude of effect was not considered to be clinically relevant.

2.7.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

The effect of body weight on PK is not clinically important given the flatness of E-R relationship for efficacy, so no dose adjustment is warranted with regard to body weight.

2.7.2.1 Severity of Disease state

A popPK analysis (report 2014N210473) did not identify asthma severity as a significant covariate for mepolizumab clearance.

2.7.2.2 Body Weight

In all population PK analyses, body weight was identified as a statistically significant covariate. The effect of body weight on mepolizumab CL/F following 100 mg SC was evaluated by pooling PK data from Study MEA115588 and Study MEA115575. The CL/F increased 54% from body weight quantile ranged 45 – 63 kg to 86 – 140 kg (Figure 2.4).

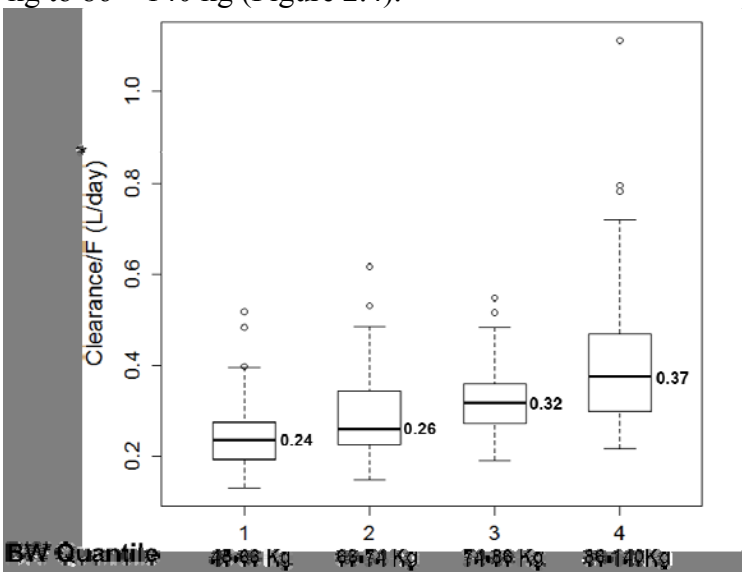

Figure 2.4 Box plot of CL/F of mepolizumab by body weight quartiles (N ~ 66 for each quartile) via popPK model analyzing mepolizumab 100 mg SC data from Study MEA115588 and Study MEA115575 (Model 008, reviewer's analysis).

2.7.2.3 Elderly

A popPK analysis (report 2014N210473) did not identify age as a significant covariate for mepolizumab clearance.

2.7.2.4 Pediatric Patients

In total 7 and 2 adolescents received mepolizumab 100 mg SC treatment from Study MEA115588 and Study MEA115575, respectively. The geometric mean of post-hoc CL/F and body weight of these 9 adolescents was 0.197 (CV=20.1%) L/day and 59.4 (CV=18.8%) kg, respectively (Model 008). The mean CL/F value was 35% less than that of adults [0.302 (CV=33.9%, N=254) L/day, from Model 008] (Figure 2.5). This could be contributed by lower body weight observed in adolescent patients.

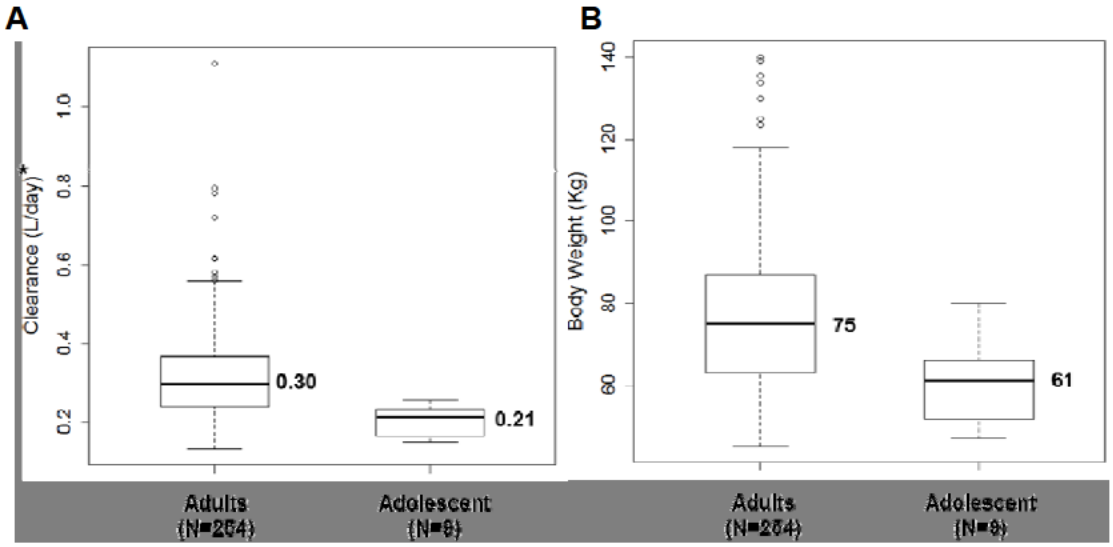

Figure 2.5 Box plot of CL/F of mepolizumab by age group (adults and adolescents) via popPK model analyzing mepolizumab 100 mg SC data from Study MEA115588 and Study MEA115575 (Model 008, reviewer's analysis).

The clinical benefit of mepolizumab 100 mg SC once every 4 weeks for the treatment of severe asthma in children 12-17 years of age was unknown because of the limited data and unknown relevance of this severe asthma phenotype associated with eosinophilic inflammation in the pediatric population. These issues were raised and discussed during the June 11, 2015 Pulmonary Allergy Drugs Advisory Committee Meeting. Consistent with the panel's discussion and recommendation, further PREA required post marketing studies in adolescents and younger pediatric patients are needed. For details, refer to primary review by medical officer Dr. Sofia Chaudhry.

2.7.2.5 Race/Ethnicity

A popPK analysis (report 2014N210473) did not identify race/ethnicity as a significant covariate for mepolizumab clearance.

2.7.2.6 Renal Impairment

A popPK analysis (report 2014N210473) did not identify creatinine clearance as a significant covariate for mepolizumab clearance.

2.7.2.7 Hepatic Impairment

A popPK analysis (report 2014N210473) did not identify the liver function indicators, such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, significant covariates for mepolizumab clearance.

2.7.2.8 What pregnancy and lactation use information is available?

Adequate and well-controlled trials with mepolizumab have not been conducted in pregnant women. Based on animal data, NUCALA is not predicted to increase the risk of developmental abnormalities.

2.7.3 Does genetic variation impact exposure and/or response?

No analysis was conducted on genetic variation impact on exposure and/or response.

2.7.4 Immunogenicity

2.7.4.1 What is the incidence of the formation of the ADA, including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

An integrated analysis was performed using pooled data from 3 Phase 3 studies (MEA112997, MEA115588, and MEA115575) that used the 6th generation of ADA assay. Three to four samples per subject were collected over time (including baseline) in these studies for ADA assessment. Overall, 15/260 (6%) of subjects treated with 100 mg SC and 13/633 (2%) of subjects treated IV had anti-mepolizumab antibodies identified in at least one sample after having received at least one dose. Of the 28 subjects (3%) who tested positive for anti-mepolizumab antibodies in these studies, 7 (0.8%) patients were positive in placebo group or before mepolizumab treatment. The majority (68%) developed antibodies by the first time point collected post-treatment. Antibodies were low titer and mostly transient, with 50% of antibody positive subjects having only 1 positive test result.

2.7.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

The effect of immunogenicity on mepolizumab CL/F following 100 mg SC was evaluated by pooling PK data from Study MEA115588 and Study MEA115575. ADA result (considered as positive if positive in at least one time point) was introduced as a categorical covariate to evaluate its effect on CL/F. It appeared that the distribution of inter-subject variability of mepolizumab CL/F was visually different between ADA-positive and ADA-negative patients (Figure 2.6). Introduction of covariate ADA significantly reduced objective function by 6.236 ($p<0.05$). The geometric mean of post-hoc CL/F was 0.294 (CV=33.4%) L/day and 0.360 (CV=46.6%) L/day for ADA-negative and ADA-positive patients, respectively (Figure 2.7). The mean body weight was comparable between ADA-negative [74.2 kg (CV=23.7%)] and ADA-positive patients [73.2 kg (CV=26.9%)]. Therefore, there was slight increase (22.4%) of CL/F by point estimate in ADA-positive patients compared to ADA-negative patients following 100 mg SC treatment.

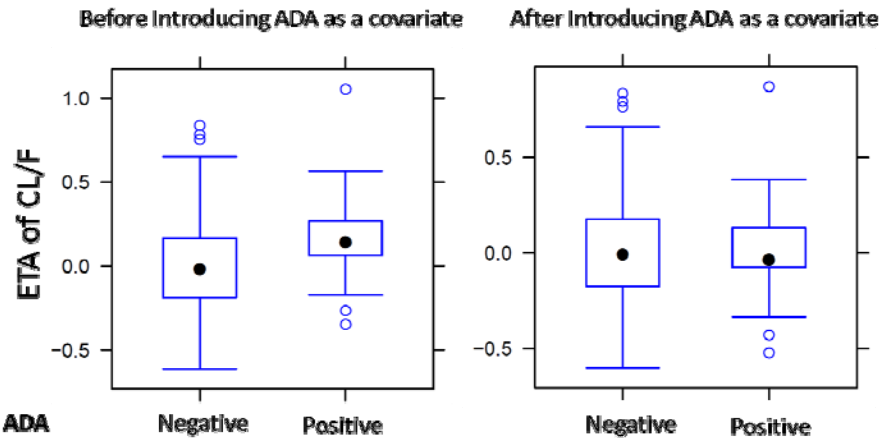

Figure 2.6 Box plot of inter-subject variability (ETA) of mepolizumab CL/F grouped by ADA results before and after introduction of the ADA results in the popPK model analyzing mepolizumab 100 mg SC data from Study MEA115588 and Study MEA115575 (reviewer's analysis).

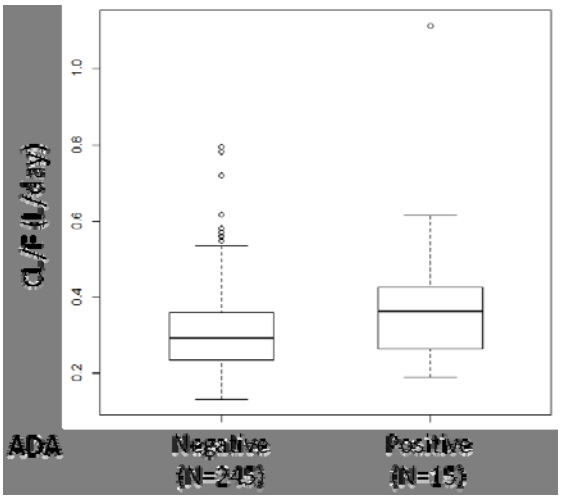

Figure 2.7 Box plot of CL/F of mepolizumab grouped by ADA results in the popPK model analyzing mepolizumab 100 mg SC data from Study MEA115588 and Study MEA115575 (Model 008, reviewer's analysis).

Any PK differences did not contribute toward changes in the PD response and there was no evidence of a correlation between antibody titre and change in blood eosinophil count.

2.7.4.3 Does the ADA have neutralizing activity?

Among 28 ADA positive patients from 3 Phase 3 studies (MEA112997, MEA115588, and MEA115575), there was only one patient from Study MEA115575 tested positive for anti-mepolizumab neutralizing antibody at the early withdraw visit (Week 13) and at the follow-up visit (Week 17). Subject 1733 was 66-yeal-old female. The subject entered the treatment phase on a maintenance OCS dose of 5 mg/day and met protocol criteria for OCS dose reduction to 2.5 mg/day following 4-week treatment of 100 mg mepolizumab sc (first dose) and reduction to 1.25 mg/day following 8-week treatment (second and the last dose). The subject had a significant asthma exacerbation at 9 days, and the second exacerbation 37 days, following the second and the last dose. The subject withdrew at 63 days (Week 13) following the second and the last dose.

2.7.4.4 What is the impact of ADA on clinical efficacy?

Overall, there did not appear to be any loss of disease control associated with ADA-positive findings in Phase 3 trials.

2.7.4.5 What is the impact of ADA on clinical safety?

There were no signals for serious acute hypersensitivity reactions or serum sickness-like reactions associated with positive anti-mepolizumab antibody status. Importantly, adverse events evaluated as potential systemic allergic reactions were uncommon across the Phase 3 trials (≤2%) and not related to study drug in antibody positive subjects. Among antibody positive subjects, there was only 1 injection site reaction (ISR) (2%) compared with 43 (3%) in antibody negative subjects.

2.8 Extrinsic Factors

The effects of smoking status and co-medications on tiotropium exposure in asthma patients were investigated in PK meta-analysis report.

2.8.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The effects of Mepolizumab (60-600000 ng/mL), IL-5 and IL-6 (10-100000 pg/mL) on the mRNA levels of CYP3A4 were evaluated in cultured human hepatocytes in an in vitro study 10DMW042. Following exposure of cultured human hepatocytes to mepolizumab for 48 hours, no notable changes in the mRNA levels of CYP3A4 were observed (Figure 4.30).

The IC_{50} of IL-5 on reduction of CYP3A4 mRNA levels was 142 pg/mL. By considering the free IL-5 levels were mostly LOQ (3.91 pg/mL) in healthy subjects or asthma patients, the in vivo effect of physiological level of IL-5 on CYP3A4 transcription is expected to be neglected.

2.8.2 What are the drug-drug interactions?

The potential for drug-drug interactions with mepolizumab is classified as low in consideration of mepolizumab target, elimination mechanism, favorable safety profile at doses up to 750 mg IV and the lack of mechanism of action rationale for a potential interaction. No drug interaction studies have therefore been conducted.

2.8.3 Does the label specify co-administration of another drug?

Mepolizumab is indicated for add-on maintenance treatment of severe asthmatic patients. Maintenance treatment of severe asthma includes regular treatment with high dose inhaled corticosteroids, with or without maintenance oral corticosteroids.

2.8.4 What other co-medications are likely to be administered to the target population?

Patients in Phase 3 Study MEA112997 and Study MEA115588 were required to have additional controller medication, e.g., long-acting beta-2 receptor agonist, leukotriene receptor antagonist or theophylline in the 12 months prior to the screening visit.

2.9 General Biopharmaceutics

2.9.1 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

The to-be-marketed drug product is MDP2 with strength of 100 mg/vial. MDP2 was used in the open-label extension studies MEA115666 and MEA115661 with long-term safety as the primary objective. Drug product MDP1 with strength of 250 mg/vial was used in 3 pivotal Phase 3 studies (MEA112997, MEA115588, and MEA115575) with efficacy as the primary objective. The same (b) (4) (b) (4) was used to manufacture MDP1 and MDP2. Biochemical and biophysical comparability data have shown these two drug products to be comparable. The excipients compositions were the same between MDP1 and MDP2.

No BE studies were conducted comparing the PK profiles of MDP1 and MDP2. This is acceptable as there were only minor manufacturing process changes, (b) (4) . For details, refer to primary review by Product Quality Reviewer Dr. Marjorie Shapiro.

Phase 3 study MEA115588 compared mepolizumab CL via 75 mg IV administration and CL/F via 100 SC administrations. The geometric mean of post-hoc individual CL and CL/F was 0.225 (CV=32%) L/day and 0.293 (CV=36%) L/day, respectively. Therefore, the systemic exposure is expected to be similar between 75 mg IV and 100 mg SC. The efficacy and safety profile of 75 mg IV and 100 mg SC were also comparable in Study MEA115588. For detail, refer to primary review by medical officer Dr. Sofia Chaudhry.

Three drug products were developed in mepolizumab clinical program: PPMP, MDP1, and MDP2. MDP2 is the to-be-marketed product. PPMP had strength mostly 50 mg/vial. MDP1 had strength of 250 mg/vial. MDP2 had strength of 100 mg/vial (Table 2.10). The (b) (4) used for PPMP was different from MDP1/2 as their formulations were different. (b) (4) The excipients composition was also different between PPMP and MDP1/2: (b) (4) PPMP to MDP1/2. However, there was a lack of PK bridging study to investigate the formulation effect on mepolizumab absorption between PPMP and MDP1/2 via SC administration. Therefore, it is inappropriate to apply the PK parameters obtained from PPMP to the final product MDP2.

Table 2.10 Differences between Three Mepolizumab Drug Products Used in Clinical Studies

	PPMP	MDP1	MDP2
Strength	Mostly 50 mg/vial	250 mg/vial*	100 mg/vial#
(b) (4)			(b) (4)
Used in Clinical Studies	Early Phase 1/2	Phase 1/2/3	Phase 3 Open-label extended studies To-be-marketed
Composition of excipients			
Sucrose			(b) (4)
Sodium Phosphate			

Diabasic, heptahydrate			
PS80			(b) (4)

* with (b) (4) overfill
# with (b) (4) overfill
(Source: section 3.2.P.2 pharmaceutical-development-p22.pdf, page 2, Table 1)

On the other hand, there were only minor manufacturing process changes between MDP1 and MDP2, (b) (4) According to the conclusions from EOP2 CMC meeting (held on 11/07/2012), FDA concurred that (b) (4) /MDP2 were comparable with (b) (4) /MDP1, and FDA agreed that no additional nonclinical or clinical studies will be required in support of commercial registration of the (b) (4) and MDP2 processes. For details, refer to the meeting minutes dated 02/08/2013 and the primary review by Product Quality Reviewer Dr. Marjorie Shapiro.

The list of studies used those products were listed in Table 2.11. It was not uncommon that multiple batches of the drug product were used in single study.

Table 2.11 Summary of Investigational Formulations Used in Mepolizumab Clinical Studies

Study ID	Mepolizumab Drug Product				Mepolizumab Drug Substance	
	Batch #	Presentation	Manufacturing Process	Date of Manufacture	Batch#	Manufacturing Process
001 035	U96257	50 mg/vial	Pilot	09/13/1996	SB-036-01	(b) (4)
006	U97281	50 mg/vial	Pilot	10/07/1997	SB-036-03	
006 017	U97282	50 mg/vial	Pilot	10/14/1997	SB-036-04	
006 017 035	U99001	50 mg/vial	Pilot	01/12/1999	SB240563-KA0-C06	
006 035	U99002	50 mg/vial	Pilot	01/19/1999	SB240563-NO0-C07	
018	U00079	250 mg/vial	Pilot	06/27/2000	240563-0VB0-C02	
MEA112997	6001	250 mg/vial	MDP1	01/19/2006	T04H012	
MEA112997 MEA114092	7001	250 mg/vial	MDP1	11/03/2007	T04L001	
MEA112997 MEA114092	7002	250 mg/vial	MDP1	11/10/2007	T04L006	
MEA112997	7003	250 mg/vial	MDP1	11/19/2007	T04L008	
MEA112997 MEA114092 MEA115705	0001	250 mg/vial	MDP1	07/02/2010	T04L009	
MEA115588 MEA115575 MEA115666	2001	250 mg/vial	MDP1	03/30/2012	T04L011	
MEA115588 MEA115575 MEA115666	2002	250 mg/vial	MDP1	06/08/2012	T04L012	
MEA115588	2003	250 mg/vial	MDP1	07/11/2012	T04L014	

MEA115666 MEA115661						
MEA115666 MEA115661	2004	250 mg/vial	MDP1	11/28/2012	T04M014	(b) (4)
MEA115666 MEA115661	3502	100 mg/vial	MDP2	05/29/2013	T0413006	
MEA115666 MEA115661	3504	100 mg/vial	MDP2	07/11/2013	T0413005	
MEA115666	3507	100 mg/vial	MDP2	12/04/2013	T0413007	

(Source: section 3.2.P.2 formulation development.pdf, page 4-8, Table 3)

2.9.2 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The subcutaneous administration route is unaffected by food and no food-effect studies have been conducted.

2.10 Analytical Section

2.10.1 What bioanalytical methods were used to assess mepolizumab plasma concentrations?

Plasma concentrations of mepolizumab in Study MEA112997 were determined by a single ELISA method by (b) (4) (2011N113224_02). The assay used biotinylated recombinant human IL-5 immobilized on a streptavidin microtiter plate to capture mepolizumab and Fc-specific mouse anti-human IgG1 labelled with horseradish peroxidase to detect mepolizumab allowing quantitation by a chemiluminescent signal. Human plasma samples were diluted 5-fold in Tris, Tween, Bovine serum albumin (TBB) buffer before loading to the microtiter plate.

Plasma concentrations of mepolizumab in Study MEA114092 was determined using two methods by (b) (4). Mepolizumab plasma concentrations were quantified by either using an ELISA (2011N113224_02) or a second ELISA which was an adaption of the first resulting from the lack of consistent supply of the recombinant human IL-5 capture reagent (2012N133378_02). The second assay used a neutralizing idiotypic antibody specific for the binding portion of the drug passively adsorbed to a polystyrene microtiter plate to capture mepolizumab and Fc specific mouse anti-human IgG1 labelled with horseradish peroxidase to detect mepolizumab allowing quantitation by a chemiluminescent signal. Human plasma samples were diluted 5-fold in Tris, Tween, Bovine serum albumin buffer (TTB buffer) before loading to the microtiter plate.

Subsequently, plasma concentrations of mepolizumab studies MEA115705, MEA115588, and MEA115575 were all determined by the second method used in MEA114092.

2.10.2 For all moieties measured, is free, bound, or total measured?

Free mepolizumab was measured.

2.10.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

The bioanalytical assays used in Phase 2/3 studies (MEA112997, MEA115588, MEA115575) were shown to be sensitive, selective, reproducible and accurate for the determination of free mepolizumab in human serum, with an LLOQ of 50 ng/ml and a coefficient of variance (CV) for the inter- and intra-assay precision of less than 15%.

Method 2011N113224_02 was used in Study MEA114092 and MEA112997.The range of the standard curve for this method was 50 to 5000 ng/mL; the lower limit of quantitation was 50 ng/mL using 100 µL of 5-fold diluted plasma; the within-run precision and between-run precision was ≤ 18.5% and ≤ 5.0%, respectively; the within-run accuracy and between-run accuracy was -18.8% ≤ bias ≤ 18.5% and -14.5 ≤ bias ≤ 6.7%, respectively. No significant matrix effect was observed in five out of six different lots of human plasma after a 1:5 dilution in TTB buffer. Freeze thaw stability confirmed for up to three freeze thaw cycles (from -70 ºC to room temperature and -20ºC to room temperature). Long term stability at -70 ºC confirmed for up to one month and up to 12 months at -20 ºC (Table 2.12).

Table 2.12 Summary of Plasma Mepolizumab Bioanalytical Validation by Method 2011N113224_02

LLQ	50 ng/mL using 100 µL of 5-fold diluted plasma
Validated Range	50 to 5000 ng/mL
Within-run Precision (%CV)	≤ 18.5%
Between-run Precision (%CV)	≤ 5.0%
Within-run Accuracy (%Bias)	-18.8 ≤ Bias ≤ 8.9%
Between-run Accuracy (%Bias)	-14.5 ≤ Bias ≤ 6.7%
Dilution Integrity	Up to 4,000,000 ng/mL
Prozone Effect	Not observed at 4000000 ng/mL SB240563 in human plasma
Stability in Human Plasma	Freeze thaw stability confirmed for up to three freeze thaw cycles (from -70ºC to room temperature and -20ºC to room temperature). Long term stability at -70ºC confirmed for up to one month and up to 12 months at -20ºC.
Processed Sample Stability	Processed plasma stability confirmed for samples diluted 1:5 in TTB buffer ON at 4ºC
Selectivity	No significant matrix effect was observed in five out of six different lots of human plasma after a 1:5 dilution in TTB buffer [c]

(Source: section 2.7.1, summary-biopharm.pdf, page 29, Appendix Table 2)

Table 2.13 Summary of Plasma Mepolizumab Bioanalytical Validation by Method 2012N133378_02

LLQ	50 ng/mL using 100 µL 10-fold diluted plasma
Validated Range	50 to 5000 ng/mL

Within-run Precision (%CV)	≤ 10.6%
Between-run Precision (%CV)	≤ 8.1%
Within-run Accuracy (%Bias)	-15.0 ≤ Bias ≤ 5.4%
Between-run Accuracy (%Bias)	-5.6 ≤ Bias ≤ -1.1%
Dilution Integrity	Up to 3,750,000 ng/mL
Prozone Effect	Not observed at 3750000 ng/mL SB240563 in human plasma
Stability in Human Plasma	Room temperature stability confirmed for at least 24 hours. Freeze thaw stability confirmed for up to eight freeze/thaw cycles (from -70ºC to room temperature and -20ºC to room temperature). Long term stability at -20ºC confirmed for up to 43 months at -20ºC. Whole blood stability at 37ºC for 4 hours.
Processed Sample Stability	Refer to previous validation report number: 2011N113224_02
Selectivity	No significant matrix effect was observed in six different lots of human plasma after a 1:10 dilution in TTB buffer. No significant interference effect was observed in hemolysed or lipemic plasma.
Tolerance to non-neutralizing ADA	Tolerance observed for all non-neutralizing ADA samples examined (≤ 128 titre)
Tolerance to neutralizing ADA	No tolerance observed in neutralizing ADA samples examined (n=2)

(Source: section 2.7.1, summary-biopharm.pdf, page 30, Appendix Table 2)

Method 2012N133378_02 was used in Study MEA115588, MEA115575 and MEA115705. The range of the standard curve for this method was 50 to 5000 ng/mL; the lower limit of quantitation was 50 ng/mL using 100 µL of 5-fold diluted plasma; the within-run precision and between-run precision was ≤ 10.6% and ≤ 8.1%, respectively; the within-run accuracy and between-run accuracy was -15.0% ≤ bias ≤ 5.4% and -5.6 ≤ bias ≤ 1.1%, respectively. No significant matrix effect was observed in six different lots of human plasma after a 1:10 dilution in TTB buffer. No significant interference effect was observed in hemolysed or lipemic plasma. Room temperature stability confirmed for at least 24 hours. Freeze thaw stability confirmed for up to eight freeze/thaw cycles (from -70ºC to room temperature and -20ºC to room temperature). Long term stability at -20ºC confirmed for up to 43 months at -20ºC. Whole blood stability at 37ºC was 4 hours (Table 2.13).

2.10.4 What bioanalytical methods are used to assess therapeutic protein concentrations?

The concentration of IL-5 present in human serum was determined by a quantitative sandwich enzyme immunoassay technique. The serum IL-5 present in samples, assay standards and validation/quality controls (QC) bind to a capture antibody coated onto a microplate. Serum IL-5 is detected by an enzyme-linked polyclonal antibody specific for IL-5. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-5 bound in the initial step. The color development is stopped and the intensity of the color is measured. The assay was shown to be sensitive, selective, reproducible and accurate for the determination of IL-5 in human serum, with an LLOQ of 3.0 pg/ml and a coefficient of variance (CV) for the inter- and intra-assay precision of less than 15%.

2.10.5 What bioanalytical methods are used to perform eosinophil blood count?

Studies MEA112997, MEA115588 and MEA115575 all utilized (b) (4) as the central laboratory. Eosinophil blood counts were performed as part of the hematology and differential

sample. Two milliliters of venous blood was drawn into lavender top EDTA tubes. Samples were shipped to (b) (4) at room temperature on the day of sample collection.

This laboratory uses the Coulter LH750 which is widely used in the clinical laboratory industry. Automated differential analysis and classification are based on simultaneous measurement of cell volume, high frequency conductivity and laser light scatter. These measurements occur as the specimen is drawn through a very small aperture on the instrument as it rapidly measures the individual cells as they flow through. The aperture is large enough for one cell at a time to pass through. Thousands of cells are counted from each sample. Scatter plots as well as numeric values are then generated following this process. The normal range of blood eosinophil count was reported as 50 to 500 cells/μL. For details, refer to consult review from CDRH dated 4/24/2015.

2.10.6 What bioanalytical methods are used to assess the formation of the anti-drug antibodies?

In total six generations of assay were developed to detect anti-mepolizumab antibody (Table 2.14). Although both the 5th and 6th generation methods were used in Studies MEA112997 and MEA114092, only the results from the 6th generation method was summarized in the report.

Table 2.14 Six Generations of the Anti-Mepolizumab Binding Antibody Assay

Assay Generations	Year of Development	Testing Facility Document No.	Technology (b) (4)	Detailed in GM2008/00201/00	Key Parameters	Studies Used
G1	(b) (4)					
G2						
G3						
G4						
G5						
G6*	2011	GSK (b) (4)	MSD 6000	[Attachment 4 The GlaxoSmithKline Document number 2012N137701_00]	Cut point: (b) (4) Sensitivity Drug tolerance: (b) (4) μg/mL	MEA112997 MEA114092 MEA115705 MEA115575 MEA115588 MEA115666 MEA115661

(Source: section 5.3.5.3, report 2014N216074, page 26, Table 1)

(b) (4) 6th generation assays are electrochemiluminescent (ECL) immunoassay which anti-mepolizumab binding antibodies present in the serum samples could bind to both the biotin- and TAG-labelled mepolizumab and form immune-complexes (Figure 2.8). (b) (4)

The 6th generation assay introduced an additional step to use an anti-IL5 antibody (Mab205) to remove the IL-5 from serum before loading the serum into the MSD plate.

The limit of quantitation, the accuracy, precision, and cut point at these limits are listed in Table 2.15.

Table 2.15 Summary of the 6th Generation of Mepolizumab ADA Bioanalytical Validation Assay

Sample analysis volume	20 µL
Sample Dilution (before conjugates)	1:20 in Assay Diluent and/or Confirmation Buffer
Intra-Assay Precision (Runs 1, 5-8, 10, 11)	NC: 1.0 to 4.8% LQC: 0.8 to 6.6% MQC: 1.6 to 4.0% HQC: 1.8 to 7.4%
Inter-Assay Precision (Runs 1, 5-8, 10, 11)	NC: 4.0% LQC: 5.9% MQC: 8.8% HQC: 6.6%
Precision of Antibody Titration	The titer is within ±2 dilutions on each of at least 6 runs, with LQC having a titre of 16.
Assay Sensitivity (Absolute) Screening Cut Point (Normal) Screening Cut Point (Diseased) Confirmation Cut Point (at 7.5 ng/mL PC)	(b) (4) ng/mL of PC (b) (4) RECL (from 3x 50 individuals) RECL (from 3x 50 individuals) % inhibition (from 3x 20 individuals)
Drug Interference: Antibody Concentration 250 ng/mL 500 ng/mL	Drug Concentration- for Screening Positive response (b) (4) µg/mL µg/mL
QC (MQC, LQC, NC) Stability: Bench Top Stability 2 C to 8 C Stability Freeze/Thaw Stability	 up to 22 hours 24 minutes up to 7 days up to 6 cycles

(Source: section 5.3.1.4, report 2012N137701, page 6)

2.10.7 What is the performance of the neutralizing assay?

The Sponsor developed three generations of methods to detect mepolizumab neutralizing antibodies. The third generation was an indirect binding assay using a ruthenium-labelled secondary anti-human IgG1 (Figure 2.9). The indirect ligand binding assay showed an improved sensitivity of (b) (4) µg/mL. The cut-points were determined by a GSK statistician using data from at least 3 runs and a 99% confidence limit. This assay was first implemented in the Study MEA112997 and has been used in all studies going forward. The neutralizing antibody assessment was conducted for all samples testing positive for anti-mepolizumab antibodies.

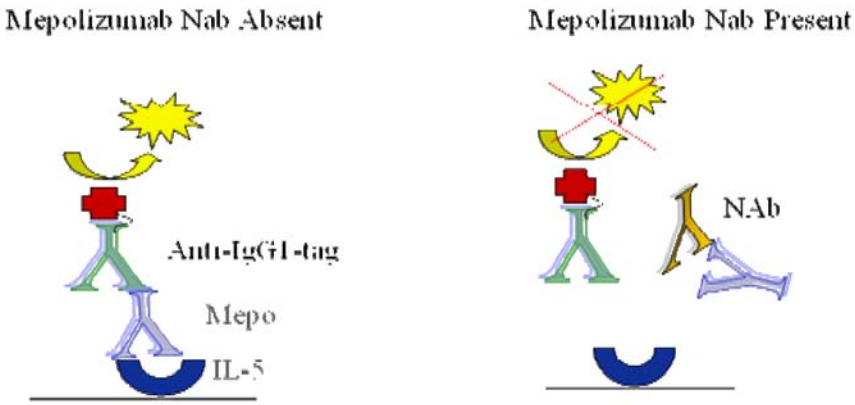

Figure 2.9 Configuration of anti-mepolizumab neutralizing antibody assay: MSD indirect ligand-binding assay. Anti-human IgG1 is labelled with ruthenium-Tag. (Source: section 5.3.5.3, immunogenicity-report.pdf, Page 38, Figure 9)

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4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study SB-240563/001 (Study 001)

Study Type: Phase 2a single dose, dose-ranging PK, PD and safety study in male patients with asthma
Study Dates: 05/06/1997 – 04/20/1998
Drug Product: 50 mg/vial from pilot manufacturing process (b) (4)

Title:
A double blind, placebo controlled, dose rising study to assess safety, pharmacokinetics and effect on the early and late phase response to allergen challenge of SB-240563 in male patients with mild asthma

Objective:

- To evaluate the safety and tolerability of SB-240563 in patients with mild asthma after single IV doses of SB-240563.
- To provide preliminary PK data for single IV doses of SB- 240563 in patients with mild asthma.
- To assess whether antibodies to SB-240563 develop after single IV doses of SB-240563.
- To provide preliminary evidence of clinical activity as demonstrated by attenuation of the early and late phase responses following bronchial allergen challenge (amended to apply to dose groups 3 and 4 only).
- To assess the effect of SB-240563 on bronchial hyperresponsiveness.
- To assess the number and activation state of sputum eosinophils (amended to apply to dose groups 3 and 4 only).

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, four-parallel-group, single IV dose (infusion time 30 min), dose-ranging (0.05 mg/kg, 0.5 mg/kg, 2.5 mg/kg and 10 mg/kg) study in 42 male patients with mild allergic asthma. The study was conducted in four groups and within each group patients were randomized to SB-240563 or placebo in a 2:1 ratio:

Group	Placebo	Active	Active Dose	
1	n=2	n=4	0.05 mg/kg body weight	
2	n=3(4)	n=5(8)	0.50 mg/kg body weight	(Planned numbers in brackets)
3	n=4	n=8	2.50 mg/kg body weight	
4	n=4	n=8	10.0 mg/kg body weight	

Dosing between groups was separated by 4 weeks. Each patient participated for approximately 5 months. Only patients from group 3 and group 4 participated in the allergen and histamine challenges.

Potential patients with a documented history of asthma and a bronchial hyper-responsiveness to histamine (PC20 less than 8 mg/ml measured in the last 3 months) were selected. All subjects were currently using only inhaled β2-agonists to control their asthma.

At baseline (day –14) subjects received a histamine challenge, followed 2 h later by an allergen challenge that gave ≥15% reduction in FEV1. The late response was monitored up to 10 h post allergen challenge. At 24 h another histamine challenge was performed. Sputum induction was conducted 1 hr later for assessment of inflammatory markers. Single IV dose of SB-240563 or placebo was administered on Day

1. On days 8 and 29 post-dose, each subject was given an allergen challenge, histamine challenges and induced sputum assessment of inflammatory markers as done at baseline.

Blood samples (approximately 3 mL) for PK evaluation were drawn 30 min pre-dose, and at the following times after the start of the infusion on Day 1: 15, 30 and 35 minutes, and 1, 2, 4, 8, 12 and 24 hours. Additionally, samples were collected on each of the following study days: 3, 4, 5, 8, 9, 15, 29, 30, and at Week 6, 8, 10, 12 and 16. Anti-SB-240563 antibody samples were collected at Week 6, 8, 10, 12, and 16 following the single-dose administration.

Samples were assayed for SB-240563 using an electrochemiluminescent (ECL) immunoassay method by GSK. The lower limit of quantification (LLQ) was 50.0 ng/mL using 50 µL of 10-fold diluted human plasma. NQ values were replaced with 25.0 ng/mL (1/2 LLQ) for the calculation of mean concentrations. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}inf}$ were estimated by non-compartmental analysis.

Primary Endpoints:

- The primary PD endpoint was the maximum % fall from post-saline baseline in FEV1 during the late (4-10 hours after challenge) response following allergen challenge. The secondary PD endpoints included serum total IL-5 concentration, sputum and blood eosinophil counts.

- The PK endpoints were plasma concentration-time profiles and other PK parameters (i.e. C_{max}, AUC, CL, V_{ss}) summarized descriptively by dose groups.

PK Results:

Following a 30 minute continuous infusion, SB-240563 concentrations declined in a bi-exponential manner (Fig. 4.1). The median T_{max} was 1.21, 1.80, 0.95 and 1.05 hours for 0.05, 0.5, 2.5 and 10 mg/kg treatment group, respectively. C_{max} and $AUC_{0\text{-}inf}$ increased approximately 216 and 209 fold for the 200 fold increase in dose from 0.05 to 10 mg/kg (Table 4.1). In addition, mean CL and V_{ss} were similar across the dose range studied, indicating linear PK. The inter-subject variability in C_{max} and $AUC_{0\text{-}inf}$ was low, with coefficients of variation generally less than 20%. The mean terminal half-life was about 19 days.

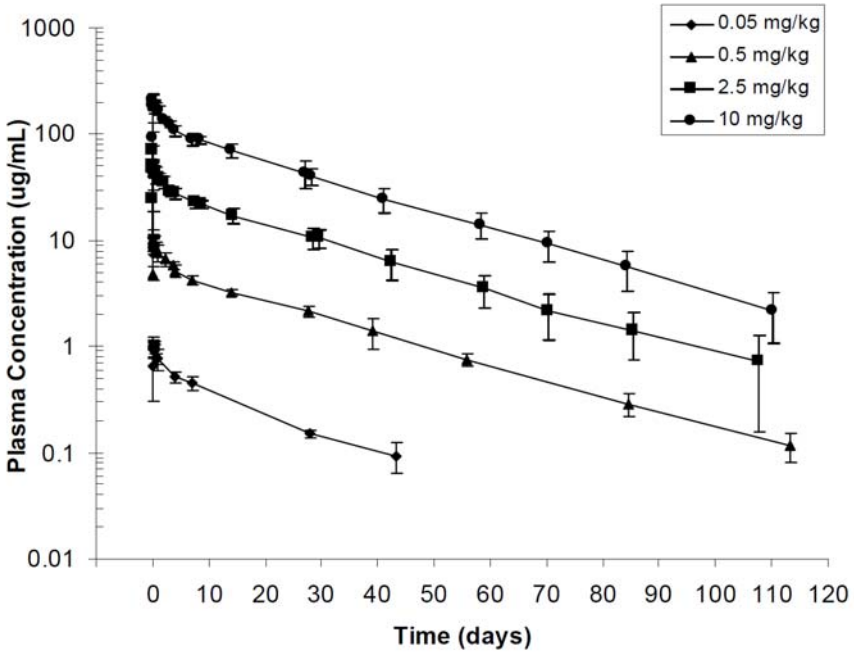


Figure 4.1 Mean (SD) SB-240563 plasma concentration-time profiles (semi-log scale) following single dose IV administration of 0.05 mg/kg (n=4), 0.5 mg/kg (n=5), 2.5 mg/kg (n=8), and 10 mg/kg (n=8) SB-240563. (Source: CSR 001, page 1015, Figure 12.45)

There were no positive titres for antibodies to SB-240563 for up to 12 weeks postdose.

Table 4.1 Mean (SD) PK Parameters for SB-240563 Following Single Intravenous Administration

Parameter (units)	0.05 mg/kg (n=4)	0.5 mg/kg (n=5)	2.5 mg/kg (n=8)	10 mg/kg (n=8)
AUC(0-inf) (ug.d/mL)	15.5 (2.7)	168 (19)	846 (164)*	3345 (324)
Cmax (ug/mL)	1.03 (0.21)	10.6 (2.2)	51.4 (7.9)**	215 (28)
T½ (days)	19.7 (7.6)	20.0 (1.9)	19.3 (2.9)	19.0 (2.5)
CL (mL/h/kg)	0.137 (0.022)	0.125 (0.014)	0.129 (0.023)	0.126 (0.013)
Vss (mL/kg)	85.0 (19.8)	82.2 (14.5)	80.6 (7.8)	78.9 (11.0)

(Source: CSR 001, page 72)

PD Results:
In both group 3, the maximal % fall in FEV1 from post-saline baseline during the early and late response following allergen challenge was similar on days –14, 8 and 29 for SB-240563 treatment and placebo (Table 4.2). In group 4 there was a 14% baseline difference between the active treatment and placebo groups (placebo group had greater fall in FEV1). This difference was reduced to 11% and 7% on days 8 and 29, respectively.

Table 4.2 Maximal % Fall in FEV1 (4-10h) following Allergen Challenge

		SB-240563			Placebo		
		Day -14	Day 8	Day 29	Day -14	Day8	Day 29
2.5mg/kg	N	8	8	7	4	3	4
v placebo	Mean	32.14	32.06	35.65	32.3	39.62	31.21
(Group 3)	SD	11.11	16.62	13.26	17.31	21.02	24.08
10 mg/kg	N	8	8	8	4	4	4
v placebo	Mean	33.61	31.14	29.67	47.52	42.15	36.93
(Group 4)	SD	11.94	11.76	7.34	5.51	8.84	10.48

(Source: CSR 001, page 67)

Levels of sputum eosinophils following the baseline (day –13) allergen challenge were similar for those on active and placebo in both dose groups. On 2.5 mg/kg SB-240563 post-allergen challenge sputum eosinophils were reduced from a mean of 13.19% at baseline (day –13) to a mean of 9.10% on day 9 and a mean of 8.01% on day 30 (Table 4.3) following challenge. The levels of sputum eosinophils on placebo in group 3 showed no consistent trend. On 10 mg/kg SB-240563 sputum eosinophils were reduced from a

mean of 13.09% at baseline to 1.70% on day 9, and remained similar (1.42%) on day 30. There was no overall change in the levels of sputum eosinophils on placebo in group 4.

Table 4.3 Sputum Eosinophils (%) following Allergen Challenge

		Placebo			SB-240563		
		Day -13	Day 9	Day 30	Day -13	Day 9	Day 30
2.5mg/kg	N	3	3	3	7	6	7
v placebo	Mean	9.57	20.90	13.85	13.19	9.10	8.01
(Group 3)	SD	3.92	21.27	9.33	11.13	7.43	8.32
10mg/kg	N	4	4	4	7	6	6
v placebo	Mean	12.30	10.50	14.35	13.09	1.70	1.42
(Group 4)	SD	15.76	8.15	11.45	9.98	2.08	1.32

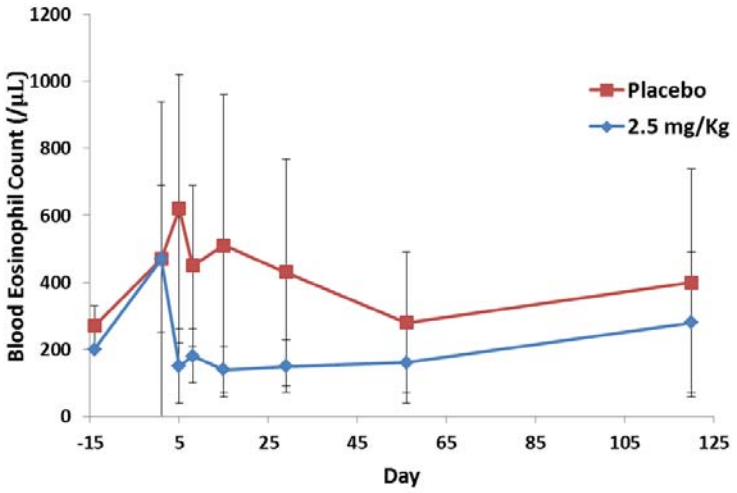
(Source: CSR 001, page 70)

Mean levels of blood eosinophils at baseline (Day -14) were similar for subjects on SB-240563 and placebo in group 3 (Fig 4.3A). The pre-challenge mean levels of eosinophils reduced from 470 /µL on Day 1 to 150 /µL on day 5 following 2.5 mg/kg SB-240563 treatment (N=8) and remained at that level till Week 8. Following placebo treatment (N=4), the pre-challenge mean levels of eosinophils increased from 470 /µL on Day 1 to 620 /µL on day 5 followed by gradual decrease to 280/ µL at Week 8.

In group 4, mean levels of blood eosinophils at baseline (Day -14) were higher in placebo treatment group (500 /µL) than in SB-240563 10 mg/kg treatment group (300 /µL) (Fig 4.3B). The pre-challenge mean levels of eosinophils reduced from 210 /µL on Day 1 to 60 /µL on day 29 following 10 mg/kg SB-240563 treatment and remained at that level till Week 8. The pre-challenge mean levels of eosinophils in placebo group kept higher than the SB-240563 treatment group throughout the study. The ratio (placebo/SB-240563) of eosinophil counts increased from 1.8 fold on Day 1 to 6.8-fold at Week 8.

Allergen challenge generally increased blood eosinophil counts, but the absolute increase values were much less in the SB-240563 treatment group than the placebo group.

A



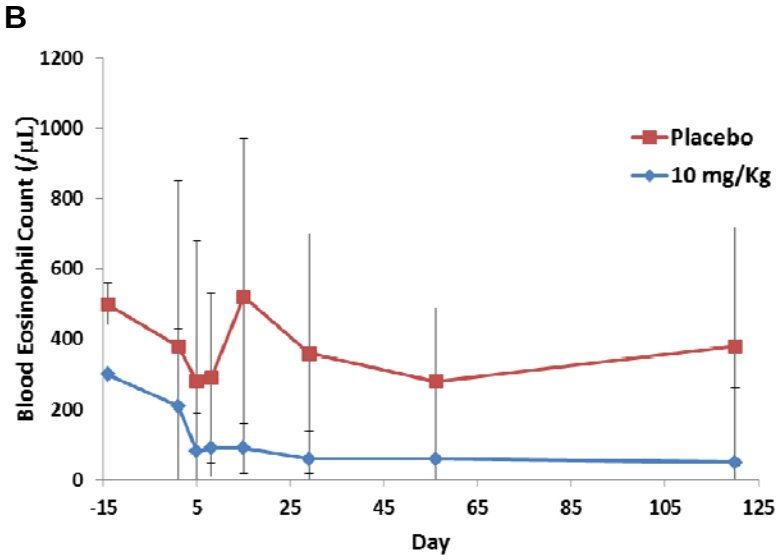


Figure 4.2 Mean (±SD) blood eosinophil count at baseline (Day -14), before allergen challenge on Day 1, 8, 29 and on follow up days (Week 8 and Week 16) in group 3 (A) and group 4 (B). In each group, 8 patients were assigned to active treatment of SB-240563 and 4 patients were assigned to placebo treatment. (Source: adapted from CSR 001, page 935 - 940, Table 11.48, Table 11.49)

Plasma total IL-5 concentrations at baseline were similar for subjects on active and placebo in treatment group 3. On 2.5 mg/kg SB-240563 there was an increase in the overall pre challenge levels of IL-5 between day -14 and day 29. This type of increase was not observed on placebo. There were no clear effects of 10 mg/kg of SB-240563 on serum total IL-5 levels.

Conclusions:
As the primary endpoint of this study, the mean maximum %fall in FEV1 for the late response (4-10hrs post-challenge) was similar for SB-240563 2.5mg/kg and placebo in group 3. The treatment effect in group 4 was not clear as the baseline was lower in SB-240563 treatment group compared to the placebo group.

Following a single 30 minute intravenous infusion, SB-240563 exhibited dose-proportional pharmacokinetics and a long elimination half-life of approximately 19 days, which was independent of dose. Plasma clearance and volume of distribution were relatively constant across the dose range studied.

4.1.2 Study SB-240563/035 (Study 035)

Study Type: Phase 1 single dose, dose-ranging PK, PD and safety study in male patients with asthma
Study Dates: 07/21/1997 – 01/08/1998
Drug Product: 50 mg/vial from pilot manufacturing process (b) (4)

Title:
A double blind, placebo controlled, dose rising study to assess safety and pharmacokinetics of SB-240563 in male patients with mild asthma

Objective:
- To evaluate the safety and tolerability of SB-240563 in patients with mild asthma after single IV doses of SB-240563
- To provide preliminary PK data for single IV doses of SB-240563 in mild asthmatic patients
- To assess whether antibodies to SB-240563 develop after single IV doses of SB-240563

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, three-parallel-group, single IV dose (infusion time 30 min), dose-ranging (0.5 mg/kg, 2.5 mg/kg and 10 mg/kg) study in 18 male patients with mild allergic asthma. The study was conducted in three groups and within each group patients were randomized to SB-240563 or placebo in a 2:1 ratio:

Placebo	Active	Active Dose
n=2	n=4	0.50 mg/kg body weight
n=2	n=4	2.50 mg/kg body weight
n=2	n=4	10 mg/kg body weight

Male patients with mild allergic asthma, aged 18-45 years, who were otherwise healthy, were recruited. Their asthma was treated with prn β2 agonists with or without inhaled corticosteroids ≤ 800 mcg/day. At screening each subject's FEV1 was > 64% of that predicted.

Blood samples (approximately 3 mL) for PK evaluation were drawn at pre-dose, and at the following times after the start of the infusion on Day 1: 15, 30 and 35 minutes, and 1, 2, 4, 8, 12 and 24 hours. Additionally, samples were collected on each of the following study days: 3, 4, 5, 8, 15, 29, and during weeks 6, 8, 10, 12 and 16. 12-lead ECG was monitored at pre-dose, 1, 6, 12 and 24 hours post-dose. Additionally, ECG was monitored on each of the following study days: 5, 8, 15, 29, and at week 16.

Plasma was assayed for SB-240563 using an ECL immunoassay method by GSK. The same analytical method was used in study 001. The value of lower limit of quantification was 50.0 ng/mL. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}inf}$ were estimated by non-compartmental analysis.

Samples will be analyzed for the presence of anti-SB 240563 antibodies by ECL assay. If sera contain anti-SB 240563 antibodies, they will be further analyzed for the presence of anti-idiotype species.

Primary Endpoints:
- Safety endpoints include vital signs, ECG intervals (PR, QRS, QTc), lung function, and blood eosinophil count.

- PK: The primary PK parameters of interest are C_{max}, AUC, CL, and V_{ss} of SB 240563.

PK Results:
Following a 30 minute continuous infusion, SB-240563 concentrations declined in a bi-exponential manner (Fig. 4.3). The median T_{max} was 0.79, 1.50, and 1.99 hours for 0.5, 2.5 and 10 mg/kg treatment group, respectively (Table 4.4). A 23 and 21 fold increase in C_{max} and AUC, respectively, were observed for a 20 fold increase in dose (from 0.5 mg/kg to 10 mg/kg). Additionally, mean clearance and volume of distribution values were similar over the examined dose range. The inter-subject variability in pharmacokinetic parameters of SB- 240563 was low (C.V.% values of 20% or less). The mean terminal half-life was about 21 days.

The values of $AUC_{0\text{-inf}}$ and C_{max} obtained from this study were about 1.1 to 1.6-fold as the values obtained from the same doses in study 001. Whether the differences were contributed by inter-study variability or study population, is not clear.

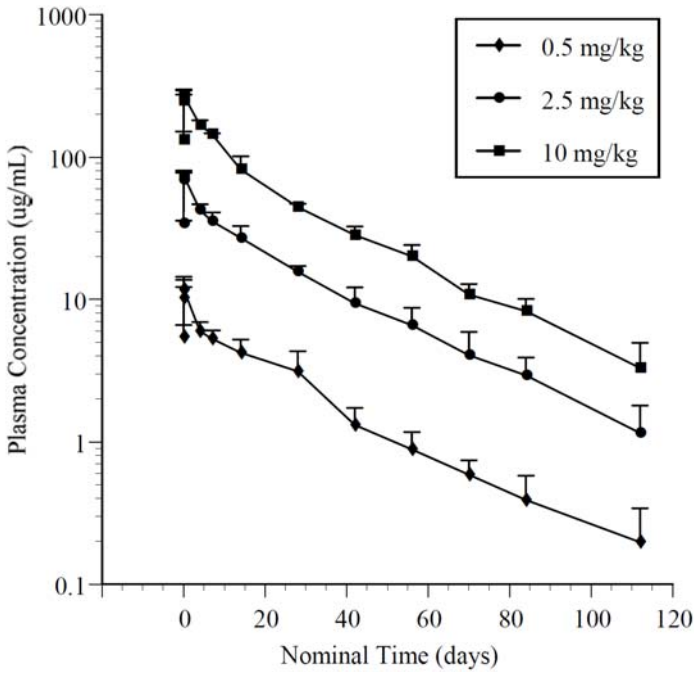


Figure 4.3 Mean (SD) SB-240563 plasma concentration-time profiles (semi-log scale) following single dose IV administration of 0.5 mg/kg (n=4), 2.5 mg/kg (n=4), and 10 mg/kg (n=4) SB-240563. (Source: CSR 035, page 311, Figure 12.1)

Table 4.4 Mean (SD) PK Parameters for SB-240563 Following Single Intravenous Administration

	Dose Range (mg/kg)		
Parameter	**0.5**	**2.5**	**10**
AUC(0-inf) (ug.day/mL)	207 (34)	1327 (247)	4361 (168)
Cmax (ug/mL)	12.1 (2.4)	79.0 (4.3)	278 (29)
CL (mL/h/kg)	0.103 (0.017)	0.081 (0.015)	0.096 (0.004)
Vss (mL/kg)	68.4 (2.5)	55.4 (5.2)	59.3 (3.7)
T1/2 (days)	20.9 (4.0)	21.7 (2.8)	20.9 (2.6)

(Source: CSR 035, page 49, Table 9)

The samples taken on days 8, 15 and 29 and weeks 6, 8, 10 and 16 were analyzed for the presence of antibodies to SB-240563 and none was detected.

PD Results:
The pre-dose levels of FEV1 of placebo (pooled together, N=6), 0.5 mg/kg (N=4), 2.5 mg/kg (N=4), and 10 mg/kg (N=4) treatment groups were 3.54 L, 3.62 L, 4.01 L, and 3.39L, respectively. It appeared that the FEV1 change from baseline on Day1 did not have an obvious dose-response relationship following SB-240563 treatment. The lowest dose (0.5 mg/kg) appeared having better long-term FEV1 response than placebo whereas the higher two doses having lower long-term FEV1 response than placebo (Fig. 4.4). However, no meaningful clinical conclusions could be drawn from the observation as the subjects was too few in this study.

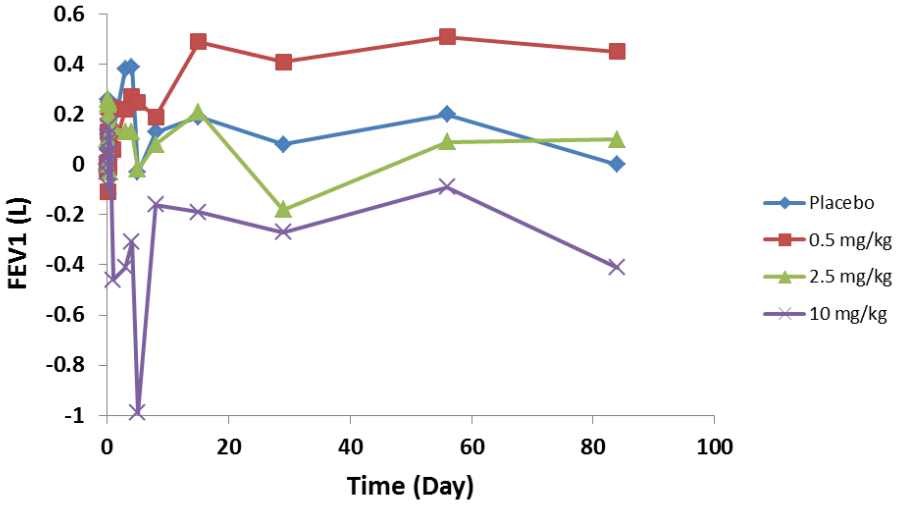


Figure 4.4 Mean FEV1 (L) response at pre-dose, 0.5, 1, 2, 4, 6, 8, 12 h on Day 1, and Day 3, 4, 5, 8, 15, 29, Week 8 and 12 following administration of placebo or SB-240563. Subjects on placebo treatment in each group were pooled (N=6) together and plotted here. There were 4 subjects in each active treatment group. (Source: CSR 035, page 300 - 301, Figure 11.15)

Mean levels of blood eosinophils at predose were similar between groups (340 ~ 390 /µL) except higher for 0.5 mg/kg treatment group (590 /µL). Following drug administration, blood eosinophil count decreased in a time dependent manner with the maximum reduction reached approximately at Day 5 (Fig.4.5). The maximum percentage reduction values for placebo, 0.5 mg/kg, 2.5 mg/kg, and 10 mg/kg groups were approximately 30%, 80%, 85%, and 90% from the baseline, respectively (or maximally reduced to 230, 130, 60, and 30 / µL, respectively). A more than 50% reduction was observed at 24 hours following the active treatment.

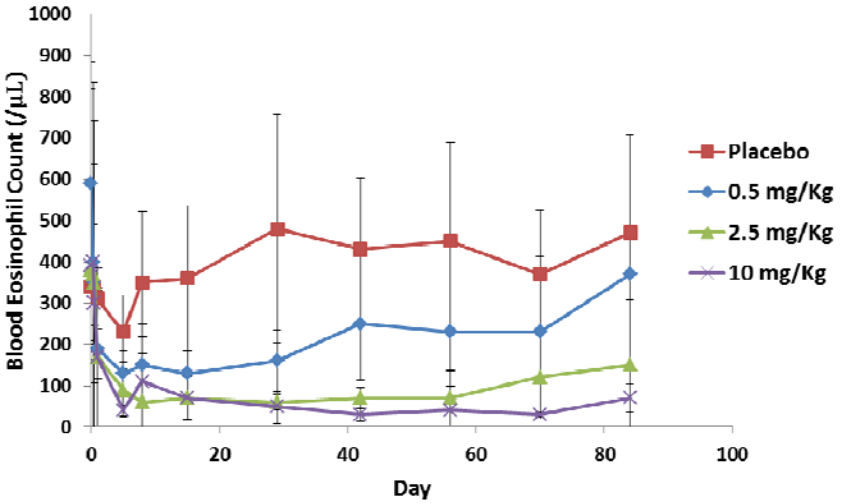


Figure 4.5 Mean (±SD) blood eosinophil count at pre-dose, 8, 12 h on Day 1, and Day 2, 5, 8, 15 and 29, Week 6, 8, 10 and 12 following administration of placebo or SB-240563. Subjects on placebo treatment in each group were pooled (N=6) together and plotted here. There were 4 subjects in each active treatment group. (Source: adapted from CSR 035, page 245 - 246, Table 11.14)

ECG Results:
All the ECGs were assessed as normal and no values were flagged. On review of the blinded safety data during the study, the sponsor noted evidence of right bundle branch block (RBBB) in the ECGs of subject 010, who received 0.5 mg/kg SB-240563, at 1, 6, 12 and 24 hours post-dose. This was discussed with the investigator who had observed RBBB at screening and considered it a normal variant for this subject. It was agreed that the ECG of the subject had not changed and there was no evidence of a drug related effect.

Conclusions:
Following a single 30 minute intravenous infusion, SB-240563 exhibited dose-proportional PK and a long elimination half-life of approximately 21days, which was independent of dose. Plasma clearance and volume of distribution were relatively constant across the dose range studied.

Blood eosinophil count decreased in a time dependent manner following SB-240563 treatment. The maximum reduction reached approximately at Day 5. The maximum reductions of placebo, 0.5 mg/kg, 2.5 mg/kg, and 10 mg/kg were approximately 30%, 80%, 85%, and 90% from the baseline, respectively. A more than 50% reduction was observed at 24 hours following the active treatment.

No obvious dose-response relationship for FEV1 response was observed on Day 1 and 12-week period of time following SB-240563 treatment. The subject number (4 subjects on active treatment per group) is too small to draw any conclusion.

4.1.3 Study SB-240563/006 (Study 006)

Study Type: Phase 2 PK, three monthly-dose, safety and efficacy study in patients with asthma
Study Dates: 02/16/1999 – 10/05/1999
Drug Product: 50 mg/vial from pilot manufacturing process (b) (4)

Title:
A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and efficacy of intravenous SB 240563 (250 mg and 750 mg) in patients with asthma

Objective:

- Primary objective:
  To evaluate, compared to placebo, the safety and efficacy (as determined by pulmonary function and symptoms) of SB 240563 administered intravenously at a dose of 250 mg or 750 mg once a month on three occasions in patients with asthma.

- Secondary objectives:
  - To investigate the time course of the response to SB 240563 on clinical endpoints (pulmonary function and symptoms)
  - To investigate further the effect of SB 240563 on eosinophil numbers in blood and induced sputum and their relationship with the clinical endpoints of pulmonary function and asthma symptoms
  - To investigate the effect of treatment with SB 240563 on quality of life as determined by the Asthma Quality of Life Questionnaire
  - To investigate the effect of treatment with SB 240563 on symptoms of rhinitis

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, three-parallel-group, three IV monthly-dose study in 362 patients with asthma. After a 4-week run-in period, eligible patients were randomized in a ratio of 1:1:1 to receive intravenously SB 240563 750 mg, 250 mg, and placebo once monthly. Total 3 doses were given in 12-week treatment period followed by an 8-week follow-up period. Each dose was administered as a concentration of 25 mg/mL and infused for 30 minutes.

Male and female patients between 18 and 55 years of age with a diagnosis of asthma, as defined by the GINA/WHO 1995 guidelines, for at least 12 months were included in the study. Additional inclusion criteria were FEV1 between ≥ 50% and ≤ 80% of predicted; FEV1 reversibility of 12% or greater; current treatment with inhaled corticosteroid up to a maximum dose of 1000 mcg/day beclomethasone dipropionate or equivalents at Week -4.

Five blood samples for pharmacokinetic analysis of SB 240563 plasma concentration data were collected from all randomized patients. Sampling times were: Day 1 immediately after the end of the infusion, Week1, Week 2, Week 4 prior to administration of the second dose, Week 8 prior to start of the infusion and immediately after the end of the infusion, Week 12, Week 16 and Week 20.

Plasma samples were assayed for SB 240563 using an immunoassay method by GSK (The lower limit of quantification was 50.0 ng/mL using a 100 µL aliquot of 10% human plasma.). Compared with the analytical method used in study 001/035, this method was improved for ease of use and increased sample throughput. Predicted SB 240563 concentrations for each dosing regimen were generated in WinNonlin Professional, Version 2.1, using a 2-compartment IV infusion model and mean PK parameter estimates estimated from a previous single-dose study 001.

Blood samples for analysis of anti-SB 240563 antibodies were collected at Weeks 0, 4, 8 and 20. Samples were analyzed for the presence of anti-SB 240563 antibodies by ECL assay. If sera contained anti-SB 240563 antibodies, they were further analyzed for the presence of anti-idiotype species.

Primary Endpoints:

- Efficacy:
  - The primary efficacy variable was change from baseline in domiciliary morning PEFR.
  - Secondary measures of efficacy were:
    - Change from baseline in FEV1
    - Asthma summary symptom score (total of daytime, overnight and morning scores)
    - Use of rescue medication (albuterol or salbutamol)
    - Eosinophil count in blood and sputum.
  - Tertiary efficacy variables were asthma exacerbation rates, percent of asthma free days, percent of asthma free nights, FVC, FEF25-75, FEF75, clinic PEFR, evening domiciliary PEFR, peak flow variability, daytime asthma

- Safety was evaluated by monitoring adverse experiences, laboratory data, electrocardiogram parameters, and vital signs. Also, the presence of anti-SB 240563 antibodies in serum was measured at Weeks 0, 4 and 8 prior to study medication infusion, and at Week 20.

- PK: prediction of SB 240563 concentrations for each multiple dosing regimen (250 mg or 750 mg)

PK Results:

SB 240563 concentration in the plasma of these placebo patients were non-quantifiable. Plasma concentrations of SB-240563 were generally quantifiable at all study visits. Mean plasma concentrations of SB-240563 at each visit increased in an approximately dose-proportional manner between the 250 and 750 mg doses (Table 4.5). The means of the actual concentrations at each visit were similar to the predicted multiple-dose concentration data, which were simulated using a 2-compartment IV infusion model and pharmacokinetic (PK) parameters estimated from previous single-dose data (Fig. 4.6).

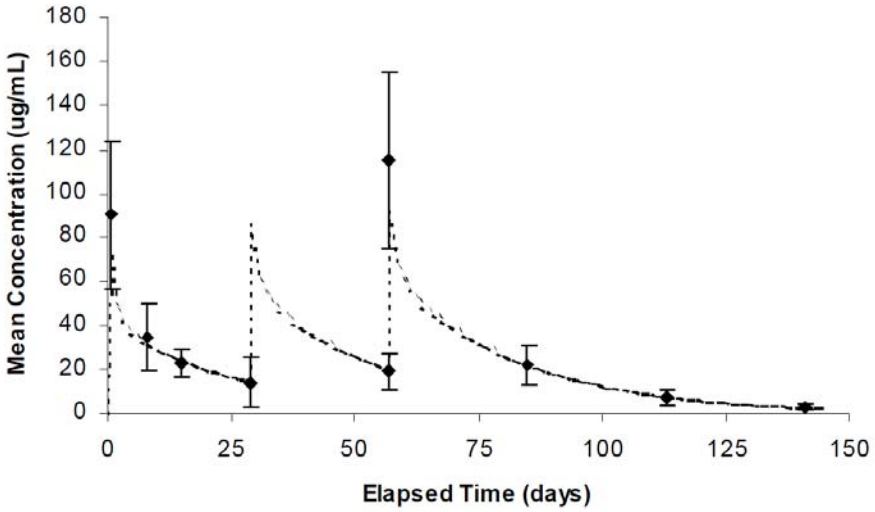
Table 4.5 Mean (SD) Plasma SB-230563 Concentrations (µg/mL) by Dose and Visit

	Visit 3 Day 1	Visit 4 8 ± 2 Days*	Visit 5 15 ± 2 Days*	Visit 6 29 ± 2 Days*	Visit 8 Predose 57±7 Days*	Visit 8 Postdose 57±7 Days*	Visit 10 85±7 Days*	Visit 11 113±7 Days*	Visit 12 141±7 Days*
Dose (mg)	n=55	n=53	n=51	n=51	n=86	n=49	n=36	n=32	n=25
250	90.0 (33.2)	34.8 (15.4)	23.1 (6.4)	14.0 (11.5)	18.9 (8.1)	115 (40.0)	22.2 (9.1)	7.03 (3.8)	3.17 (1.8)

	Visit 3 Day 1	Visit 4 8 ± 2 Days*	Visit 5 15 ± 2 Days*	Visit 6 29 ± 2 Days*	Visit 8 Predose 57±7 Days*	Visit 8 Postdose 57±7 Days*	Visit 10 85±7 Days*	Visit 11 113±7 Days*	Visit 12 141±7 Days*
Dose (mg)	n=47	n=46	n=45	n=42	n=84	n=53	n=47	n=42	n=27
750	221 (60.0)	90.9 (34.3)	60.2 (15.5)	34.5 (9.9)	49.0 (14.1)	254 (74.0)	51.2 (19.5)	18.2 (7.8)	7.04 (3.4)

(Source: CSR 006, page 208, Table 62)

A



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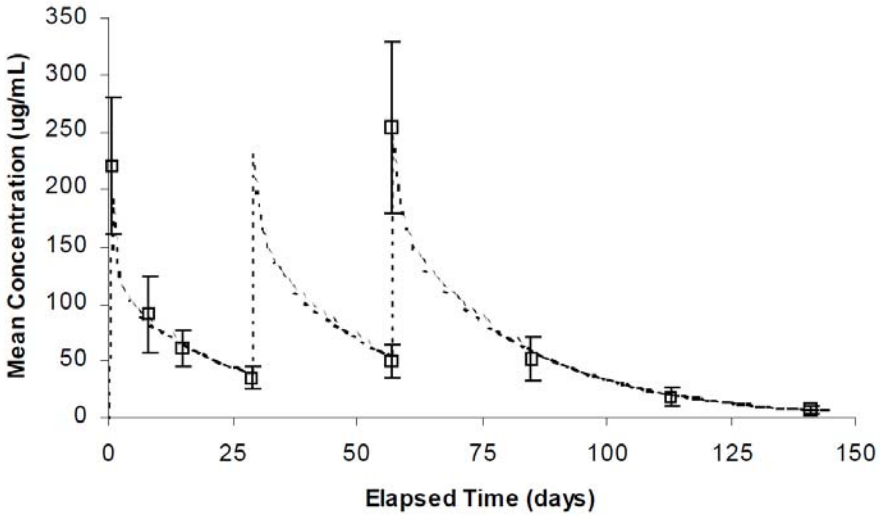

Figure 4.6 Mean (SD) SB-240563 plasma concentration (µg/mL, dots) following administration of three doses of 250 mg (A) and 750mg (B) SB-240563. The dashed lines represent simulated plasma concentrations using a 2-compartment IV infusion model and mean PK parameter estimates estimated from a previous single-dose study 001. (Source: CSR 006, page 211, Figure 9)

No SB 240563 antibodies were detected by ECL, either anti-idiotypic or anti-framework, in any of the patients at any time.

Efficacy Results:

- Primary Efficacy Variable

No significant differences were observed in mean change from baseline in morning domiciliary PEFR between the placebo group and both the 250 mg and the 750 mg treatment groups at Week 12, Week 20 or at endpoint.

- Secondary Efficacy Variable
  - FEV1

No significant differences were observed in mean change from baseline in clinic FEV1 at trough between the placebo group and both the 250 mg and the 750 mg treatment groups at Week 12, Week 20 and at endpoint (Fig. 4.7). At baseline, the clinic FEV1 for the 750 mg group was statistically significantly higher than the placebo group (p=0.019) but this difference was not seen at Week 12, 20 or at endpoint.

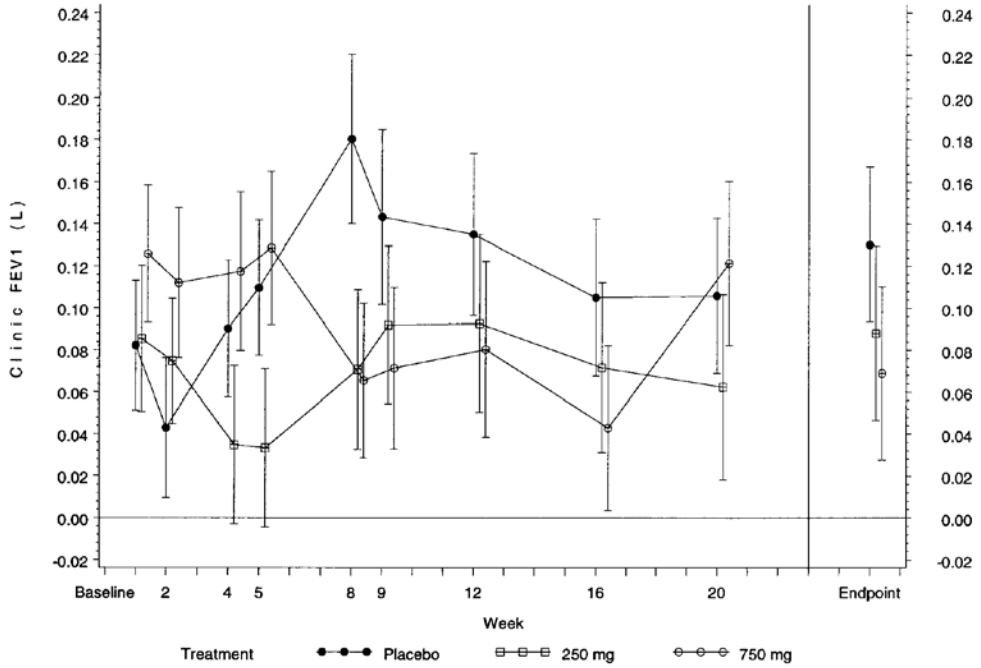

Figure 4.7 Mean (SE) change from baseline for FEV1 (L) following placebo (N=126), SB-240563 250 mg (N=119) and 750 mg (N=116) treatment. (Source: CSR 006, page 109, Figure 3)

- Asthma summary symptom score

The mean asthma summary symptom score decreased from baseline to Week 12, Week 20 and to endpoint in all three treatment groups. No significant differences were observed in mean change from baseline in the asthma summary symptom score between the placebo group and both the 250 mg and the 750 mg treatment groups at Week 12, Week 20 and at endpoint.

- Use of rescue medication

The mean albuterol/salbutamol use decreased slightly from baseline to Week 12, Week 20 and at endpoint for all three treatment groups. No significant differences were observed in mean change from baseline in β2-agonist use between the placebo group and both the 250 mg and the 750 mg treatment groups at Week 12, Week 20 and at endpoint.

- Eosinophil count in blood

The mean blood eosinophil counts at baseline was slightly higher in placebo group (400 /μL) than SB-240563 250 mg group (350 /μL) and 750 mg group (370 /μL). The maximum reduction of blood eosinophil counts appeared reached no later than Week 4 (Fig. 4.8). The maximum percentage reduction values for placebo, 250 mg, and 750 mg groups were approximately 12%, 83%, and 86% from the baseline, respectively (or maximally reduced to 350, 60, and 50 /μL, respectively).

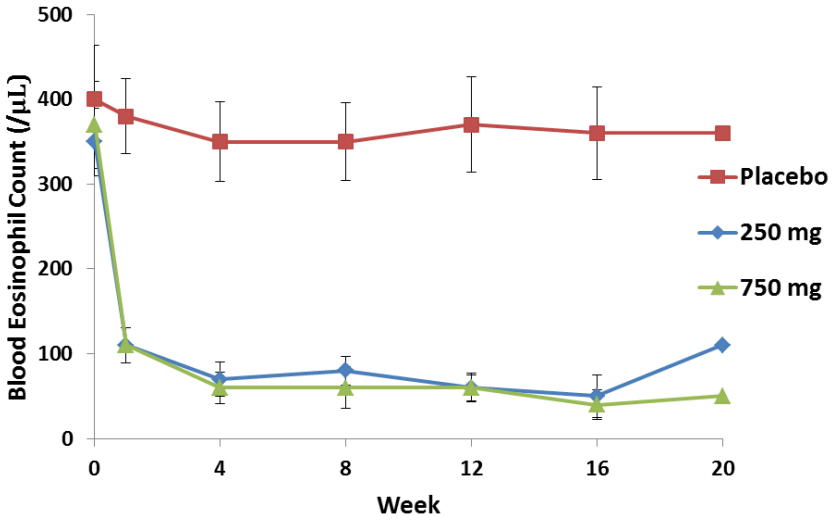

Figure 4.8 Mean (SE) change from baseline for blood eosinophil counts (/µL) following placebo (N=126), SB-240563 250 mg (N=120) and 750 mg (N=116) treatment. (Source: CSR 006, page 462, Table 14.5.1.1)

- Eosinophil count in sputum

The mean sputum eosinophil count at baseline was higher in SB-240563 250 mg group (9.08%) than placebo (7.00%) and 750 mg group (4.11%). The mean sputum eosinophil levels in the placebo group kept more than 6% throughout the study. The mean sputum eosinophils levels decreased in 250 mg and 750 mg groups (Fig. 4.9). The maximum percentage reduction values for 250 mg and 750 mg groups were approximately 87% and 77% from the baseline, respectively (or maximally reduced to 1.49% and 1.1%, respectively). In the 750 mg group, sputum eosinophil levels showed a statistically significant decrease from baseline to Week 12 (p=0.013).

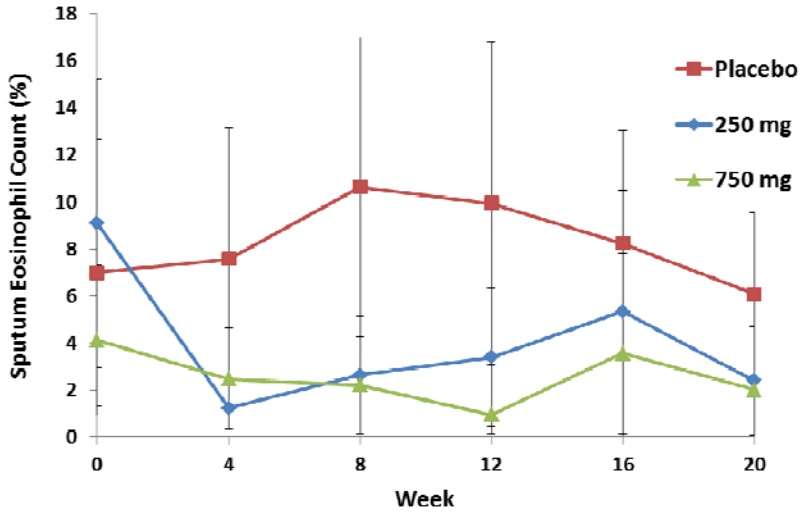

Figure 4.9 Mean (SE) change from baseline for sputum eosinophil counts (%) following placebo (N=14), SB-240563 250 mg (N=13) and 750 mg (N=11) treatment. (Source: adapted from CSR 006, page 476, Table 14.6.1.2)

There was no clinically significant difference in the mean change from baseline between placebo group and the active treatment group for all the Tertiary efficacy variables.

ECG Results:
There were four patients with ECG-related adverse experiences, two in the 250 mg group and two in the 750 mg group. None was considered related to study medication. The most commonly reported ECG values of potential concern were borderline QTc (expressed as an increase from baseline) and borderline QTc (expressed in absolute values). The highest percentage of patients meeting borderline QTc criteria were in the 750 mg (23.5%) and 250 mg (21.4%) treatment groups for increases from baseline as compared to placebo (16.8%).

Conclusions:
The means of the observed S-240563 concentrations at each visit were similar to the predicted multiple-dose concentration data, which were simulated using a 2-compartment IV infusion model and PK parameters estimated from previous single-dose data in study 001.

SB 240563 decreased blood and sputum eosinophil count maximally by approximately 85% and 80%. In contrast, there was no effect of SB 240563 on pulmonary function (domiciliary morning peak flow, FEV1), asthma symptoms or use of rescue medication.

4.1.4 Study SB-240563/017 (Study 017)

Study Type: Phase 2, three-dose, PK, PD and safety study in patients with asthma
Study Dates: 05/28/1999 – 01/11/2000
Drug Product: 50 mg/vial from pilot manufacturing process (b) (4))

Title:
A double-blind, placebo controlled, parallel group study to assess tolerability and pharmacokinetics of three 250 mg subcutaneous doses of SB-240563 in male and female patients with asthma

Objective:
- Primary
  To evaluate the tolerability of SB-240563 in patients with mild asthma after three subcutaneous doses
- Secondary
  - To provide preliminary PK data for single and repeat subcutaneous doses of SB-240563 in mild asthmatic patients.
  - To assess whether antibodies to SB-240563 develop after subcutaneous doses (up to three) of SB-240563.
  - To assess the levels of peripheral blood eosinophils following single and repeat subcutaneous doses of SB-240563.

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, two-parallel-group, three 250 mg subcutaneous dose study in 16 patients with mild to moderate asthma. The study was conducted in two parallel groups with one group (8 subjects) received three doses of 250 mg SB-240563 and another group (8 subjects) received three doses of placebo. The dosing interval between the first and the second dose was 6 weeks, and the dosing interval between the second and the third dose was 2 weeks. At each dose, 2.5 mL of 100 mg/mL SB-240563 was administered as at 2 sites on the antero-lateral abdominal wall.

Sixteen male and female patients with mild to moderate asthma, aged between 18 and 50 years, who were otherwise healthy were recruited and randomized to either SB-240563 or placebo. Their asthma was treated with prn β2 agonists with or without inhaled corticosteroids ≤ 1,000 mcg/day.

Blood samples (approximately 3 mL) for PK evaluation were drawn at the following times:
- Pre-dose and 8 hours following the first dose on Day 1. Day 2, 3, 4, 5, 6, 8, 15, 22 and 29.
- Pre-dose of the second dose.
- Pre-dose and 8 hours following the first dose on Day 1. Day 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20.

Plasma concentrations of SB-240563 were measured using an immunoassay method by GSK based on binding to recombinant human IL-5. The lower limit of quantification (LLQ) of 50.0 ng/mL for a 100 µL aliquot of 10% human plasma. The same analytical method was used in study 006. PK parameters such as C_{max}, T_{max}, $T_{1/2}$ and $AUC_{0\text{-}inf}$ were estimated by non-compartmental analysis.

Samples will be analyzed for the presence of anti-SB 240563 antibodies by ECL assay. If sera contain anti-SB 240563 antibodies, they will be further analyzed for the presence of anti-idiotype species.

Primary Endpoints:

- Safety endpoints include vital signs, ECG intervals (PR, QRS, QT, QTc), lung function, and antibodies to SB-240563
- PD endpoint was the blood eosinophil count.

- PK: The primary PK parameters of interest are C_{max}, AUC, T_{max} and $T_{1/2}$ of SB 240563.

PK Results:

Following the single dose subcutaneous injection of SB-240563 at abdomen site, the median T_{max} was 4.50 hours. The geometric mean values of $AUC_{0\text{-}inf}$ and C_{max} were 531 µg·d/mL and 16.6 µg/mL following the first dose, respectively. The geometric mean values of $AUC_{0\text{-}inf}$ and C_{max} were 908 µg·d/mL and 31.5 µg/mL following the third dose, respectively. The $AUC_{0\text{-}inf}$ and C_{max} values almost doubled following three dose administration. The terminal half-life of SB-024563 following three doses was comparable to that following the first dose. The mean concentration-time profile of SB-240563 following three doses was displayed in Fig.4.10.

Table 4.6 Arithmetic Mean (SD) PK Parameters for SB-240563 Following Single or Three doses of 250 mg SB 240563

Parameter (units)	Dose 1	Dose 3
AUC(0-inf) (ug.d/mL)	560 (197)	924 (189)
Cmax (ug/mL)	17.7 (7.1)	32.2 (7.8)
Tmax (days)*	4.50 (3.00-7.02)	8.01 (2.02-13.96)
T½ (days)	20.5 (5.3)	16.2 (2.1)

*** median (range)**
(Source: CSR 017, page 9)

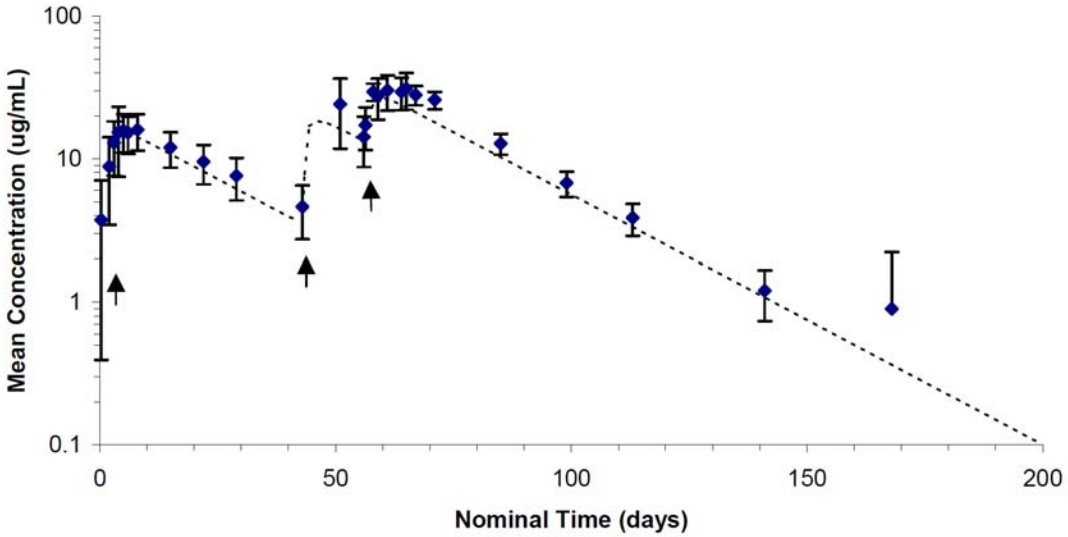

Figure 4.10 Mean (±SD) SB-240563 plasma concentration-time profiles (semi-log scale) following three doses of 250 mg SB-240563 subcutaneous injection on Day 1, Day 43 and Day 57 (N=8). (Source: CSR 017, page 296, Figure 13.1)

The samples taken prior to each dose and at weeks 4, 12, 16 after the last dose were analyzed for the presence of antibodies to SB-240563 and none was detected.

PD Results:
Mean levels of blood eosinophils at predose were higher in placebo group (430 /µL) than in SB-240563 treatment group (260 /µL). The 50% of reduction of eosinophil count was observed 4 days following the first dose (Fig. 4.11). Compare to maximal reduction effect observed on absolute eosinophil count in study 035 (130, 60, and 30 /µL by 0.5 mg/kg, 2.5 mg/kg and 10 mg/kg IV single dose), the maximal effect of single 250 mg subcutaneous dose of SB-240563 reached 90 /µL (or 65% reduction). The maximal reduction reached to 70 /µL (~75% reduction) on Day 4 following the third dose of 250 mg SC-240563. The reduction phase (80 - 110 /µL) was maintained for at least 12 weeks following the third dose.
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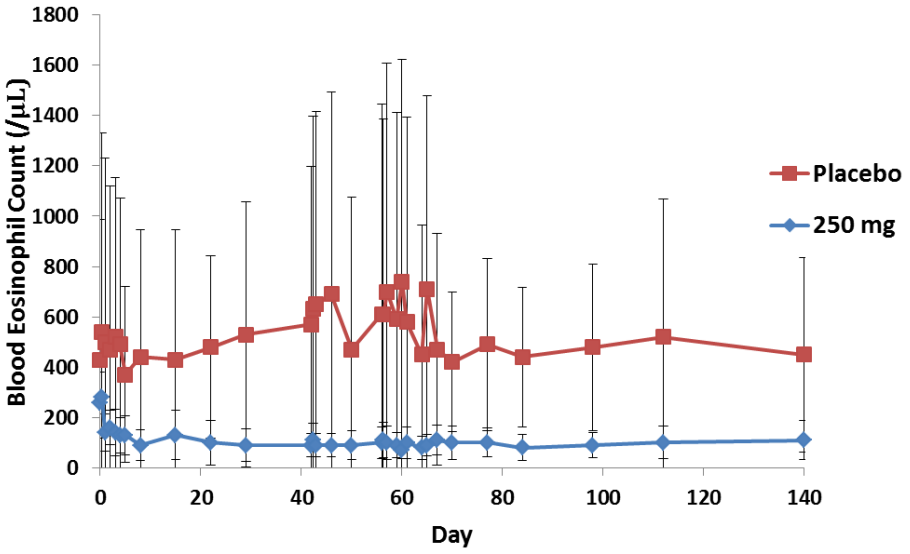

Figure 4.11 Mean (±SD) blood eosinophil count following administration of three doses of placebo or SB-240563 (on Day 1, Day 43 and Day 57). There were 8 subjects in each group. The high variability in placebo group is due to subject 001 kept having eosinophil counts above 1000 /µL throughout the study (Source: adapted from CSR 017, page 225 - 230, Table DS20)

Lung Functions:
At screening, subjects had FEV1 values ranging from 73% to 119% of predicted, confirming that the subjects' asthma was well controlled by medication. At each visit FEV1, FVC, and PEFR were measured. FEV1 was measured at 8 hours and 24 hours post-dose on the dosing day. There were no clinically important changes in lung function during the study.

ECG Results:
ECGs were recorded at screening, pre-dose and 8 hours post-dose on each dosing day, day 8 after each dose and at follow-up. All the ECGs were assessed as normal and only 3 values, PR on 3 occasions for subject 006 who was on placebo, were flagged. This subject had a baseline PR interval of 103 msec but the screening value was 116 and all subsequent readings were higher. In the light of a baseline value that was lower than any other recorded for this subject during the study the subsequent flagged values of 169, 155 and 179 were not considered to be of clinical importance by the investigator.

Conclusions:
The systemic exposure following the single-dose 250 mg SB-240563 subcutaneous injection at abdomen site in this study was approximately half the value obtained from study 018. The maximal reduction effect of blood eosinophil count (in terms of absolute count values) following single-dose 250 mg SB-240563 was between the efficacy of 0.5 mg/kg and 2.5 mg/kg IV single dose of SB-240563 from study 035. There were no clinically important changes in lung function during the study.

4.1.5 Study SB-240563/036 (Study 036)

Study Type: Phase 2, three-dose, PD and safety study in patients with atopic asthma
Study Dates: 01/21/2000 – 08/15/2001
Drug Product: 50 mg/vial from pilot manufacturing process (b) (4)

Title:
Effect of 750 mg SB-240563 (Anti-IL-5) on Clinical Features, Cutaneous Late-Phase Reactions and Bronchial, Nasal, Skin, Bone Marrow and Blood Eosinophils in Male and Female Patients with Atopic Asthma

Objective:

- Primary: To evaluate the effect of SB-240563 on:
  - The number of eosinophils in the bronchial mucosa and bronchial alveolar lavage (BAL).
  - Eosinophil infiltration following nasal allergen challenge.
  - The cutaneous late-phase reaction (in response to cutaneous allergen challenge), both size and eosinophil infiltration.
  - The number of eosinophils in bone marrow.
  - The number of eosinophils in blood.

- Secondary: To investigate the effect of SB-240563 on:
  - The clinical features of atopic asthma.
  - The provocative concentration 20% (fall in FEV1) (PC20) for histamine.
  - Eosinophil formation from bone marrow precursors (comparing mature and immature cells).
  - CD34+ cells in lung, blood and bone marrow.

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, two-parallel-group, three 750 mg IV dose (infusion time 30 min) study in 24 patients with mild allergic asthma. The study was conducted in two parallel groups with one group (12 subjects) received three IV doses of 750 mg SB-240563 and another group (12 subjects) received three IV doses of placebo. The dosing interval was 4 weeks. All the PD markers were assessed one week following the last dose (Week 9).

24 subjects (17 male, 7 female), aged 19 to 52 years, with a documented history of asthma were recruited into and completed the study. Active and placebo groups were well matched in terms of demographic characteristics and markers of asthma severity such as lung function, β2 agonist use and airway hyper-responsiveness (histamine PC20).

All the PD markers were measured as:

- Baseline blood sample for eosinophil and basophil count;
- fiber optic bronchoscopy and bronchial biopsies with BAL;
- Bone marrow biopsy;
- Allergen-induced cutaneous late phase response (biopsy at 6 hours and 48 hours);
- Baseline nasal lavage and lavage 6 hours after nasal allergen challenge.

For allergen challenge test, allergen was injected intradermally into the volar aspect of the forearm. Diluent control was then injected in the other forearm. The participant was observed for 2 hours before leaving the clinic. After 6 hours and 48 hours (Visit 7) the mean diameter of the late phase response (mm) was measured and a single skin biopsy taken from both sites for assay of PD variables.

PD Endpoints:

- Primary:
  1. The number of eosinophils in the bronchial mucosa: biopsy (cells/mm2), BAL (% total leukocytes).
  2. Eosinophil infiltration following nasal allergen challenge (6 and 48 [if feasible] hours).
  3. The cutaneous late-phase reaction (6 & 48 hours): mean diameter of late phase response (mm), number of eosinophils in the skin (cells/mm2).
  4. The numbers of eosinophils in bone marrow (% total cells).
  5. The numbers of eosinophils in blood (from haematology laboratory full blood count [FBC] and cytospin with Kimura stain) (% total cells and cells/field).

- Secondary:
  1. The clinical features of atopic asthma: domiciliary PEFR (L/min), β2-agonist use (puffs), symptom scores.
  2. The PC20 for histamine (mg/mL).
  3. Comparison of numbers of eosinophil precursors and mature eosinophils in bone marrow.
  4. Numbers of CD34+ cells in: bone marrow (% total cells), blood (% total cells), lung biopsy (cells/mm^2); CD34+/IL-5Rα mRNA cells were counted if feasible (cells/mm^2 in lung biopsy).

PD Results:

Due to administration errors, three subjects were wrongly dosed, resulting in 11 subjects receiving SB-240563 and 13 subjects receiving placebo.

The results of primary PD endpoints were listed in Table 4.7. Of all the parameters, only the mean diameter of flare at 6 hour post-allergen challenge did not show significant difference between the SB-240563 treatment group and the placebo group.

Table 4.7 Primary PD Endpoints of Eosinophil Count (Difference from Placebo) in Different Tissues or body Fluids fro Study 036

Eosinophil Count in	Difference from Placebo[#]	95% CI
Bone Marrow (per 200 cells)	-5	(-8, -1)*
Bronchial Mucosa Biopsy (cells/mm^2)	-38.74	(-68.89, -8.60)*
Blood (per 10^9 cells)	-0.2	(-0.3, -0.1)*
Skin Biopsy 6 h Post-Allergen Challenge (cells/mm^2)	-55.14	(-95.11, -15.18)*
Skin Biopsy 48 h Post-Allergen Challenge (cells/mm^2)	-58.46	(-91.98, -24.94)*
Mean Diameter of Flare 6h Post-Allergen Challenge (mm)	2.2	(-8.3, 12.6)
BAL (% total)	-0.4	(-1.30, 0.45)
Nasal Lavage Pre-Challenge (per 200 cells)	-5.5	(-10.0, -2.0)*
Nasal Lavage Post-Challenge (per 200 cells)	-4.8	(-8.0, -0.3)*

[#] 13 subjects received placebo treatment and 11 subjects received SB-240563 treatment
*** Statistically significant**
Source: adapted from tables from CSR036, page 9

Since diary data were not always collected for 2 weeks prior to dosing and on several occasions diary data were missing for part of the post-treatment phase, PEFR (L/min), β2-agonist use (puffs) and symptom scores were not evaluated. It appeared that the eosinophil precursor cells and CD34+ cells were not evaluated in the clinical study report 036. The Sponsor only submitted the histamine PC20 results among claimed secondary PD endpoints (Table 4.8).

Table 4.8 Comparison of SB-240563 and Placebo on Doubling Dose Shifts for Histamine PC20

Comparison	Point Estimate of the Doubling Dose Shift	95% CI
Placebo: Week 12 – Baseline	0.7	(0.0, 2.8)
SB-240563: Week 12 – Baseline	1.4	(-0.6, 1.9)

Source: CSR036, page 9

Conclusions:
Although statistically significant differences were observed from placebo treatment on eosinophil counts in bone marrow, bronchial mucosa, blood, skin (post-allergen challenge), and nasal lavage, there were no parallel changes in clinical outcomes, i.e. no difference in mean diameter of flare following allergen challenge (cutaneous late phase response) or in airways hyper-responsiveness (histamine PC20).

4.1.6 Study SB-240563/018 (Study 018)

Study Type: Phase 1 PK, bioavailability single-dose study in healthy volunteers
Study Dates: 02/16/2001 – 06/22/2001
Drug Product: 250 mg/vial from pilot manufacturing process (b) (4)

Title:
An open, randomized, parallel group study to assess the bioavailability following administration at 3 subcutaneous sites and 1 intramuscular site relative to intravenous administration of single 250 mg doses of SB-240563 to healthy volunteers

Objective:
- To estimate the bioavailability of a single 250mg dose of SB-240563 from three different subcutaneous sites and an intramuscular site compared to an intravenous dose

- To make a preliminary assessment of the safety and tolerability of SB-240563 and its effect on eosinophil counts in healthy volunteers after subcutaneous doses and an intramuscular dose.

Study Design and Method:
This investigation was an open-label, randomized, five-parallel-group, single-dose study in 60 healthy volunteers. Each group contained 12 subjects and each group received one of the following administrations of 250 mg SB-240563: subcutaneous injection at abdomen, subcutaneous injection at the upper arm, subcutaneous injection at the thigh, intramuscular injection at the thigh, and intravenous injection through the forearm vein. Each 250 mg dose was administered as two 125 mg subcutaneous bolus injections or one 250 mg intramuscular bolus injection or an intravenous infusion over approximately 30 minutes.

Blood samples for PK analysis and eosinophil counts were collected at predose, and 2 h, 4 h, 6 h, 8 h, 24 h, Day 3, Day 4, Day 5, Day 6, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, and Week 12 following all the administrations. Extra blood samples were collected at 15 minutes, 30 minutes, and 35 minutes only following the intravenous infusion. 12-lead ECG was monitored at screening visit, pre-dose, 8 h, Day 8, Week 4 and Week 12 post-dose.

Plasma samples were assayed for SB 240563 using an immunoassay method by GSK (lower limit of quantification, 0.05 ug/mL for a 0.1 mL aliquot of 10% human plasma). The same analytical method was used in study 006/017. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}inf}$ were estimated by non-compartmental analysis.

Primary Endpoints:
- PK: $AUC_{0\text{-}inf}$, C_{max}, T_{max} and $T_{1/2}$ of SB-240563
- PD:
  (i) Duration of reduction of eosinophil count by at least 50%
  (ii) Time to maximum reduction in eosinophil count
  (iii) Maximum reduction in eosinophil count

PK Results:
Following the 30 minute intravenous infusion of 250 mg SB-240563, the plasma concentrations of SB-240563 declined in a seemingly bi-exponential manner (Fig. 4.11). T_{max} ranged from 0.5 to 4 hours, relative to the start of the 30 minute infusion (Table 4.9).

Following administration of bolus subcutaneous injections at three different sites and the bolus intramuscular injection, the mean SB-240563 plasma concentration-time profiles were similar in shape (Fig. 4.12). However, overall the mean plasma concentrations were higher following IM administration. SB-240563 was absorbed slowly, with T_{max} values ranging between 2 and 14 days (Table 4.9).

Table 4.9 Summary of PK Parameters following Different Administration Route of 250 mg SB-240563 in Healthy Volunteers (12 Subjects/Group)

Parameter [units]	Subcut (abdomen) [A]	Subcut (arm) [B]	Subcut (thigh) [C]	IM [D]	IV [E]
AUC(0-inf) [ug.d/mL]	1110 (372)	1238 (228)	1196 (254)	1395 (348)	1557 (250)
Cmax [ug/mL]	34.1 (12.1)	34.9 (7.3)	38.2 (9.1)	46.9 (10.6)	109 (17)
Tmax* [days]	7 (4-14)	5 (3-14)	5 (2-7)	4 (3-7)	0.08 (0.02-0.2)
T1/2 [days]	17.9 (3.3)	20.4 (2.6)	18.5 (3.5)	19.2 (4.2)	18.5 (2.3)

*** Displayed as arithmetic mean (SD) for all the parameters except T_{max}, which is median (range) (Source: CSR 018, the first table of page 18)**

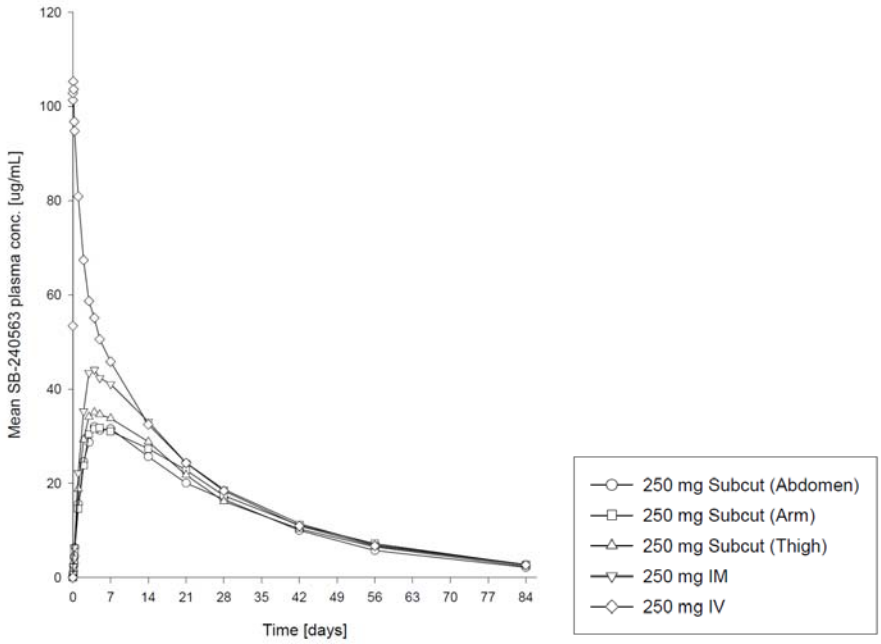

Figure 4.12 SB-240563 plasma concentrations (arithmetic mean) following administration of 250 mg SB-240563 through different route. (Source: CSR 018, page 816, Figure 12.1)

The relative bioavailability of intramuscular route, and subcutaneous route at sites of abdomen, arm and thigh were 81% (90% CI = 71% to 94%), 64% (90% CI = 55% to 73%), 75% (90% CI = 66% to 86%), and 71% (90% CI = 62% to 82%), respectively (Table 4.10). The $AUC_{0\text{-inf}}$ and C_{max} values of 250 mg subcutaneous route at site of abdomen from this study were about 2-fold as the values obtained from study 017 (Table 4.6). The median Tmax via the abdomen site in this study is 7 days, which is longer than that

of study 017 (4.5 days). Whether these differences were contributed by inter-study variability or study populations, is not clear.

Table 4.10 Bioavailability of SB-240563 following Different Administration Route and Injection Site

Parameter	Comparison	Point Estimate	90% CI
AUC(0-inf)	A:E	0.64	(0.55, 0.73)
	B:E	0.75	(0.66, 0.86)
	C:E	0.71	(0.62, 0.82)
	D:E	0.81	(0.71, 0.94)
Cmax	A:E	0.27	(0.24, 0.31)
	B:E	0.29	(0.26, 0.33)
	C:E	0.31	(0.27, 0.36)
	D:E	0.38	(0.33, 0.43)
Tmax	A:E	6.93	(4.21, 7.09)
	B:E	5.13	(4.99, 6.91)
	C:E	5.12	(4.04, 6.86)
	D:E	3.96	(3.12, 5.03)

A = 250 mg Subcut (abdomen)
B = 250 mg Subcut (arm)
C = 250 mg Subcut (thigh)
D = 250 mg IM
E = 250 mg IV

***non-inferiority p-values (delta = 0.05 L)**
(Source: CSR 018, the second table of page 18)

PD Results:
Visual inspection of eosinophil counts indicated that there was a marked decrease of 50% or more so SB-240563 has a similar effect in healthy subjects to that previously observed in asthmatics. It was decided that a more detailed analysis of the pharmacodynamic effect in healthy subjects would not be of value in deriving dose regimens for patients.

ECG Results:
There were no clinically important changes in the 12-lead ECGs from subjects in the study. There were no differences between groups, or trends or changes over time. No ECG interval exceeded the pre-set limits (QTc interval > 500 msec) of potential clinical concern. Only one ECG was reported as abnormal, this was subject 046 (SC arm) who had a QTc of 457 msec on Day 29. It was measured as 467 msec on a repeat ECG but 10 m later had fallen to 440 msec. This subject had a baseline QTc of 447 msec and a follow-up value of 446 msec so the 457 and 467 msec readings were not considered to be clinically relevant.

Conclusions:
The relative bioavailability of intramuscular route, and subcutaneous route at sites of abdomen, arm and thigh in healthy subjects were 81%, 64%, 75%, and 71%, respectively, when compared to values obtained after administration by the intravenous route. There were no clinically important changes in the 12-lead ECGs from subjects in the study.

4.1.7 Study MEA114092 (Study 114092)

Study Type: Phase 2a PK, PD, three-dose, dose-ranging study in asthma patients
Study Dates: 02/21/2011 – 03/07/2012
Drug Product: 250 mg/vial of MDP1

Title:
A multicenter, open-label, dose ranging study to determine the pharmacokinetics and pharmacodynamics of mepolizumab administered intravenously or subcutaneously to adult asthmatic subjects with elevated blood eosinophil levels.

Objective:

- The primary objective was to demonstrate that the PK/PD relationship between the exposure of subcutaneously administered mepolizumab and a marker of response, blood eosinophil, is comparable to that observed following intravenous administration.

- The secondary objectives were:
  - To assess the absolute bioavailability of mepolizumab administered subcutaneously, compared with mepolizumab administered intravenously
  - To assess the immunogenicity of repeat doses of mepolizumab
  - To assess the safety and tolerability of repeat doses of mepolizumab when administered subcutaneously and intravenously

Study Design and Method:
This investigation was an open-label, randomized, four-parallel-group, three-dose study in 70 asthma patients with 66 completed the study. The treatments for four groups were 75 mg iv, 12.5 mg, 125 mg and 250 mg sc. The subcutaneous administration site was in the upper arm. The randomization ratio of subject numbers for the above four groups was 2:4:3:4. The dosing interval was every 4 weeks.

Enrolled subjects were males or females aged 18 to 65 years, who showed evidence of airway reversibility (FEV1 ≥12%) within 30 minutes of inhalation of albuterol or airway hyper-responsiveness documented in the 12 months prior to randomization. Subjects' FEV1 value was ≥45% and <90 % of predicted normal value during screening. Subjects were required to be on a stable dose of an inhaled corticosteroid or combination (ISC and LABA) therapy for at least 12 weeks prior to screening. Subjects were required to have documented evidence of elevated blood eosinophilia levels (≥200 cells /μL in accordance with protocol amendment 1) within 12 months of screening and evidence of elevated blood eosinophilia levels (≥200 cells /μL in accordance with protocol amendment 1) at screening.

Blood samples for PK analysis were collected at predose, 0.5, 1 and 2 h post-dose on the dosing days. Additional samples were collected on Day 3, 7, 29, 56, 70, 84,112 and 140. The PK parameters were estimated via 2-compartment model by population PK analysis.

Human plasma samples were analyzed for mepolizumab using two validated ELISA methods by (b) (4) . The LLQ for mepolizumab was 50.0 ng/mL, using a 100μL aliquot of 5-fold or 10-fold assay buffer diluted plasma with a higher limit of quantification of 5000 ng/mL for both methods.

Three samples (predose, Day 112 and Day 140) were collected for immunogenicity assessment in the study. Regarding the immunogenicity sample analysis, it was discovered during the course of the study that the initially validated MSD chemiluminescent assay was characterizing samples with elevated levels of total IL-5 as positive for immunogenicity. During treatment with mepolizumab, serum total IL-5 levels

increased due to the formation of mepolizumab-IL-5 complexes. Since the complex IL5-mepolizumab formed is in equilibrium with IL5 in the assay, IL5 can be released from the complex. As a homodimer, IL-5 can form a bridge in the MSD assay between the biotinylated drug and ruthenylated drug, just like the targeted ADAs. To minimize the interference due to elevated total IL-5, a purified competitive anti-human IL-5 antibody was included as an assay component in the MSD ADA assay. Since sample analysis was already in progress, it continued with the original assay (screening, confirmation, and titration); however, only those samples that confirmed positive in the original assay were re-analyzed with the improved assay. However, only confirming anti-drug antibody (ADA) and titre results based on the improved assay were included in summary tables.

Samples for blood eosinophil counts and IL-5 concentrations measurement (PD) were collected throughout the study. A total of nine blood samples (excluding the screening sample) per subject were collected on Days 1 (pre-dose), 3, 7, 29 (pre-dose), 56 (pre-dose), 70, 84, 112 and 140 (follow-up visit). The PK/PD relationship was assessed based on the PK and PD blood samples obtained on the same date. Sputum induction assay was performed at Day 1 (pre-dose), Day 7, Day 28 (pre-dose), Day 56 (pre-dose), and Day 84. At each time, the induction was performed after the completion of the routine spirometric assessments.

Primary Endpoints:

- Primary endpoints:
  - Change from baseline in blood eosinophil levels as assessed by the exposure-response relationship
  - Area under the blood eosinophil time curve (AUEC), maximum change from baseline in blood eosinophils (E_{max}), time to maximum change in blood eosinophil levels (T_{maxeos}), time to 50% eosinophil repletion (T_{rep})
  - PK parameters including AUC, C_{max}, T_{max} and $T_{½}$ of mepolizumab

- Secondary endpoints:
  - Bioavailability comparison (AUC and C_{max}) between IV and SC administrations
  - Levels of anti-mepolizumab antibodies
  - Spontaneous and elicited adverse events, vital signs, ECGs and clinical laboratory values

PK Results:

A total of 69 subjects provided plasma concentration data. All subjects (except Subject 3001) who received mepolizumab had at least one PK sample with a measurable mepolizumab level. No mepolizumab plasma concentration data were excluded from the population PK analyses. Nine subjects displayed a measurable plasma concentration of mepolizumab at pre-dose before the first dose (ranging from 59 to 467 ng/mL); these values were replaced by zero.

Table 4.11 Estimated Typical* Values of Mepolizumab PK Parameters by Population PK Analysis

75 mg Intravenous		Subcutaneous (12.5 mg, 125 mg, 250 mg)	
Parameters	**Estimate**	**Parameters**	**Estimate (12.5 mg)**
CL (L/day)*	0.210 (0.189, 0.232)	**CL/F (L/day)***	0.310 (0.275, 0.349)
V1 (L)*	3.60 (3.19, 4.05)	**V2/F (L)***	4.57 (4.02, 5.20)
K_{12} (/Day)*	0.280 (0.214, 0.367)	**K_{23} (/Day)**	0.280
K_{21} (/Day)*	0.283 (0.233, 0.344)	**K_{32} (/Day)**	0.283
		Ka (/Day)*	0.194 (0.155, 0.242)

*** Typical values of subject weighing 70 kg**
(Source: CSR 114902, page 55 and 56, Table 12 and Table 13)

The observed and predicted plasma concentrations following 3 doses of IV or SC doses are plotted in Figure 4.13. The estimated PK parameters were listed in Table 4.11. The point estimate of peripheral volumes of mepolizumab following IV and SC administration were 3.56 L and 4.52 L, respectively.

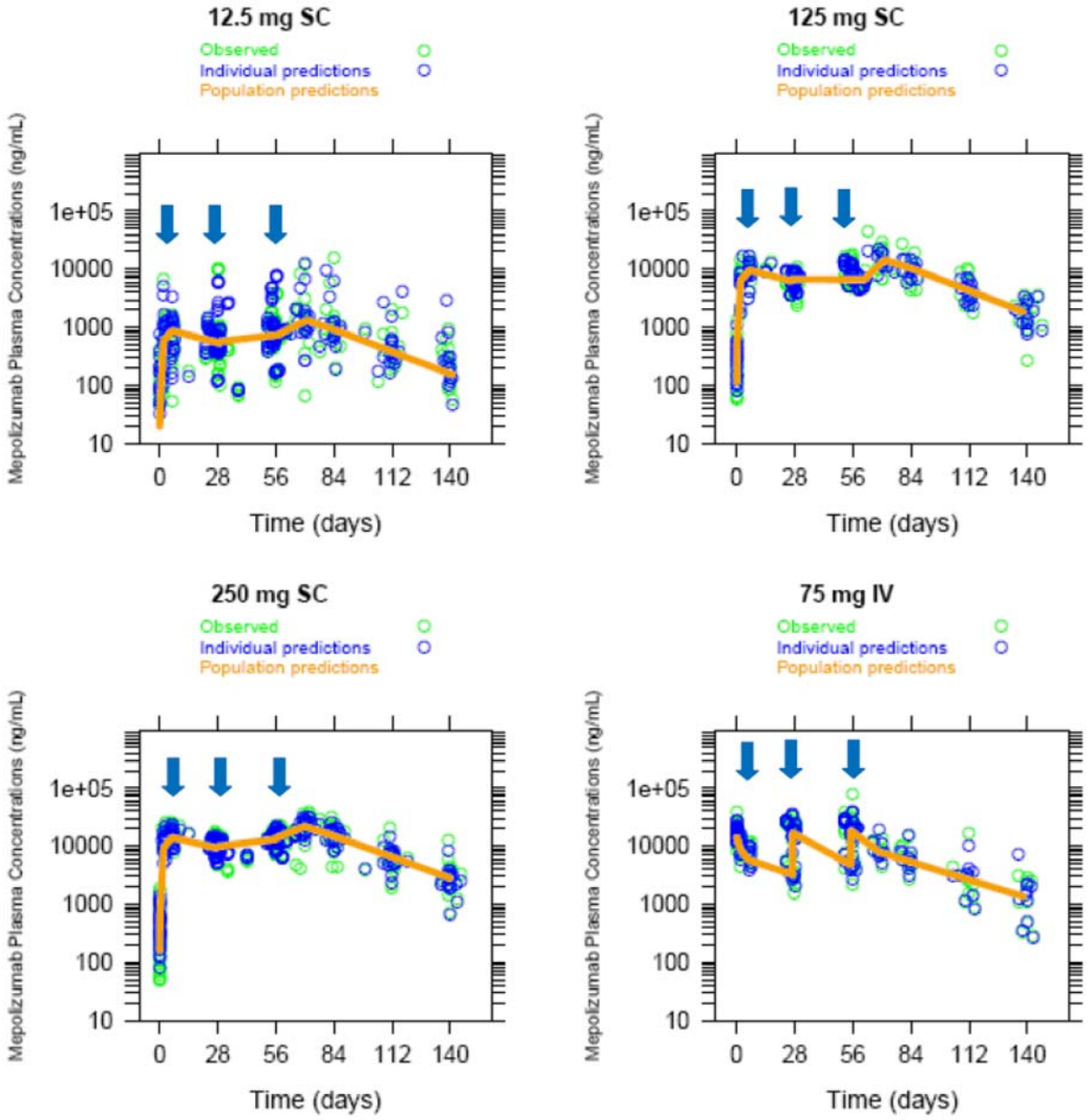

Figure 4.13 Mepolizumab population predicted (yellow), individual predicted (blue) and observed (green) plasma concentrations following three intravenous doses [75 mg (N=11)] or subcutaneous doses [12.5 mg (N=21). 125 mg (N=15), and 250 mg (N=23)] of Mepolizumab. The blue arrows represent the dosing event. The dosing interval was 4 weeks. (Source: CSR MEA114092, page 54, Figure 10)

In the subcutaneous injection groups, $AUC_{0-\tau}$ and C_{max} increased in a slightly less than dose proportional manner in particular between the 125 and 250 mg dose. T_{max} was reached 6–8 days post-dosing in the subcutaneous dose groups (Table 4.12). CL/F and V/F were dose independent. After three doses following intravenous or subcutaneous injection, the accumulation ratios of $AUC_{0-\tau}$ were approximately 1.7. The estimated absolute bioavailability (based on clearance) for different subcutaneous cohorts was 81%, 82%, and 64% for the 12.5, 125 and 250 mg SC administration, respectively. The overall bioavailability was 74%.

Table 4.12 Summary Statistics of Model Predicted Mepolizumab Derived PK Parameters

Parameters (Unit)		Mepo SC 12.5 mg N=21	Mepo SC 125 mg N=15	Mepo SC 250 mg N=22	Mepo IV 75 mg N=11
$AUC_{(0-\tau)}$ (μg*h/mL)	Dose 1	n=21 524 (346, 793)	n=15 5091 (4116, 6299)	n=22 8674 (7635, 9853)	n=11 3986 (3254, 4882)
	Dose 2	n=21 794 (517, 1219)	n=14 8391 (7064, 9968)	n=22 13078 (11596, 14748)	n=11 5959 (4746, 7483)
	Dose 3	n=20 909 (586, 1408)	n=14 8838 (7140, 10940)	n=21 14228 (12458, 16250)	n=11 6714 (5271, 8553)
Cmax (μg/mL)	Dose 1	n=21 1.06 (0.67, 1.68)	n=15 9.90 (8.11, 12.10)	n=22 16.11 (14.14, 18.36)	n=11 18.10 (15.19, 21.58)
	Dose 2	n=21 1.58 (1.01, 2.46)	n=14 14.9 (12.3, 18.0)	n=22 24.1 (21.3, 27.2)	n=11 21.9 (18.2, 26.5)
	Dose 3	n=20 1.78 (1.13, 2.81)	n=14 16.6 (13.7, 20.1)	n=21 27.3 (24.0, 31.0)	n=11 23.6 (19.4, 28.6)
Tmax (days for SC cohorts, h for IV cohort)	Dose 1	n=21 8.35 (1.54, 31.74)	n=15 7.95 (4.41, 19.05)	n=22 8.07 (4.20, 15.75)	n=11 0.6 (0.5, 0.75)
	Dose 2	n=21 6.57 (1.56, 20.98)	n=14 6.20 (4.00, 13.31)	n=22 6.40 (3.64, 11.00)	n=11 0.5 (0.33, 0.83)
	Dose 3	n=20 5.97 (1.56, 18.96)	n=14 6.16 (3.89, 10.68)	n=21 5.87 (3.69, 9.05)	n=11 0.533 (0.42, 0.75)
t½ (days)		n=21 21.8 (20.0, 23.5)	n=15 22.1 (20.5, 23.7)	n=22 21.8 (20.2, 23.3)	n=11 28.2 (21.1, 35.3)

$AUC_{0-\tau}$ and C_{max} were presented as geometric mean (95% CI); T_{max} was presented as median (range); $T_{1/2}$ was presented as arithmetic mean (95% CI)
(Source: CSR 114902, page 57, Table 14)

A total of eight subjects out of 70 (11%) had 13 positive samples out of 201 (6%) utilizing the improved assay (Table 4.13). No anti-mepolizumab antibodies were detected at any point in subjects in the 75 mg IV group. Two subjects (subject 4103 in 12.5 mg group and subject 4002 in 125 mg group) were positive on anti-mepolizumab in their pre-dose samples. Only subject 4002 were positive for the anti-mepolizumab antibody in all three blood samples. There was no consistent trend of increase or decrease of the titre of anti-mepolizumab antibody against time in this study. All neutralizing antibody results were negative in all subjects during the study.

Table 4.13 Subjects with Confirmed Positive of Anti-drug Antibody Samples in the Improved Assay

		Time Points		
		Day 1	Day 112	Follow-Up
Group	Subjects	Titre	Titre	Titre
12.5 mg	2305			16
	4103	128		
	4104		128	32
125 mg	4002	4	128	64
	5004		4	
250 mg	2304		4	
	3205		8	4
	5200		4	4

(Source: CSR 114902, page 78, Table 27)

PD Results:

- Blood eosinophil counts

  Mean absolute blood eosinophil levels by treatment group from screening to Day 140 are presented in Fig. 4.14. The eosinophil counts at baseline (pre-dose on Day 1) were 348, 583, 461 and 586 /µL for 75 mg iv, 12.5 mg sd, 125 mg sc, and 250 mg SC groups, respectively. Blood eosinophils counts decreased from baseline in all four treatment groups. Reduction of blood eosinophils was in the same range for the mepolizumab SC 250 mg, SC 125 mg and IV 75 mg groups, while less reduction was observed in the mepolizumab SC 12.5 mg group. More than 50% of reduction from the baseline was observed for all 4 treatment groups. Generally eosinophil counts began to recover from Day 84 (4 weeks post-last dose).

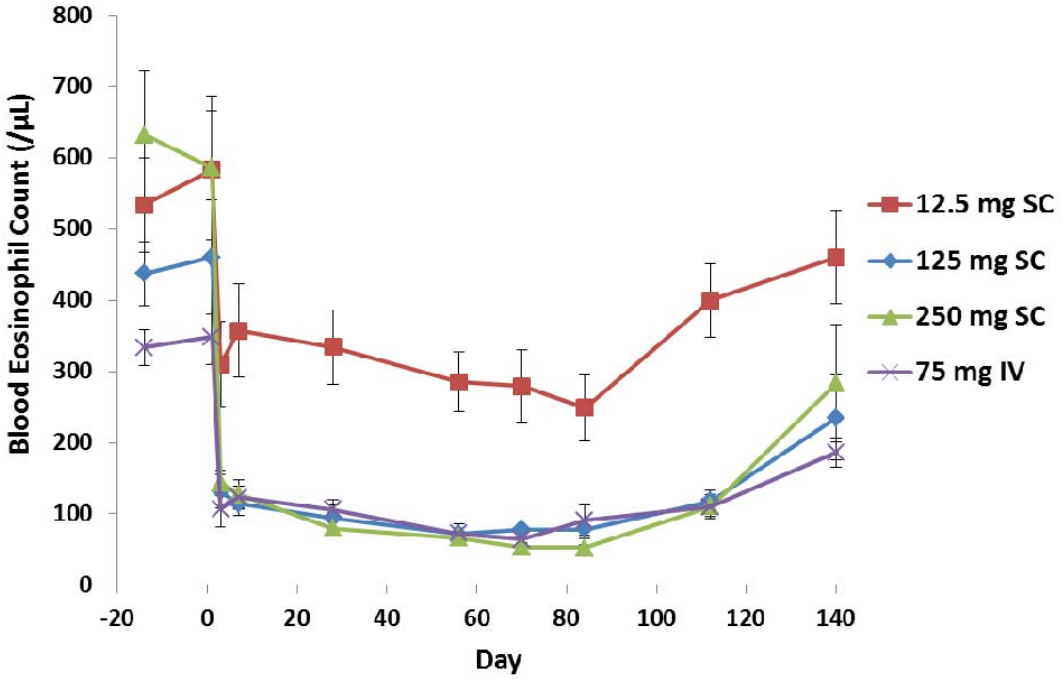

Figure 4.14 Arithmetic mean (± SE) absolute blood eosinophil counts-time profile following three doses (blue arrows) treatment by 75 mg IV (black, N= 11), 12.5 mg SC (blue, N=21), 125 mg SC (red, N=15), and 250 mg SC (green, N=22). (Source: adapted from CSR 114092, page 40, Figure 1)

Derived blood eosinophil parameters such as area under the absolute blood eosinophil time curve to Day 84 ($AUEC_{eos(0–Day\ 84)}$), weighted mean absolute eosinophil count ($wmean_{eos}$), eosinophil maximum reduction from baseline (Max_{eos}), and time to first occurrence of maximum reduction (T_{maxeos}) were presented in Table 4.14. The absolute mean values of blood eosinophil counts reduced maximally to 64 /µL, 249 /µL, 71 µL, and 52 /µL (or reduced by 82%, 57%, 85%, and 91% from the baseline) for 75 mg iv, 12.5 mg sc, 125 mg sc, and 250 mg SC groups, respectively. The mean T_{maxeos} was generally reached around Day 47 – Day 59.

Both linear and non-linear (I_{max}) dose-response models were fitted to the blood eosinophil data. In order to include the 75 mg IV group in the analysis, the 75 mg IV dose was considered to equate to 100 mg SC assuming that the absolute bioavailability of the SC route was 75%.

The final non-linear model was as follows:

$R_{eos} = \beta_0(BL_{eos}) + (D^S \times I_{maxeos})/(D^S + ID^S_{50})$, where:

R_{eos} = Change from baseline in log-transformed blood eosinophil levels on Day 84)

D = Dose (mg)
I_{maxeos} = Maximum reduction from baseline in log-transformed blood eosinophil levels on Day 84with a baseline adjustment within the model
ID_{50} = Dose which induces half maximal drug effect

The estimated IC_{50} dose was 11 mg SC (95% CI = 5.19, 16.85), and the estimated IC_{90} dose was 99 mg SC (95% CI = 47, 152). The estimated I_{max} was 110 /µL (95% CI = 80, 140).

Table 4.14 Summary of Derived Blood Eosinophil Parameters by Treatment Group

Parameter (Unit)	Summary Statistics	Mepolizumab Dose			
		SC 12.5 mg N=21	SC 125 mg N=15	SC 250 mg N=23	IV 75 mg N=11
$AUEC_{eos(0–Day\ 84)}$ (Gl.d/L)	n	20	14	21	11
	Geo Mean	21.551	7.198	6.381	7.556
	95% CI	15.486, 29.991	5.290, 9.796	4.915, 8.284	5.459, 10.459
Proportional Inhibition $AUEC_{eos(0–Day\ 84)}$	n	20	14	21	11
	Geo Mean	0.396	0.743	0.818	0.687
	95% CI	0.263, 0.596	0.679, 0.813	0.780, 0.857	0.602, 0.784
$wmean_{eos(0–Day\ 84)}$ (Gl/L)	n	21	15	23	11
	Geo Mean	0.251	0.090	0.083	0.090
	95% CI	0.183, 0.345	0.066, 0.121	0.063, 0.109	0.065, 0.125
$wmean_{eos(Day\ 84–140)}$ (Gl/L)	n	20	14	21	11
	Geo Mean	0.311	0.110	0.100	0.116
	95% CI	0.239, 0.405	0.076, 0.158	0.069, 0.146	0.087, 0.155
$wmean_{eos(0–tlast)}$ (Gl/L)	n	21	15	23	11
	Geo Mean	0.283	0.102	0.096	0.102
	95% CI	0.216, 0.372	0.075, 0.138	0.071, 0.129	0.077, 0.135
Max_{eos} (Gl/L)	n	21	15	23	11
	Geo Mean	0.203	0.113	0.082	0.141
	95% CI	0.124, 0.331	0.079, 0.162	0.057, 0.119	0.085, 0.233
$Tmax_{eos}$ (Days)	n	21	15	23	11
	Arithmetic Mean	50.0	49.4	47.0	58.8
	95% CI	34.6, 65.5	34.0, 64.8	32.0, 62.0	42.0, 75.6
Subjects achieving ≥50% repletion	n (%)	8 (38)	1 (7)	2 (9)	1 (9)

(Source: CSR 114902, page 42, Table 9)

- Serum IL-5 concentrations
  The serum total IL-5 pre-dose baseline level was low. Only 14%, 13%, 4% and 18% of subjects had measurable serum total IL-5 levels at baseline in the 12.5 mg SC, 125 mg SC, 250 mg SC and 75 mg IV cohorts, respectively. Serum total IL-5 levels increased from baseline in almost all the subjects following the treatments (Fig. 4.15). The peak total IL-5 reached at least 2 weeks after the final dose for all the groups with approximately 10- to 27-fold of the baseline value. There was no clear dose-response relationship for serum total IL-5 concentrations.

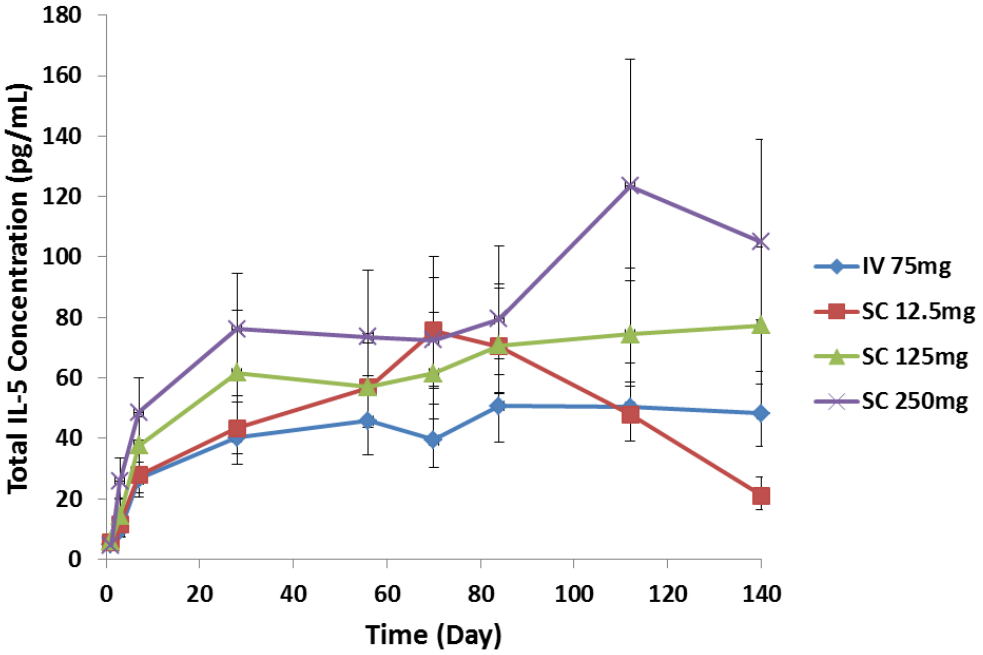

Figure 4.15 Geometric mean (± SE) serum total IL-5 concentrations following three doses treatment by 75 mg IV (blue, N= 11), 12.5 mg SC (orange, N=21), 125 mg SC (green, N=15), and 250 mg SC (purple, N=22). Values below the LOQ (7.81 pg/mL) were imputed with half the LOQ (3.91 pg/mL). (Source: adapted from CSR 114092, page 45, Figure 4)

The free IL-5 concentrations were below the LLQ (3.91 pg/mL) in more than 80% of the samples obtained from Day 1 to Day 84 in 75 mg iv, 125 mg sc, and 250 mg SC groups. The free IL-5 concentrations were above more than 50% of the samples in 12.5 mg SC group starting Day 28. The peak free IL-5 of 12.5 mg SC group reached at Day 120 with geometric mean value of 5.75 pg/mL.

There was no relationship between serum total IL-5 and blood eosinophils based on the exploratory plots and correlation analyses.

- Percent sputum eosinophils

The sputum eosinophil counts (%) at baseline (pre-dose on Day 1) were not balanced between 4 treatment groups. The values were 6.78%, 22.97%, 10.94%, 20.88% for 75 mg iv, 12.5 mg sc, 125 mg sc, and 250 mg SC groups, respectively. There was a general trend of reduction of the eosinophil count in sputum by visual check (Fig. 4.16). The largest decrease from baseline was observed in the mepolizumab 125 mg and 250 mg SC groups, with less of a decrease in the mepolizumab12.5 mg SC group. It is worth noting that the number of subjects who provided sputum data was small and the data were variable.

- FEV1

FEV1 was not the primary or secondary endpoint of this study. FEV1 was only measured as a safety endpoint. The FEV1 values were obtained at screening and on Day 112. There was a mean increase from baseline on FEV1in all four groups. The Mean FEV1 increase from baseline was 87 mL, 165 mL, 146 mL, and 433 mL for 75 mg iv, 12.5 mg sc, 125 mg sc, and 250 mg SC groups, respectively.

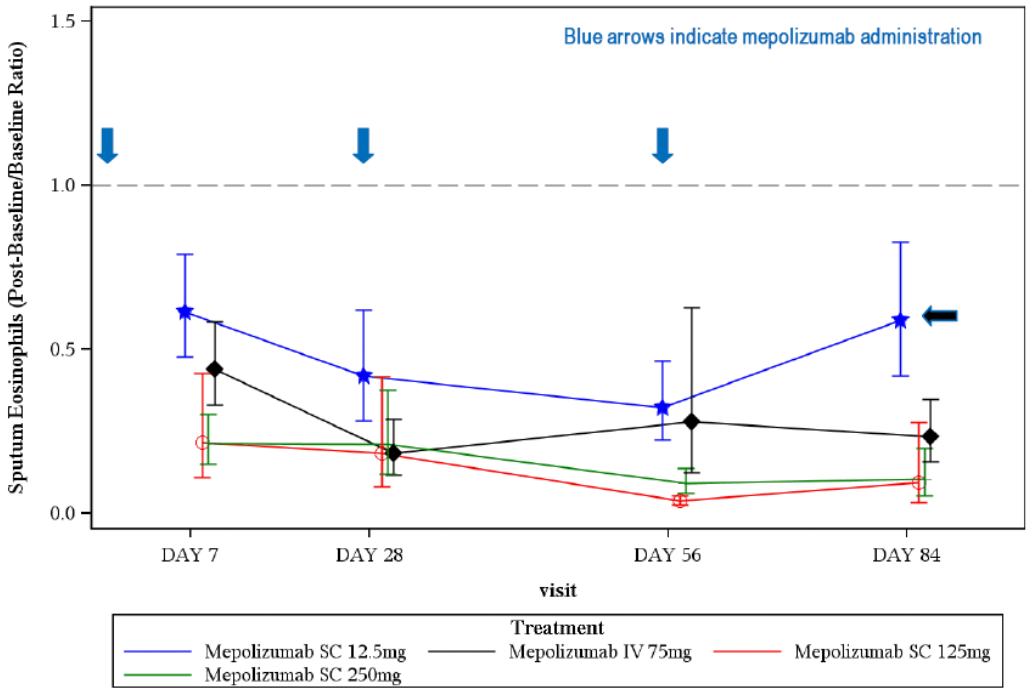

Figure 4.16 Induced sputum eosinophil counts (%) represented by post-baseline/baseline ratio following three doses treatment by 75 mg IV (black, N= 7), 12.5 mg SC (blue, N=16), 125 mg SC (red, N=8), and 250 mg SC (green, N=13). (Source: CSR 114902, page 49, Figure 7)

PK/PD Results:

The blood eosinophils count (PD) - mepolizumab plasma concentration (PK) plot was shown in Fig. 4.17. The PK/PD measures were obtained at the same day.

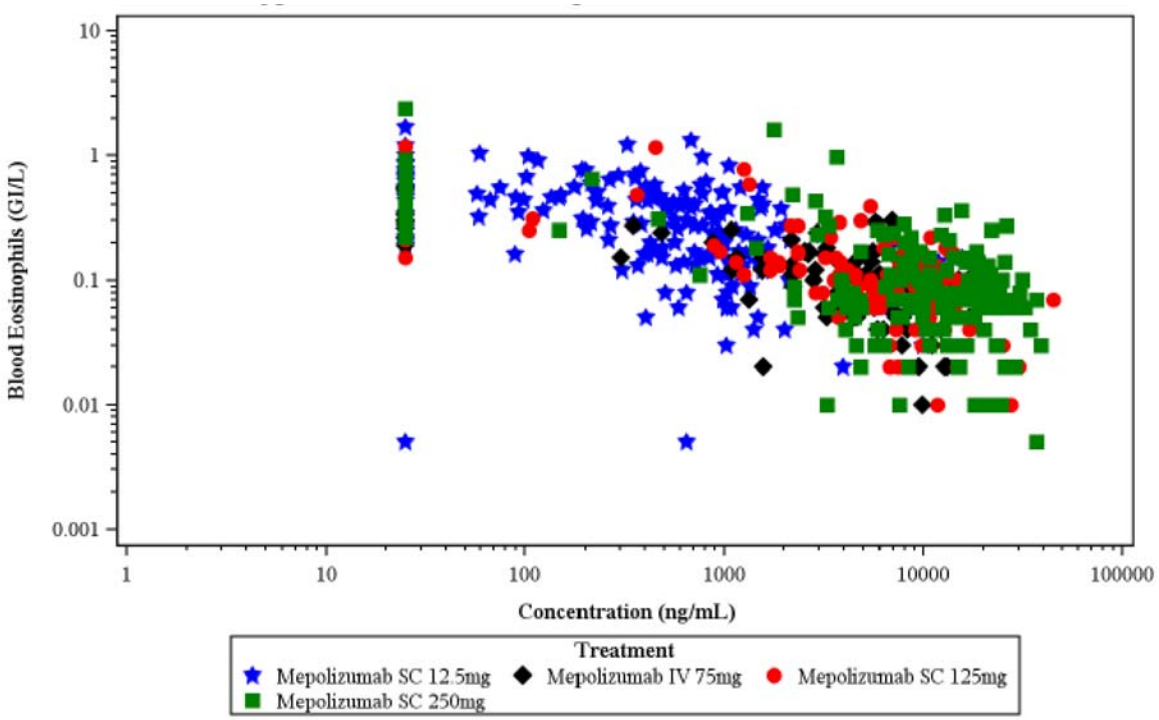

Figure 4.17 Blood eosinophil counts versus mepolizumab plasma concentration following administrations of mepolizumab at four different doses. (Source: CSR 114902, page 59, Figure 11)

An exposure-response relationship was explored by an I_{max} model. The blood eosinophil counts were described by the time-dependent response manor. The 75 mg IV dose was considered to equate to 100 mg SC assuming that the absolute bioavailability of the SC route was 75%.

The final model was as follows:
Eosinophil count = $K_{RO} \times K_{out} \times [1 - Conc \times I_{max} / (IC_{50} + Conc)]$ where:

K_{RO} (estimated baseline blood eosinophil counts) = $e^{[\theta 1 + \theta 5 \times Log (observed\ baseline) + \eta 1]}$

K_{out} = blood eosinophil elimination rate

Conc = mepolizumab concentration

I_{max} = maximal reduction

IC_{50} = mepolizumab concentration of 50% reduction

The IC_{50} estimate was 1.26 µg/mL (Table 4.15). The I_{max} estimate was approximately 93% from the baseline. The null hypothesis was not rejected which the concentration-response relationship was not different between IV and sc.

Table 4.15 Population PD Parameter Estimates from Population PK/PD Analysis

Parameters	Estimate (95% CI)
KRO (GI/L)	0.710 (0.642, 0.784)
KOUT (/day)	0.414 (0.297, 0.578)
IC_{50} (ng/mL)	1261 (878, 1813)
IMAX	0.928 (0.875, 0.959)
BL covariate on KRO	0.701 (0.544, 0.858)

(Source: CSR 114902, page 62, Table 15)

ECG Results:
No clinically significant ECG abnormalities were recorded. There were no clinically relevant changes from baseline at Day 3 between the four groups on any ECG parameter.

Conclusions:

- Blood and sputum eosinophils decreased in all four groups following mepolizumab treatment. The reduction effect was the least in 12.5 mg SC dose whereas the effects were similar among other three treatments.

- The SC doses estimated to provide 50% and 90% of maximal inhibition of blood eosinophils attributable to the drug at Week 12 were 11 mg and 99 mg, respectively.

- There was no major deviation from dose proportionality over the range of SC doses tested and mepolizumab PK was time and dose independent after SC repeat dosing.

- The geometric mean C_{max} following the first dose of 250 mg SC mepolizumab was comparable between this study (16.1 µg/mL) and study 017 (16.6 µg/mL) (Table 4.16). The average T1/2 was also similar between this study (21.8 Day) and study 017 (20.5 Day). The estimated mean CL/F was 28% higher in study 017 whereas the median Tmax was 3.6 Days longer in this study. The estimated bioavailability when injected at upper arm from this study (64%) was the same as estimated from study 018.

Table 4.16 Comparison of PK Parameters of 250 mg SC between Study 017 and Study 114092

	Study 017 (N=8)	**Study 114092 (N=22)**
Drug Product	50 mg/vial from pilot manufacturing process (b) (4)	250 mg/vial of MDP1
PK estimation method	Non-compartment	popPK
AUC (μg·d/mL)*	531 (34.1%)[1]	361 (29.4%)[2]
C_{max} following the first dose (μg/mL)*	16.6 (34.2%)	16.1 (30.1%)
CL/F (L/Day)*	0.471 (34.1%)	0.367 (28.9%)
T_{max} following the first dose (Day)[#]	4.50 (3.00-7.02)	8.07 (4.20-15.75)
$T_{1/2}$ (Day)[§]	20.5 (26.0%)	21.8 (15.9%)

*** geometric mean (CV%)**
[#] median (range)
[§] arithmetic mean (CV%)
[1] $AUC_{0\text{-}inf}$ following the first dose
[2] $AUC_{0\text{-}\tau}$ following the first dose
(Source: reviewer's analysis)

- A 1.7 accumulation ratio was observed for AUC and C_{max} after three 4-weekly SC administrations.
- No clinically relevant trends were observed in ECG data.
- Incidence of immunogenicity was low, with generally low titres. All samples were negative for neutralizing antibodies

4.1.8 Study MEA112997 (Study 12997)

Study Type: Phase 2b/3 efficacy, safety, PD, popPK, three IV doses, dose-ranging study in asthma patients
Study Dates: 11/09/2009 – 12/05/2011
Drug Product: 250 mg/vial of MDP1

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.

Objective:

- The primary objective was to evaluate the dose response, based on efficacy and safety of three IV doses of mepolizumab (75 mg, 250 mg and 750 mg) over a 52 week treatment period in adult and adolescent subjects with severe uncontrolled refractory asthma

- The secondary objective was to assess the pharmacodynamic effect of mepolizumab on the number of eosinophils in blood, serum IL-5 and number of eosinophils in induced sputum

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, four-parallel-group, three IV dose, dose ranging study in approximately 604 patients (151 subjects per group) with severe uncontrolled refractory asthma. There was one adolescent aged 15 years (ID2460) enrolled in the study and assigned to 250 mg IV treatment group. In total 520 subjects completed study. The IV doses for three mepolizumab treatment groups were 75 mg, 250 mg and 750 mg. The dosing interval was every 4 weeks. The treatment duration was 48 weeks.

Enrolled Subjects required for regular treatment with high dose inhaled corticosteroids, with or without maintenance oral corticosteroids in the 12 months prior to Visit 1. Subjects had persistent airflow obstruction as indicated by a pre-bronchodilator forced expiratory volume in 1 second (FEV1) <80% predicted or peak flow diurnal variability of >20%. Subjects had airway inflammation that was likely to be eosinophilic in nature, and a history of two or more asthma exacerbations requiring treatment with oral or systemic corticosteroids in the 12 months prior to Visit 1. Subjects with airway inflammation which was likely to be eosinophilic in nature as indicated by one of the following characteristics demonstrated at Visit 1 or documented in the previous 12 months:

- 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 following a ≤ 25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in the previous 12 months

Blood samples for PK analysis were collected at pre-dose on Day1, pre-dose and within 30 minutes after the end of the infusion at Week 20, and at the end of Week 56 or early withdrawal. The PK parameters were estimated by population PK analysis.

Human Plasma concentrations of mepolizumab in Study MEA112997 were determined by a single ELISA method by (b) (4). The method had slight changes to the minimum required dilution and

calibration range to maintain the sensitivity from previous reported mepolizumab plasma concentration assays. The LLQ for mepolizumab was 50.0 ng/mL. The assay range was 50 - 5000 ng/mL.

Immunogenicity samples and serum IL-5 samples were collected pre-dose at Day 1, Week 16, Week48 and Week 56 or early withdrawal. Samples for blood eosinophil counts were collected pre-dose at Day 1, and every 4 weeks from Week 4 to Week 56 or early withdrawal. Induced sputum was collected at selected sites in subjects at Day 1 or Week 2, Week4, Week16, Week 52, and Week56 or early withdrawal. Fractional exhaled NO (FeNO) was collected at selected sites in subjects at Day 1 or Week 2, Week4, Week16, Week 32, Week 52, and Week56 or early withdrawal.

PK/PD Endpoints:

- Eosinophils in blood and induced sputum
- FeNO
- Serum interleukin (IL)-5
- Plasma levels of mepolizumab
- Presence of anti-mepolizumab binding antibodies
- Presence of neutralizing antibodies

PK Results:

A total of 443 subjects had at least one measurable concentration of mepolizumab. The number of data per subject ranged from 1–3; the majority of subjects (345/443) had three samples. PK samples from 148, 147, and 148 subjects were collected from 75, 250, and 750 mg treatment group, respectively. The PK samples were collected from the only adolescent enrolled in this study. A total of 1193 PK samples were available for the PK analysis. 27 observations were excluded due to data entry error.

The key parameter estimates are presented in Table 4.17. Body weight was included as a covariate for clearance and central volume by a power model. When stratify the $AUC_{0-\tau}$ by body weight, the Css was approximately 20% lower in the upper quartile of the body weight (91– 162 kg) than in the lower quartile of the body weight (65–78 kg) (Fig. 4.18). A 30% increase in body weight would result in a 16% decrease in AUC, which is within the inter-subject variability in the clearance parameter (26%) after taking into account body weight.

Table 4.17 Estimated Typical* Values of Mepolizumab PK Parameters via Population PK Analysis

Parameter	Final Estimate	95% CI
CL (L/day)	0.232	0.226 – 0.240
V1 (L)	3.21	3.10 – 3.32
Q (L/Day)	0.541	0.385 – 0.697
V2 (L)	2.21	2.05 – 2.37
V1 ~ WT exponent	0.626	0.493 – 0.759
CL ~ WT exponent	0.685	0.572 – 0.798
IIV (CL)	0.0671	0.0450 – 0.0892
IIV (V1)	0.0815	0.0448 – 0.1181
IIV (V2)	0.0858	0.0482 – 0.1234

*** Typical values of subject weighing 70 kg**
IIV: inter-individual variability
Source: adapted from CSR 12997, page 1522, Table 14.02

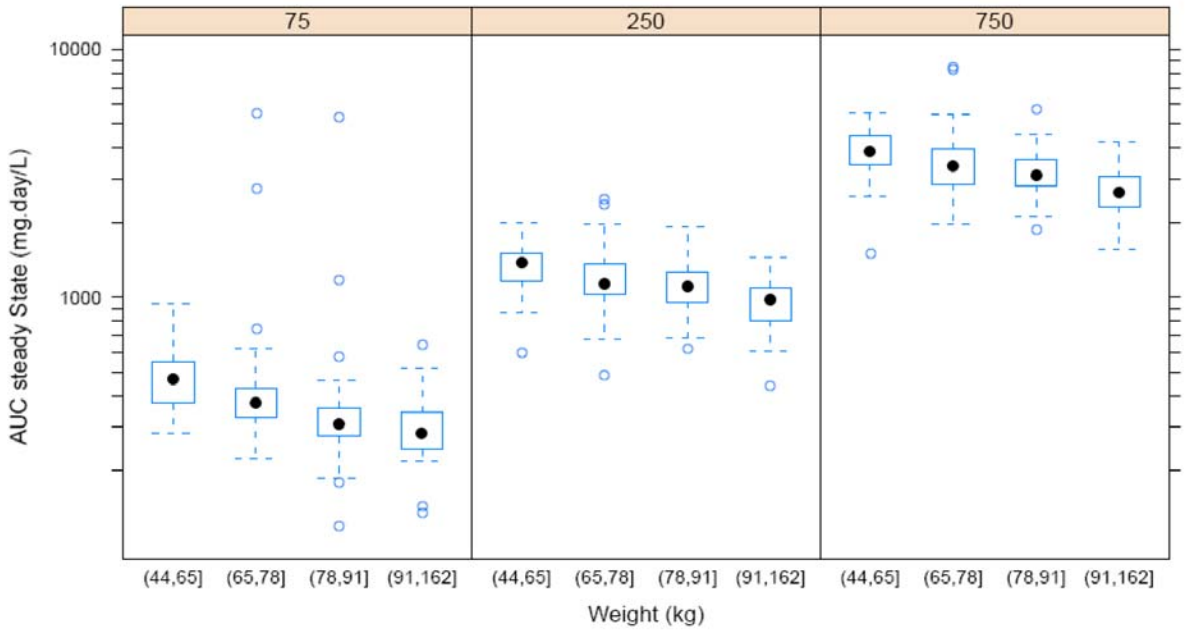

Figure 4.18 Distribution of mepolizumab $AUC_{0-\tau}$ by body weight category and dose. The parenthesis includes the body weight range in the according quantile. (Source: CSR 112997, page 138, Figure 12)

The post-hoc estimates of steady state $AUC_{0-\tau}$ and C_{min} following each dose (75, 250 and 750 mg) were presented in Table 4.18. The systemic exposure of mepolizumab appeared dose-proportional following 75 mg to 750 mg IV administration.

Table 4.18 Summary of Predicted Mepolizumab C_{min} and$AUC_{0-\tau}$ by Dose

	75 mg	**250 mg**	**750 mg**
C_{min} (ng/mL)	7191 (2135, 24219)	21247 (9431, 47868)	58680 (23970, 143654)
$AUC_{0-\tau}$ (mg·d/L)	381 (147, 990)	1127 (644, 1970)	3183 (1799, 5634)

Values were presented as geometric mean (95% CI)
Source: adapted from CSR 12997, page 137, Table 63

PD Results:

- Blood eosinophil counts
  Mean absolute blood eosinophil levels by treatment group from Day 1 to Week 56 are presented in Fig. 4.19. The eosinophil counts at baseline (pre-dose on Day 1) were 280, 250, 230 and 250 /μL for placebo, 75 mg iv, 250 mg iv, and 750 mg IV treatment group, respectively. Blood eosinophils counts decreased significantly from baseline in all three active treatment groups comparing to placebo group at any time points between Week4 and Week 52 ($p<0.001$). It appeared that the maximal reduction was reached no later than 4 weeks. The absolute values of blood eosinophil counts reduced maximally to 230 /μL, 50 /μL, 30 μL, and 30 /μL (or reduced by 18%, 80%, 87%, and 88% from the baseline) for placebo, 75 mg iv, 250 mg iv, and 750 mg IV treatment group, respectively. It appeared that the maximal reduction level could be maintained for at least 4 weeks following 48 week Q4w treatment of mepolizumab (75 mg to 750 mg iv).

- Percent sputum eosinophils
  The sputum eosinophil counts (%) at baseline (pre-dose on Day 1) were not balanced between 4 treatment groups. The values were 6.75%, 13.93%, 8.08%, and 5.8% for placebo, 75 mg iv, 250 mg iv, and 750 mg IV treatment group, respectively. There was a general trend of reduction of the eosinophil count in sputum in all treatment groups with a greater proportional in 3 active treatment

groups (Fig. 4.20). The largest decrease from baseline was observed in the mepolizumab 125 mg and 250 mg SC groups, with less of a decrease in the mepolizumab12.5 mg SC group. It is worth noting that the number of subjects who provided sputum data was small and the data were variable.

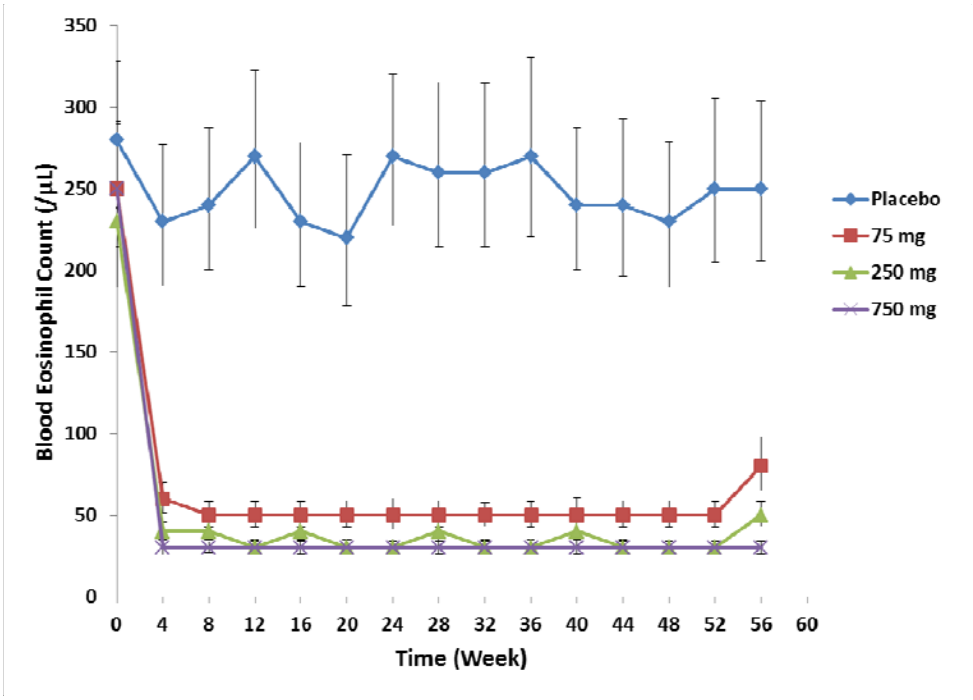

Figure 4.19 Geometric mean absolute blood eosinophil counts-time profile (±SE) in different groups: placebo (blue, N=155), 75 mg IV (brown, N=153), 250 mg IV (green, N=152), and 750 mg IV (purple, N=156). (Source: CSR 112997, page 754 - 763, Table 6.67)

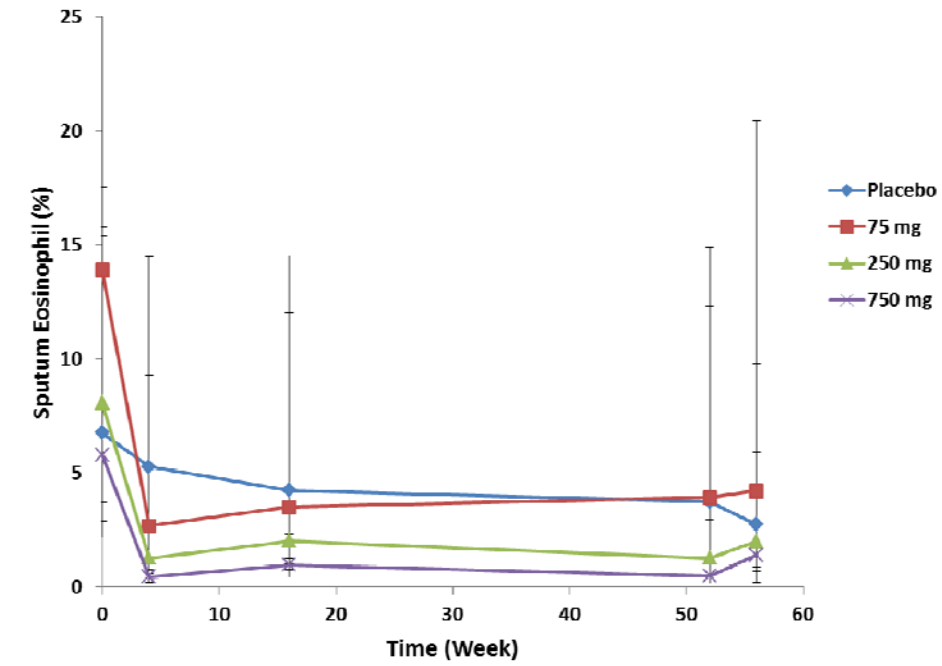

Figure 4.20 Geometric mean sputum eosinophil counts (%) over time profile (±SE) in different groups: placebo (blue, N=24), 75 mg IV (brown, N=18), 250 mg IV (green, N=23), and 750 mg IV (purple, N=21). (Source: CSR 112997, page 778 - 780, Table 6.69)

- Serum IL-5 concentrations
  The serum total IL-5 pre-dose baseline level was low. Only about 5% (30/613) subjects had measurable serum total IL-5 levels at baseline. Mean serum total IL-5 levels increased to approximately 15-fold from baseline in all the active treatment groups beginning Week 16 (Fig. 4.21). The peak level was maintained till the last dose on Week 48. There was no dose-response relationship for serum total IL-5 concentrations. The free IL-5 concentrations were below the LLQ (3.91 pg/mL) in about 95% of the samples obtained from Day 1 to Week 56. There was no dose-response relationship observed.

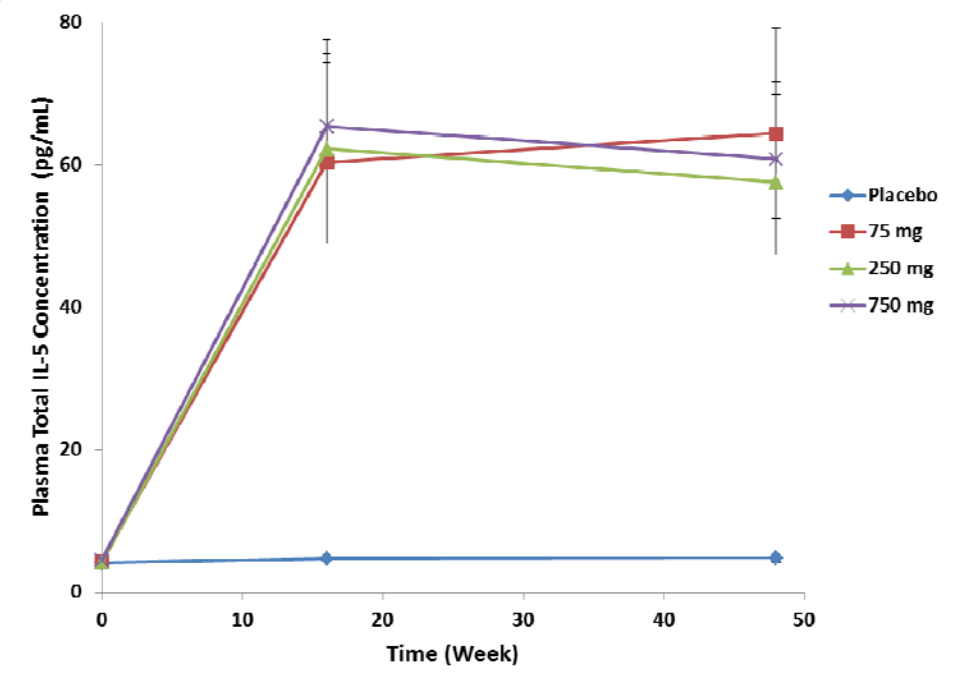

Figure 4.21 Geometric mean (± SE) serum total IL-5 concentrations in different groups: placebo (blue, N=154), 75 mg IV (brown, N=150), 250 mg IV (green, N=144), and 750 mg IV (purple, N=156). (Source: CSR 112997, page 800 and 801, Table 6.75)

- FeNO
  There were no significant reductions from baseline in FeNO in the all three mepolizumab treatment groups compared with placebo at any time during the study.

Immunogenicity Results:
The positive incidence of ADA is listed in Table 4.19 and the corresponding titre values are listed in Table 20. In the combined mepolizumab groups 6/446 (1%) subjects tested positive in the improved ADA assay at any time post-baseline. This is comparable to the false-positive rates observed in the placebo group at any time post-baseline (2/148, 1%), and at baseline in combined groups (5/607, 1%). None of the subjects receiving mepolizumab tested positive in the neutralizing antibody assay. There did not appear to be any loss of disease control or AEs associated with these ADA immunogenicity sample findings.

Table 4.19 Summary of Immunogenicity Incidence by Treatment Group

Time Points	Placebo n (%)	Mepolizumab Dose		
		75 mg n (%)	250 mg n (%)	750 mg n (%)
Week 0 (baseline)	0/155 (0)	3/152 (2)	1/150 (<1%)	1/155 (<1)
Week 16 (fourth dose of IP)	0/140 (0)	1/142 (<1)	0/141 (0)	0/148 (0)
Week 72 (16 weeks after study completion)	2/126 (2)	2/129 (2)	2/128 (2)	1/129 (<1)
At any time post-baseline	2/148 (1)	3/147 (2)	2/149 (1)	1/150 (<1)

Source: CSR 12997, page 143, Table 64

Table 4.20 Summary of the Titre of Anti-Mepolizumab Antibody in Positive Samples

			Mepolizumab Dose		
		Placebo N=155	75 mg N=153	250 mg N=152	750 mg N=156
n		148	147	149	150
Positive at any time post-baseline		2 (1%)	3 (2%)	2 (1%)	1 (<1%)
Titre value	≤4	1 (<1%)	2 (1%)	1 (<1%)	0
	>4 to ≤8	1 (<1%)	1 (<1%)	0	0
	>8 to ≤32	0	0	0	1 (<1%)
	>32	0	0	1 (<1%)	0

Source: CSR 12997, page 143, Table 64

Conclusions:

- Blood eosinophils were reduced from baseline in all three mepolizumab groups compared with the placebo group [$p<0.001$ at all measured time points (every 4 weeks from Week 4 to Week 52)].

- Although there was about 2-fold difference in sputum eosinophil baseline between different groups, there was a general trend of reduction of the eosinophil count in sputum in all treatment groups with a greater proportional in 3 active treatment groups.

- The ADA positive rate (1%) was similar between placebo group and three mepolizumab groups. The titres of ADA positive samples were low. None of the subjects receiving mepolizumab tested positive in the neutralizing antibody assay.

- The PK parameters of three doses of mepolizumab IV derived from popPK analysis from this study is compared with the PK parameters of 75 mg mepolizumab IV from study 114092 (Table 4.21). The estimated CL and V_1 were comparable between two studies.

Table 4.21 Comparison of Estimated Typical* Values of PK Parameters via Population PK analysis following IV Administration between Study 12997 and Study 114092

	Study 12997	**Study 114092**
IV Dose Range	75 mg – 750 mg	75 mg
N	460	11
CL (L/day)	0.232 (0.226, 0.240)	0.210 (0.189, 0.232)
V1 (L)	3.21 (3.10, 3.32)	3.60 (3.19, 4.05)
Q (L/day)	0.541 (0.385, 0.697)	1.01[#]
V2 (L)	2.21 (3.00-7.02)	3.56[#]

***Typical values (95% CI) of subject weighing 70 kg**
[#] Estimated from typical value of V_1, K_{12} and K_{21}
(Source: Table 4.11 and Table 4.17)

4.1.9 Study MEA115588 (Study 115588)

Study Type: Phase 3 efficacy, safety, popPK, comparison of 75 mg IV and 100 mg SC study in asthma patients
Study Dates: 10/08/2012 – 01/18/2014
Drug Product: 250 mg/vial of MDP1

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

Objective:

- The primary objective was to evaluate the efficacy of mepolizumab 75 mg IV or 100 mg SC every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent subjects with severe uncontrolled asthma with evidence of eosinophilic inflammation.

- Secondary objectives were to evaluate the safety and tolerability of mepolizumab compared with placebo and to evaluate the effects of mepolizumab compared with placebo on a range of clinical markers of asthma control including pulmonary function and St. George's Respiratory Questionnaire.

- Mepolizumab PK and the change from baseline in blood eosinophils were also evaluated.

Study Design and Method:
This investigation was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, three-parallel-group (placebo, mepolizumab75 mg IV or 100 mg SC at the back of the upper arm) study in patients with severe uncontrolled refractory asthma. A total of 580 subjects were randomized and 576 subjects received at least one dose of study drug (about 190 patients per group). 539 subjects completed study. Total 25 adolescents were randomized. The dosing interval was every 4 weeks. Total 8 doses were administered (last dose was given at Week 28).

Enrolled subjects had to have a documented requirement for regular treatment with high-dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids and require additional controller medication besides ICS. Subjects also had to have prior documentation or a high likelihood of eosinophilic asthma and, if ≥18 years of age, have persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 <80% predicted; subjects 12-17 years of age had to have a pre-bronchodilator FEV1 <90% predicted, or an FEV1: forced vital capacity (FVC) ratio <0.8 at Visit 1. Subjects further had to have a history of two or more asthma exacerbations requiring treatment with systemic corticosteroids (CS) in the 12 months prior to Visit 1, despite the use of high-dose ICS. At the end of the run-in period, subjects were eligible to be randomized if they had an eosinophilic phenotype characterized by peripheral baseline eosinophil level ≥150 /μL, or blood eosinophil level of ≥300 /μL within the previous 12 months while receiving high-dose ICS plus at least one other controller medication.

Blood samples for PK analysis were collected from all the treated patients at pre-dose on Day1, Week 4, Week16, Week 32 and Week 40. PK samples were collected at Week 17 in a subset of patients. The PK parameters were estimated by population PK analysis. The IV and SC data were analyzed separately by two different popPK models.

Human Plasma concentrations of mepolizumab in Study MEA115588 were determined by a single ELISA method by (b) (4). The same analytical method was used in study 114092. The LLQ for mepolizumab was 50.0 ng/mL.

Immunogenicity samples were collected pre-dose at Day 1, Week16, Week 32 and Week 40. Samples for blood eosinophil counts were collected pre-dose at Day 1, and every 4 weeks from Week 4 to Week 32.

PK Results:

- Mepolizumab 75 mg iv

Of the 191 subjects randomized to the 75 mg IV treatment group, 188 subjects contributed 605 concentrations to the analysis. Each subject contributed a median of three mepolizumab concentrations. 10 subjects displayed measurable concentration prior to initiating mepolizumab treatment and those concentrations were excluded from the analysis. A total of 14 concentrations (ten pre-treatment and four post-dosing) were excluded from the analysis.

The key parameter estimates from the final model are presented in Table 4.22. Forward and backward selection methods retained body weight, albumin concentration and creatinine clearance as statistically significant determinants of exposure. The inter-subject variability in clearance was relatively low (CV=20.8%). An increase in clearance was seen with increasing body weight. The mean clearance in patients with body weight >90 kg category was 74% higher than patients with body weight ≤ 60 kg category (Fig. 4.22).

Table 4.22 Estimated Typical* Values of Mepolizumab PK Parameters by Population PK Analysis via Intravenous Route (Final Model)

Parameter	Final Estimate	95% CI
CL (L/day)	0.220	0.210 – 0.232
V1 (L)	4.85	4.06 – 5.70
Q (L/day)	0.123	0.0719 – 0.254
V2 (L)	1.65	1.29 – 2.33
CL ~ WT exponent	0.75 FIX	-
V1 ~ WT exponent	1.0 FIX	-
V2 ~ WT exponent	1.0 FIX	-

*** Typical values of subject weighing 70 kg**
Source: adapted from CSR 115588, page 1456, Table 10.04

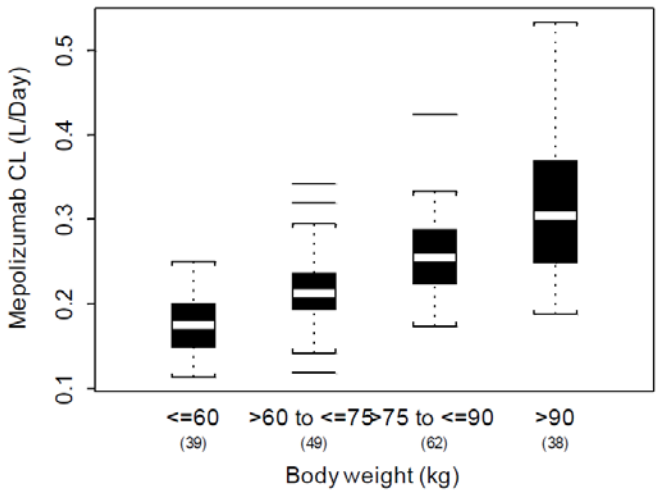

Figure 4.22 Distribution of mepolizumab clearance (L/day) by body weight category following 75 mg IV administration. The parenthesis includes the body weight range in the according quantile. (Source: CSR 115588, page 1360, Figure 10.03.6b)

Based on the model predicted C_{trough} values, the accumulation ratios for Week 16/Week 4 and Week 32/Week 4 were 1.71 (95% CI = 0.741, 2.80) and 1.66 (95% CI=0.697, 2.78), respectively. Therefore the steady state appeared achieved by Week 16.

- Mepolizumab 100 mg sc

Of the 194 subjects randomized to the SC treatment group, 189 mepolizumab-treated subjects contributed 621 concentrations to the analysis. Each subject contributed a median of three mepolizumab concentrations. 15 subjects displayed measurable concentration prior to initiating mepolizumab treatment. A total of 26 concentrations (15 pre-treatment and 11 post-dosing) were excluded from the analysis.

The key parameter estimates from the final model are presented in Table 4.23. Forward and backward selection methods only detected body weight as the significant covariate for apparent clearance (CL/F). However, to be consistent with the IV model, albumin concentration and creatinine clearance were retained in the final model. The inter-subject variability in clearance was relatively low (CV=28.7%). An increase in clearance was seen with increasing body weight. The mean clearance in patients with body weight >90 kg category was 78% higher than patients with body weight ≤ 60 kg category (Fig. 4.23).

Table 4.23 Estimated Typical* Values of Mepolizumab PK Parameters by Population PK Analysis via Subcutaneous Route (Final Model)

Parameter	Final Estimate	95% CI
CL/F (L/day)	0.280	0.267 – 0.295
V2/F (L)	4.44	4.14 – 4.76
Ka (/day)	0.289	0.212 – 0.394
K_{23} (/day)	0.280 FIX	-
K_{32} (/day)	0.283 FIX	-
CL ~ WT exponent	0.75 FIX	-
V2 ~ WT exponent	1.0 FIX	-

*** Typical values of subject weighing 70 kg**
Source: adapted from CSR 115588, page 1456, Table 10.04

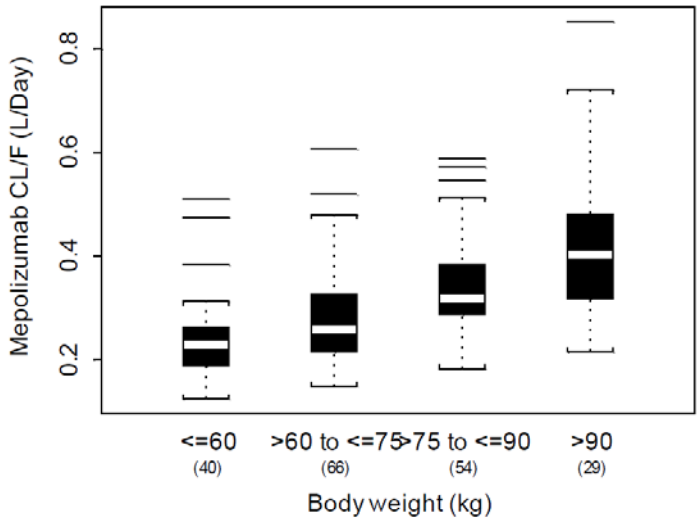

Figure 4.23 Distribution of mepolizumab apparent clearance (L/day) by body weight category following 100 mg SC administration. (Source: CSR 115588, page 1311, Figure 10.03.6b)

Based on the model predicted C_{trough} values, the accumulation ratios for Week 16/Week 4 and Week 32/Week 4 were 1.72 (95% CI = 1.05, 2.46) and 1.65 (95% CI=0.683, 2.78), respectively. Therefore the steady state appeared achieved by Week 16.

- Absolute bioavailability assessment

Log-transformed estimated CL values following IV and SC administrations were analyzed by ANOVA model in Pharsight Phoenix Build 6.2.1.51.The absolute bioavailability of the subcutaneous route was assessed and estimated to be 79.6% (90% CI: 75.5%–83.9%)

PD Results:

- Blood eosinophil counts

  Mean absolute blood eosinophil levels by treatment group from Day 1 to Week 32 are presented in Fig. 4.24. The eosinophil counts at baseline (pre-dose on Day 1) were 320, 280 and 290 /µL for placebo, 75 mg iv, and 100 mg SC treatment group, respectively. Blood eosinophils counts decreased significantly from baseline in both active treatment groups comparing to placebo group at any time points between Week 4 and Week 32 ($p<0.001$). It appeared that the maximal reduction was reached no later than 4 weeks. The absolute values of blood eosinophil counts reduced maximally to 240 /µL, 50 /µL, and 40 /µL (or reduced by 25%, 82%, and 86% from the baseline) for placebo, 75 mg iv, and 100 mg SC treatment group, respectively. It appeared that the maximal reduction level could be maintained for at least 4 weeks following 28 week Q4w treatment of mepolizumab (75 mg IV or 100 mg sc).

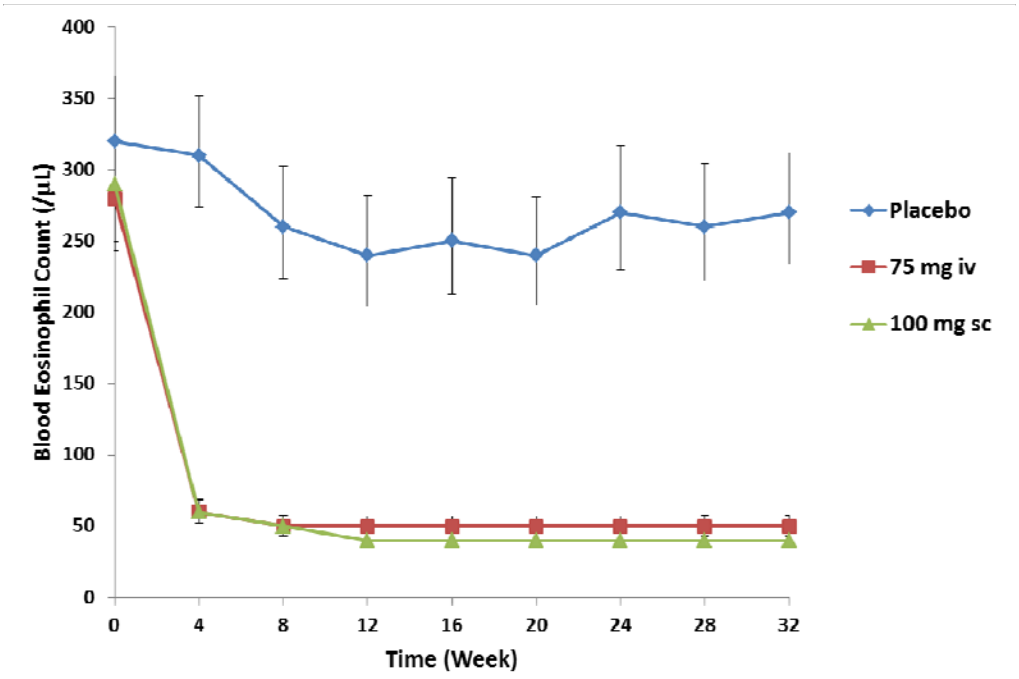

Figure 4.24 Geometric mean (±SE) absolute blood eosinophil counts-time profile in different groups: placebo (blue, N=189), 75 mg IV (brown, N=188), and 100 mg SC (green, N=192). (Source: CSR 115588, page 583 - 587, Table 6.73)

Immunogenicity Results:
A total of 576 subjects were tested for the presence of anti-mepolizumab antibody results. 2 subjects (subjects 810 and 903) were positive at baseline (Table 4.24). 19 subjects had confirmed positive anti-mepolizumab antibody results for at least one visit after baseline. 5 of these 19 subjects were in the placebo group. No subjects tested positive for neutralizing activity. Overall, there did not appear to be any loss of disease control or trends in AEs associated with these immunogenicity sample findings.

Table 4.24 Summary of Immunogenicity Incidence by Treatment Group

Time Points	Placebo N (%)	75 mg IV N (%)	100 mg SC N(%)
Week 0 (Baseline)	0/189 (0)	1/190 (<1%)	1/194 (<1%)
Week 16	3/183 (2%)	7/182 (4%)	8/186 (4%)
Week 32	2/177 (1%)	3/175 (2%)	4/179 (2%)
Week 40	0/6 (0)	1/11 (9%)	1/12 (8%)
At any time post-baseline	3/188 (2%)	7/187 (4%)	9/191 (5%)

Source: adapted from CSR 115588, page 1148, Table 8.01

Conclusions:

- The absolute bioavailability of the subcutaneous route was estimated to be approximately 80%. Therefore, the systemic exposure between 75 mg IV and 100 mg SC were comparable.

- Based on the model predicted C_{trough} values, the steady state was reached by week 16 and the accumulation ratio was approximately 1.7 at steady state.

- Body weight was identified as the only significant covariate for apparent clearance (CL/F) following SC administration. The mean clearance in patients with body weight >90 kg category was 78% higher than patients with body weight ≤ 60 kg category.

- The PK parameters of mepolizumab IV derived from popPK analysis from individual studies are compared in Table 4.25. The estimated CL were comparable across three studies.

Table 4.25 Comparison of Estimated Typical* Values of PK Parameters via Population PK analysis following IV Administration in Three Studies

	Study 114092	Study 12997	Study 115588
IV Dose Range	75 mg	75 mg – 750 mg	75 mg
N	11	460	191
CL (L/day)	0.210 (0.189, 0.232)	0.232 (0.226, 0.240)	0.220 (0.210, 0.232)
V1 (L)	3.60 (3.19, 4.05)	3.21 (3.10, 3.32)	4.85 (4.06, 5.70)
Q (L/day)	1.01[#]	0.541 (0.385, 0.697)	0.123 (0.0719, 0.254)
V2 (L)	3.56[#]	2.21 (3.00-7.02)	1.65 (1.29, 2.33)

Values presented as geometric mean (95% CI)
*** Typical values of subject weighing 70 kg**
[#] Estimated from typical value of V_1, K_{12} and K_{21}
(Source: Table 4.11, Table 4.17 and Table 4.22)

- The blood eosinophil reduction-time profiles were similar between 75 mg IV and 100 mg SC groups. The maximal reduction was reached no later than 4 weeks with trough values of 50 /μL, and 40 /μL for 75 mg IV and 100 mg sc, respectively. The placebo had much less reduction effect on blood eosinophil counts with mean trough value of 240 /μL.

- ADA was detected positive in 2 patients before mepolizumab treatment. ADA positive rates in mepolizumab treatment groups were approximately 2-fold as the values in placebo group at Week 16 and Week 32. None of the subjects receiving mepolizumab tested positive in the neutralizing antibody assay.

4.1.10 Study MEA115575 (Study 115575)

Study Type: Phase 3 efficacy, safety, popPK, 100 mg SC study in asthma patients
Study Dates: 10/29/2012 – 12/12/2014
Drug Product: 250 mg/vial of MDP1

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

Objective:

- The primary objective of the study was to compare the effects of mepolizumab adjunctive therapy with placebo on reducing the use of maintenance oral corticosteroids (OCS) in systemic corticosteroid-dependent subjects with severe asthma with elevated eosinophils.

- Secondary objectives were to compare the efficacy, safety, and tolerability of mepolizumab compared with placebo, in subjects with severe asthma with elevated eosinophils including an evaluation of the effects of mepolizumab on markers of asthma impairment and risk including asthma symptoms, pulmonary function, exacerbation rate, and quality of life (QoL) as assessed by the St. George's Respiratory Questionnaire (SGRQ).

- Mepolizumab PK and the change from baseline in blood eosinophils were also evaluated.

Study Design and Method:
This investigation was a multi-center, randomized, double-blind, placebo-controlled, two-parallel-group (placebo, mepolizumab 100 mg sc) study in patients with severe refractory asthma. A total of 135 subjects were randomized to placebo group (N=66) and mepolizumab group (N=69) and majority of subjects (95%) completed the study. Only 2 adolescents were randomized into mepolizumab group. The study consisted of 3-10 weeks optimization phase, 4-week induction phase, 16-week OCS reduction phase, and 4-week maintenance phase. Total 6 doses of mepolizumab 100 mg SC or placebo will be administered during induction and OCS reduction phases. The SC injection site was at the upper arm. The dosing interval was 4 weeks.

Enrolled subjects had to demonstrate 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 the randomization Visit or a peripheral baseline eosinophil level ≥150 cells /μL between the screening Visit and the randomization Visit that was related to asthma. Subjects with severe eosinophilic asthma had to have regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisone or equivalent) and high-dose inhaled corticosteroids (ages ≥18: ≥880 μg/day fluticasone propionate or equivalent; ages 12-17 ≥440 μg/day fluticasone propionate or equivalent) in the 6 months prior to Visit 1. Subjects had to also be receiving current treatment with an additional controller medication for at least 3 months or documentation of having used and failed an additional controller medication for at least 3 successive months during the prior 12 months.

Three blood samples per subject for the PK analysis of mepolizumab were taken pre-dose at the Week 4, Week 20, Week 24 visits and at Follow-up visits. The PK data were analyzed by popPK models.

Human Plasma concentrations of mepolizumab in Study 115575 were determined by a single ELISA method by (b) (4). The same analytical method was used in study 114092 and 115588. The LLQ for mepolizumab was 50.0 ng/mL.

Immunogenicity samples were collected pre-dose at Day 1, Week16, Week 24 and at follow up. Samples for blood eosinophil counts were collected pre-dose at Day 1, and every 4 weeks from Week 4 to Week 32.

PK Results:
A total of 69 mepolizumab-treated subjects contributed 202 concentrations to the analysis. Three concentrations were deemed to be outlier concentrations. The previously developed model following mepolizumab SC administration from study 114092 was used. Bodyweight was included as a structural covariate in the model. No formal analysis other covariates were evaluated.

The key parameter estimates from the final model are presented in Table 4.26. The inter-subject variability in clearance was relatively low (CV=32.9%). An increase in clearance was seen with increasing body weight. The mean clearance in patients with body weight >85 kg category was 44% higher than patients with body weight ≤ 70 kg category (Fig. 4.25).

Table 4.26 Estimated Typical* Values of Mepolizumab PK Parameters by Population PK Analysis via Subcutaneous Route (Final Model)

Parameter	Final Estimate	95% CI
CL/F (L/day)	0.326	0.267 – 0.398
V2/F (L)	5.75	4.85 – 6.82
K_{23} (/day)	0.280 FIX	-
K_{32} (/day)	0.283 FIX	-
Ka (/day)	0.115	0.0311 – 0.427
CL ~ WT exponent	0.75 FIX	-
V2 ~ WT exponent	1.0 FIX	-

*** Typical values of subject weighing 70 kg**
Source: adapted from CSR 115575, page 906, Table 10.04

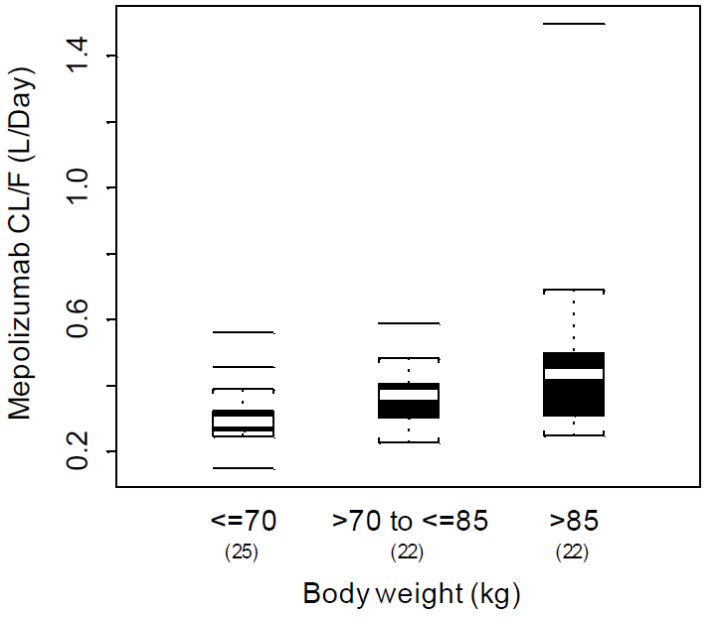

Figure 4.25 Distribution of mepolizumab clearance (L/day) by body weight category following 100 mg SC administration. The parenthesis includes the body weight range in the according quantile. (Source: CSR 115575, page 877, Figure 10.03.6)

Of note, Subject 1733, who tested positive for anti-mepolizumab neutralizing antibody at the early withdraw visit (Week 13) and follow-up visit (Week 32), had mepolizumab plasma concentrations below the limit of quantification in both samples. This was most likely due to the neutralizing antibody interference with the mepolizumab assay and therefore concentrations were not reportable.

Two adolescents, both 16 years old with bodyweights of 74 and 80 kg, were enrolled in this study and displayed plasma concentrations within the range of the adult subjects. Similarly, their predicted apparent clearance was within the adult range.

Based on the model predicted C_{trough} values, the accumulation ratios for Week 20/Week 4 and Week 24/Week 4 were 1.98 (95% CI = 1.33, 2.77) and 1.94 (95% CI=1.19, 2.78), respectively. Therefore the steady state appeared achieved by Week 20.

PD Results:

- Blood eosinophil counts
  Mean absolute blood eosinophil levels by treatment group from Day 1 to Week 32 are presented in Fig. 4.26. The eosinophil counts at baseline (pre-dose on Day 1) were similar between two cohorts with 230 /µL and 250 /µL for placebo and 100 mg SC treatment group, respectively. Blood eosinophils counts decreased significantly from baseline 100 mg SC groups comparing to placebo group at any time points between Week 4 and Week 24 ($p<0.001$). It appeared that the maximal reduction was reached no later than 4 weeks following the mepolizumab treatment. The absolute values of blood eosinophil counts reduced maximally to 40 /µL (or reduced by 84% from the baseline) for 100 mg SC treatment group. On the contrary, the absolute values of blood eosinophil counts increased to 320 /µL (or 39% increase from the baseline) for placebo group at week 24.

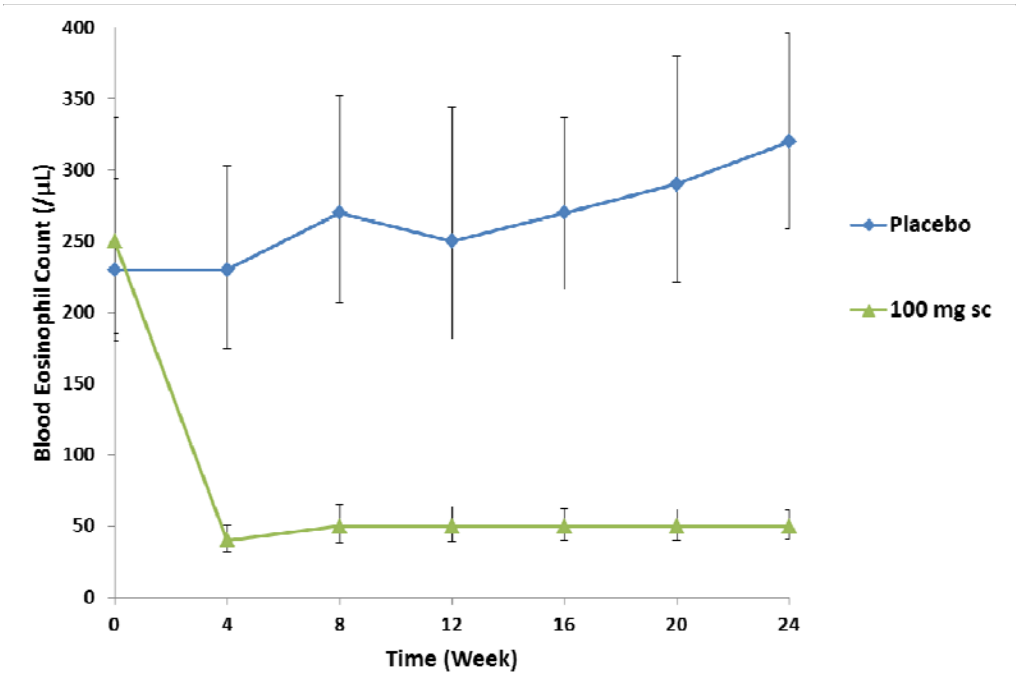

Figure 4.26 Geometric mean absolute blood eosinophil counts-time profile (±SE) in different groups: placebo (blue, N=66) and 100 mg SC (green, N=69). (Source: CSR 115575, page 428 - 430, Table 6.59)

Immunogenicity Results:
A total of 135 subjects from the mepolizumab and placebo treatment groups were tested for the presence of anti-mepolizumab antibodies. No subjects in the placebo group tested positive for anti-mepolizumab antibodies (Table 4.27). Six subjects in the mepolizumab treatment group had confirmed positive anti-mepolizumab antibody results for at least one visit after baseline. No subjects had pre-existing antibodies at baseline. Subject 1733 tested positive for anti-mepolizumab neutralizing antibody at the early withdraw visit (Week 13) and at the follow-up visit (Week 17).

Table 4.27 Summary of Immunogenicity Incidence by Treatment Group

Time Points	Placebo N (%)	100 mg SC N(%)
Week 0 (Baseline)	0/66 (0)	0/69 (<0%)
Week 16	0/64 (0)	5/67 (7%)
Week 24	0/63 (0)	4/66 (6%)
Follow Up	0/3 (0)	1/2 (50%)
At any time post-baseline	0/66 (0)	6/69 (9%)

Source: adapted from CSR 115575, page 800, Table 8.01

Subject 1733 was 66-yeal-old female. The subject entered the treatment phase on a maintenance OCS dose of 5 mg/day and met protocol criteria for OCS dose reduction to 2.5 mg/day following 4-week treatment of 100 mg mepolizumab SC (first dose) and reduction to 1.25 mg/day following 8-week treatment (second and the last dose). The subject had a significant asthma exacerbation at 9 days, and the second exacerbation 37 days, following the second and the last dose. The subject withdrew at 63 days (Week 13) following the second and the last dose.

Three PK samples were collected for this subject: the pre-second dose concentration was within the range of the other subjects' concentration; the mepolizumab concentrations in the PK samples on the early withdraw day (Week 13) and follow-up day (Week 17) were below the LOQ.

Three ADA samples were collected for this subject: at baseline (Week 0), the ADA testing was negative; at the early withdrawal visit (Week 13), the ADA results were positive with a titre of 160 and the neutralizing antibody testing was also positive; the ADA titre increased to 640 at the follow-up visit (Week 17) and the neutralizing antibody testing kept positive.

The blood eosinophil counts of this subject kept very low (0 – 10 cells /μL) from the baseline to the follow-up visit. Therefore, the impact of the neutralization antibody on blood eosinophil count is unknown.

Among ADA positive patients, the most common AE was nasopharyngitis, which occurred in 2 of the 6 subjects compared with 10 of the 66 placebo-treated subjects. No subjects with ADA positive reported an SAE on study.

Conclusions:

- Based on the model predicted C_{trough} values, the steady state was reached by week 20 and the accumulation ratio was approximately 2 at steady state.

- Body weight was kept as the significant covariate for apparent clearance (CL/F) following SC administration. The mean clearance in patients with body weight >85 kg category was 44% higher than patients with body weight ≤ 70 kg category.

- The blood eosinophil reduction-time profiles following mepolizumab 100 mg SC from this study was similar to that observed in study 115588. The maximal reduction was reached no later than 4 weeks with trough values of 40 /μL.

- ADA was not negative in all the samples from placebo group. The ADA positive rate was 9% (6/69) in mepolizumab 100 mg SC group. No samples were test positive at the baseline. One subject was positive on neutralizing antibody starting Week 13. That subject only received two doses and withdrew from the study on Week 13. The mepolizumab concentration was LOQ from the samples collected on Week 13 and Week 17. The concentration collected at predose on Week 4 appeared within the normal range of the other subjects' concentration.

- The PK parameters of mepolizumab 100 mg SC derived from popPK analysis from this study was compared with the results from study 92 and 115588 in Table 4.28. The estimated CL/F were comparable across three studies.

Table 4.28 Comparison of Estimated Typical* Values of PK Parameters via Population PK analysis following Subcutaneous Administration in Three Studies

	Study 114092	**Study 115588**	**Study 115575**
Dose Range	12.5 mg to 250 mg	100 mg	100 mg
N	59	194	69
CL/F (L/day)	0.310 (0.275, 0.349)	0.280 (0.267, 0.295)	0.326 (0.267, 0.398)
V2/F (L)	4.57 (4.02, 5.20)	4.44 (4.14, 4.76)	5.75 (4.85, 6.82)
K_{23} (/day)	0.280 FIX	0.280 FIX	0.280 FIX
K_{32} (/day)	0.283 FIX	0.283 FIX	0.283 FIX
Ka (/day)	0.194 (0.155, 0.242)	0.289 (0.212 – 0.394)	0.115 (0.0311, 0.427)

*** Typical values (95% CI) of subject weighing 70 kg**
(Source: Table 4.11, 4.23, and Table 4.26)

4.1.11 Study MEA115705 (Study 115705)

Study Type: Phase 1 single dose, dose-ranging PK, PD and safety study in healthy Japanese male patients
Study Dates: 08/09/2011 – 04/27/2012
Drug Product: 250 mg/vial of MDP1

Title:
A single blind, placebo controlled, parallel group, single ascending intravenous dose study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of SB-240563 (mepolizumab) in healthy Japanese male subjects.

Objective:

- The primary objective were:
  - To assess the PK of SB-240563 in healthy Japanese male subjects.
  - To assess the safety and tolerability of SB-240563 in healthy Japanese male subjects.

- The secondary objective were:
  - To assess the effect of SB-240563 on blood eosinophil count in healthy Japanese male subjects.
  - To assess the effect of SB-240563 on free and total IL-5 levels in healthy Japanese male subjects.
  - To assess the immunogenicity of SB-240563 in healthy Japanese male subjects.

Study Design and Method:
This investigation was a randomized, single-blind, placebo-controlled, four-parallel-group, single IV dose (infusion time 30 min), dose-ranging (10 mg, 75 mg, 250 mg and 750 mg) study in 35 male Japanese healthy subjects with 33 completed the study. The study was conducted in four groups and within each group patients were randomized to SB-240563 or placebo in a 3:1 ratio (Table 4.29):

Table 4.29 Description of Each Treatment Group in Study 115705

Cohort	N	Treatment
1, Active	6	10 mg mepolizumab iv
2, Active	6	75 mg mepolizumab iv
3, Active	7	250 mg mepolizumab iv
4, Active	7	750 mg mepolizumab iv
1-4, Placebo	9	saline iv

(Source: CSR 115705, page 17, Table 2)

Potential patients with a documented history of asthma and a bronchial hyper-responsiveness to histamine (PC20 less than 8 mg/ml measured in the last 3 months) were selected. All subjects were currently using only inhaled β2-agonists to control their asthma.

Blood samples for PK evaluation were drawn at pre-dose, and at the following times after the start of the infusion on Day 1: 15, 30 minutes, and 1, 2, 4, 8, 12 and 24 hours. Additionally, samples were collected on each of the following study days: 3, 6, 8, 15, 29, 43, 57 and follow-up days (Day 85, Day 85, Day121, and 153 for 10 mg, 75 mg, 250 mg, and 750 mg group, respectively). Samples for blood eosinophil counts were collected at predose, 12 and 24 hours. Additional samples were collected on Day 6, 15, 29, 43, 57 and follow-up days. Samples for IL-5 measurement were collected at predose, 1, 12, and 24 hours.

Additional samples were collected on Day 4, 8, 15, 29, 43, 57 and follow-up days. ADA samples were collected at predose, Day 8, Day 29, and follow-up days.

Human Plasma concentrations of mepolizumab in Study 115705 were determined by a single ELISA method by [redacted] (b) (4) The same analytical method was used in study 114092,115588 and 115575. The LLQ for mepolizumab was 50.0 ng/mL using a 100 µL aliquot of heparin plasma. The higher limit of quantification (HLQ) was 5000 ng/mL.

Primary Endpoints:

- The PK endpoints PK parameters (i.e. C_{max}, T_{max}, AUC, CL, V_{ss}) of SB-240563 summarized descriptively by dose groups.

- Safety and tolerability parameters including vital signs, electrocardiograms (ECGs), clinical laboratory tests and adverse events (AEs).

PK Results:

Following a 30 minute continuous infusion, SB-240563 concentrations declined in a bi-exponential manner (Fig. 4.27). The median T_{max} was 1, 2.5, 1 and 0.5 hours for 10 mg, 75 mg, 250 mg, and 750 mg groups, respectively (Table 4.30). C_{max} and $AUC_{0\text{-inf}}$ generally increased dose proportionally from 75 mg to 750 mg. In addition, the variations of mean CL and V_{ss} were 27% and 48% within different dosing groups. The mean terminal half-life was about 20 to 36 days.

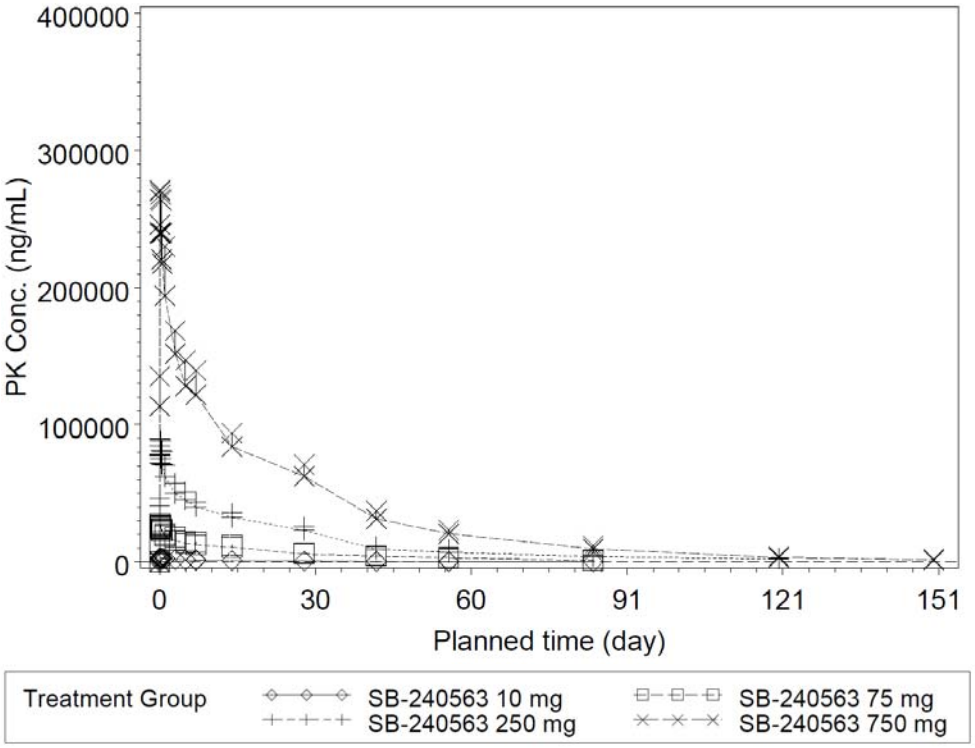

Figure 4.27 Mean (SD) SB-240563 plasma concentration-time profiles following single dose IV administration of 10 mg (n=6), 75 mg (n=6), 250 mg (n=7), and 750 mg (n=7) SB-240563. (Source: CSR 115705, page 424, Figure 3.01)

Table 4.30 Mean (SD) PK Parameters for SB-240563 Following Single Intravenous Administration

Parameter (unit)	SB-240563			
	10 mg (N=6)	75 mg (N=6)	250 mg (N=7)	750 mg (N=7)
AUC(0-∞) (day*ug/mL)	54.63 (12.27)	493.36 (41.07)	1698.66 (172.17)	4495.64 (413.79)
AUC(0-t) (day*ug/mL)	47.99 (6.47)	469.14 (42.77)	1460.74 (270.47)	4448.41 (400.21)
Cmax (ug/mL)	2.87 (0.27)	26.46 (1.81)	79.26 (11.60)	253.65 (28.28)
tmax (day)	0.042 (1*) (0.02- 0.04)	0.104 (2.5*) (0.04- 0.17)	0.042 (1*) (0.02- 0.08)	0.021 (0.5*) (0.02- 0.33)
t1/2 (day)	27.43 (10.36)	19.80 (2.42)	36.14 (11.30)	22.65 (2.32)
Vss (L)	6.52 (0.77)	4.40 (0.69)	5.65 (1.35)	4.98 (0.54)
CL (mL/hr)	7.87 (1.68)	6.37 (0.55)	6.19 (0.63)	7.01 (0.74)

All parameters reported as arithmetic mean (SD) except for Tmax which is median (range)
(Source: CSR 115705, page 34)

PD Results:

- Blood eosinophil count
  Mean levels of blood eosinophils at baseline were similar between different groups (203 – 242 /µL) except 750 mg group (354 /µL). Following single IV dose of mepolizumab, blood eosinophil count decreased to 50% at 24 hours for all the active treatment groups. The maximum reduction occurred on Day 6, 29, 29, and 43 for 10, 75, 250, and 750 mg groups, respectively (Fig.4.28). The maximum percentage reduction values for placebo, 10, 75, 250, and 750 mg groups were approximately 50%, 65%, 77%, 76%, and 90% from the baseline, respectively (or maximally reduced to 120, 75, 47, 48, and 37 /µL, respectively). The reduction plateau phase appeared lasted till Day 57 following the single dose administration.

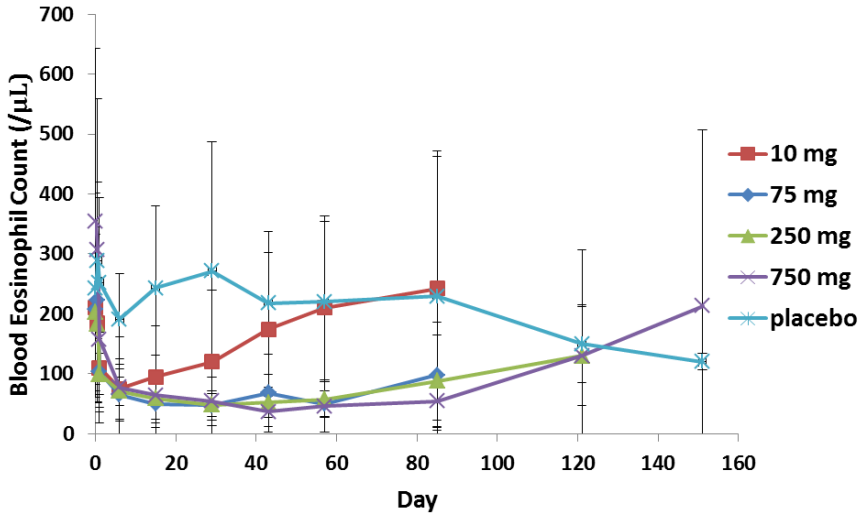

Figure 4.28 Mean absolute blood eosinophil counts-time profile (±SD) in different groups: 10 mg IV (brown, N=6), 75 mg IV (dark blue, N=6), 250 mg IV (green, N=7), 750 mg (purple, N=7) and placebo

(light blue, N=9, but only 4 subjects on Day 121 and 2 subjects on Day 151). (Source: CSR 115705, page 36, Table 13)

- Serum IL-5 concentration
  The serum total IL-5 pre-dose baseline level was low. Only about 9% (3/32) subjects had measurable serum total IL-5 levels at baseline. In the placebo group, serum total IL-5 levels remained essentially unchanged during the study. Mean serum total IL-5 levels increased from baseline post-dosing in a dose dependent manner (Fig. 4.29). The peak values were 20.3, 29.4, 39.7, and 117.3 pg/mL for 10, 75, 250, and 750 mg groups, respectively. The free IL-5 concentrations were below the LLQ (3.91 pg/mL) in about 92% of the samples collected throughout the study. There was no dose-response relationship observed.

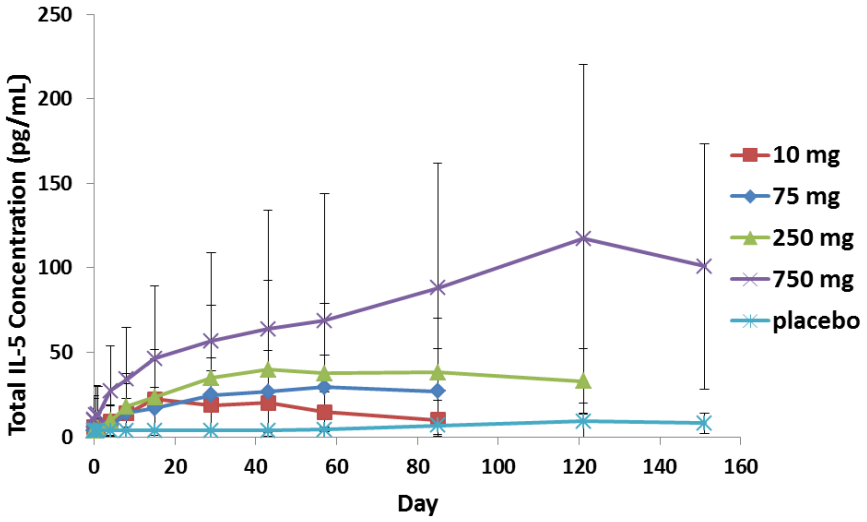

Figure 4.29 Arithmetic mean (± SD) serum total IL-5 concentrations in different groups: 10 mg IV (brown, N=6), 75 mg IV (dark blue, N=6), 250 mg IV (green, N=7), 750 mg (purple, N=7) and placebo (light blue, N=9, but only 4 subjects on Day 121 and 2 subjects on Day 151). (Source: CSR 115705, page 38, Table 14)

Immunogenicity Results:
All 35 subjects were tested for the presence of anti-mepolizumab antibody. None of the subjects were positive at baseline (Table 4.31). None of the subjects following placebo treatments were positive on ADA. 5/26 (19%) of subjects following active treatments had confirmed ADA positive. No subjects tested positive for neutralizing activity.

Table 4.31 Summary of Immunogenicity Incidence by Treatment Group

Time Points	Placebo N (%)	Mepolizumab			
		10 mg N (%)	75 mg N (%)	250 mg N (%)	750 mg N (%)
Day 1 (pre-dose)	0/9 (0)	0/6 (0)	0/6 (0)	0/7 (0)	0/7 (0)
Day 8	0/9 (0)	3/6 (50%)	1/6 (17%)	1/7 (14%)	0/7 (0)
Day 29	0/9 (0)	1/6 (17%)	0/6 (0)	0/6 (0)	0/7 (0)
Day 85	0/8 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/7 (0)
Day 121	0/4 (0)	N/A	N/A	0/6 (0)	0/7 (0)
Day 151	0/2 (0)	N/A	N/A	N/A	0/7 (0)
At any time	0/9 (0)	3/6 (50%)	1/6 (17%)	1/7 (14%)	0/7 (0)

(Source: CSR 115705, page 40, Table 16)

Conclusions:

- There was overall dose-proportional increase of mepolizumab AUCs and C_{max} following single intravenous infusions of mepolizumab over the range of 10 to 750 mg. The mean terminal half-life was about 20 to 36 days.

- There was overall dose-related reduction of blood eosinophil count over the range of 10 to 750 mg mepolizumab in terms of the maximal reduction.

- There was overall dose-related increase of serum total IL-5 values following single intravenous infusions over the range of 10 to 750 mg.

- The geometric mean of clearance summarized from 26 patients via non-compartment method from this study was 0.162 L/day (N=26, 95% CI=0.152, 0.173). The value was about 30% lower than the geometric mean obtained from study 112997 via popPK analysis [0.232 L/day (N=443, 95% CI=0.226, 0.240)].

4.1.12 In Vitro Study 10DMW042

Study Type: In vitro drug-drug interaction study in cultured human hepatocytes
Study Dates: 12/06/2010 – 05/23/2011

Title:
An In Vitro Evaluation of the Effect of Mepolizumab (SB-240563) and Cytokines IL-5 and IL-6 on the mRNA Levels of Cytochrome P450 3A4 in Cultured Human Hepatocytes

Objective:
The objective of this study is to evaluate the effects of mepolizumab, cytokines IL-5 and IL-6 on the mRNA levels of cytochrome P450 (CYP) enzymes in cultured human hepatocytes using TaqMan™ analysis.

Study Design and Method:
Acclimatized hepatic cells were incubated with mepolizumab (60, 300 600, 3000, 6000, 30000, 60000, 300000 and 600000 ng/mL), IL-5 and IL-6 (10, 50, 100, 500, 1000, 5000, 10000, 50000 and 100000 pg/mL) or rifampicin (10 μM) for 48 hours before the total RNA extraction. Extracted total RNA was treated with DNase followed by RT-PCR with CYP3A4-specific primers. The CYP3A4 mRNA levels were normalized by housekeeping gene GAPDH mRNA levels. The PCR cycling threshold values were determined by the PE Biosystems ABI 7900sequencer software. The Grafit software package was used to estimate an IC50 value with a simple weighting fit.

Results:
- Following exposure of cultured human hepatocytes to mepolizumab for 48 hours no notable changes in the mean mRNA levels of CYP3A4 were observed (Figure 4.30).

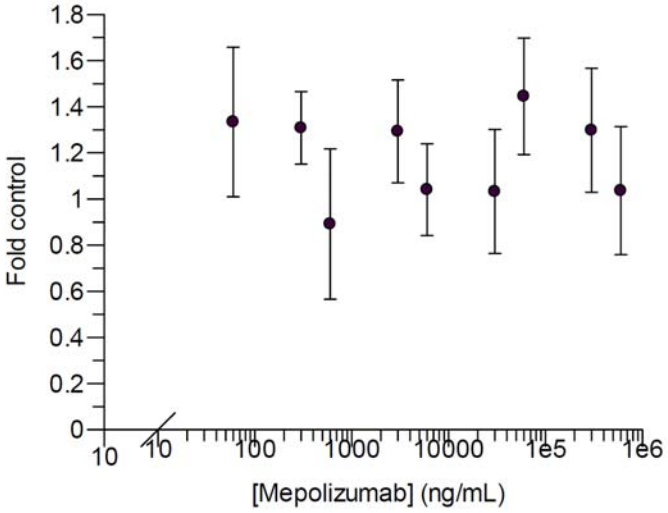

Figure 4.30 Mean (± SD) effect of mepolizumab treatment of CYP3A4 mRNA levels in cultured human hepatocytes (N=3, mean ration of treated over control). (Source: NCSR 10DMW042, Page 16, Figure 1)

- Following exposure of cultured human hepatocytes to IL-5 for 48 hours a mean decrease of >69% CYP3A4 mRNA was observed at concentrations > 1000 pg/mL. Non-linear fitting of the data was possible for the mean of the 3 donors and yielded an IC50 of 142 pg/mL (Figure 4.31).

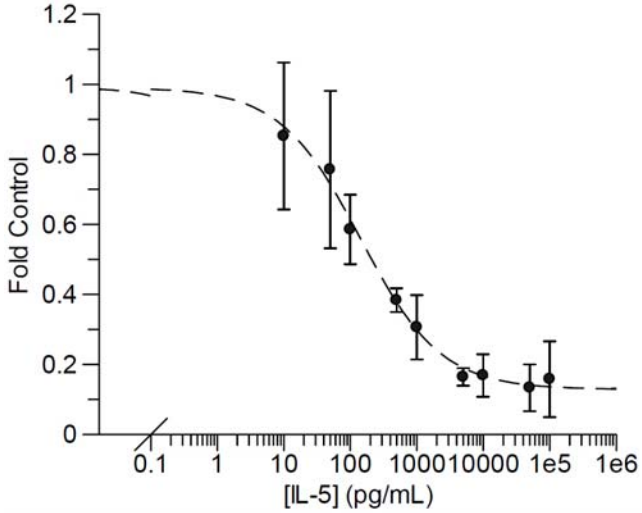

Figure 4.31 Mean (± SD) effect of IL-5 treatment of CYP3A4 mRNA levels in cultured human hepatocytes (N=3, mean ration of treated over control). (Source: NCSR 10DMW042, Page 17, Figure 2)

Conclusion:

- Mepolizumab apparently did not affect CYP3A4 mRNA levels in human hepatic cells up to 6 mg/mL.

- Although IL-5 reduced CYP3A4 mRNA levels in a concentration-dependent manor, the IC_{50} of IL-5 was 142 pg/mL. By considering the free IL-5 levels were mostly LOQ (3.91 pg/mL) in healthy subjects or asthma patients, the in vivo effect of physiological level of IL-5 on CYP3A4 transcription is expected to be neglected.

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OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

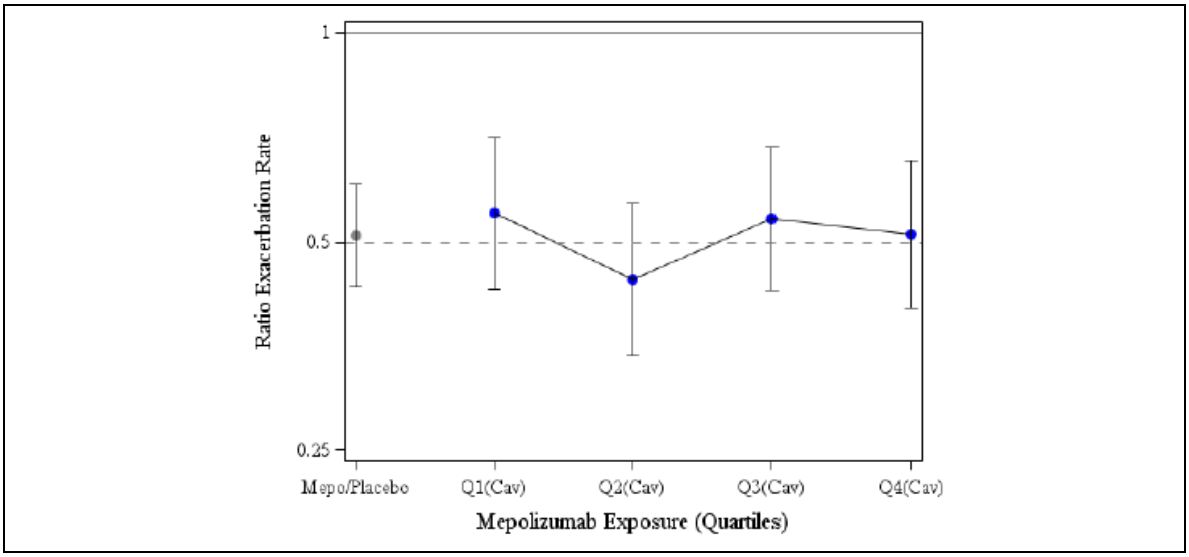
The purpose of this review is to address the following key questions.

1.1.1 What is the characteristic of exposure-response (E-R) relationship for efficacy? Does it support the proposed dose regimen?

The E-R relationship for primary efficacy endpoint (exacerbation rate) is flat based on analysis of combined data from two Phase 3 studies, MEA112997 (once every 4 weeks: 75 mg IV, 150 mg IV and 750 IV) and MEA115588 (once every 4 weeks: 75 mg IV and 100 mg SC) as shown in Figure 2.1. It is consistent with the flatness of dose-response observed in these two Phase 3 studies. A series of E-R analysis for other endpoints of clinical interest, including time to first exacerbation and frequency of exacerbations dichotomized as >= 1 to 6 exacerbations (yes or no), consistently revealed the flatness of E-R relationship for efficacy.

In addition, PK/PD data from Study MEA114092 suggested the proposed 100 mg SC dose (comparable to 75 mg IV in exposure) has reached plateau of the dose/exposure- PD response curve for reduction in blood eosinophil count, although it should be noted the correlation between blood eosinophil count and endpoints of clinical interest has not be established in the targeted patient population.

Figure 1. Exacerbation rate ratio compared with placebo by average exposure quartile



Overall, the proposed dose regimen (100 mg SC once every 4 weeks) is supported by the flat E-R relationship for efficacy based on phase 3 studies. However, the efficacy at doses lower than the proposed 100 mg SC remains unclear due to the lack of clinical efficacy data at lower doses/exposures.

1.1.2 What are the covariates contributing to the inter-subject PK variability of mepolizumab based on population PK analyses? Is dose adjustment warranted with respect to these covariates?

In all population PK analyses, body weight was identified as a statistically significant covariate. The magnitude of effect of body weight on exposure in both moderate and severe eosinophilic asthma subjects

and other populations was comparable. For a body weight range of 40–162 kg, a 52% increase to a decrease of 47% for AUC relative to a typical subject (body weight of 70 Kg) is expected based on population PK analysis. The effect of body weight on PK is not clinically important given the flatness of E-R relationship for efficacy, so no dose adjustment is warranted with regard to body weight. In addition, albumin and creatinine clearance were identified as additional covariates for severe eosinophilic asthma subjects from phase 3 study MEA115588, however, like bodyweight, neither was considered clinically important.

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in BLA 125526. This BLA is considered acceptable from a pharmacometrics perspective.

1.3 Label Statements

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

2. RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis in phase 3 study MEA115588

A population PK analysis was conducted with the PK data from a phase 3 study MEA115588 (mepolizumab 75 mg IV *vs* 100 mg SC every 4 weeks *vs* placebo.). PK data following the intravenous (IV) and subcutaneous (SC) administration were analyzed separately in population PK analysis. The effect of prospectively selected covariates on exposure was first evaluated graphically followed by a formal covariate analysis. The absolute bioavailability, F, of the SC route of administration was derived from post-hoc individual clearance (CL or CL/F) estimates obtained after SC and IV administration.

2.1.1 Population PK after IV administration

Of the 191 subjects randomised to the IV treatment group, 188 subjects contributed 605 concentrations to the analysis. Each subject contributed a median of three mepolizumab concentrations. Approximately 55% (103/188) of subjects included in the analysis were female. The median (range) age was 52 (13-82) years. The median (range) bodyweight at baseline was 77 (42-128) kg. The median (range) baseline calculated (using the Cockcroft-Gault formula) creatinine clearance (CRCL) was 108 (36-233) mL/min. The median (range) albumin at baseline was 45 (34-54) g/L. Based on subject's baseline calculated creatinine clearance, no subject had severe renal impairment (CRCL<10 mL/min), one subject (<1%) had moderate impairment (CRCL≤50 mL/min), 18% (33) had mild renal impairment (CRCL=50-80 mL/min). The remaining majority, 82% (154/188) , had normal renal function.

Table 1. Final intravenous population PK model

Parameter [Units]	NONMEM Estimates					
	Final Estimate	%RSE	Theta Estimate	SE	95% CI	
CL [L/Day]	0.220	0.540	-4.69 [L/hr]	0.0255	0.210-0.232	
V1 [L]	4.85	5.36	1.58 [L]	0.0847	4.06-5.70	
Q [L/Day]	0.123	6.02	-5.27 [L/hr]	0.317	0.0719-0.254	
V2 [L]	1.65	30.5	0.502 [L]	0.153	1.29-2.33	
CL~WT	0.75 FIX	--	0.75 FIX	--	--	
V1~WT	1.0 FIX	--	1.0 FIX	--	--	
V2~WT	1.0 FIX	--	1.0 FIX	--	--	
CL~ALB	0.480	29.1	-0.733	0.213	0.317-0.729	
CL~CRCL	1.17	33.1	0.161	0.0533	1.06-1.30	
Inter-individual variability						**CV%**
ω^2_{CL}	0.0431	12.8	--	0.00552	0.0323-0.0539	20.8
Residual variability						**CV%**
σ^2_{prop}	0.223	3.57	0.223	0.00795	0.207- 0.239	22.3

NONMEM Subroutine ADVAN3 TRANS4, FOCEI method and nonmem_v1_exclpredose.csv dataset was used in the model development. Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate *100; 95% CI= 95% confidence interval on the parameter; CMT=Compartment, CL= total clearance, V1= volume of central compartment, V2= volume of peripheral compartment , Q= Inter-compartment clearance, WT=body weight; ω^2_{CL} = variance of random effect of CL; σ^2prop = proportional component of the residual error model; CV = coefficient of variation of proportional error (=[σ^2prop]*100), SE=Standard error of the estimate, ALB=Albumin, CRCL=Creatinine clearance

Final Model description:

$CL = EXP(\theta_1 + \theta_5 * LOG(WT/70) + \theta_{10} * LOG(ALB/45)) + \theta_{11} * LOG(CRCL/108) + \eta_1)$

$V1 = EXP(\theta_2 + \theta_6 * LOG(WT/70) + \eta_2)$

$Q = EXP(\theta_3 + \eta_3)$

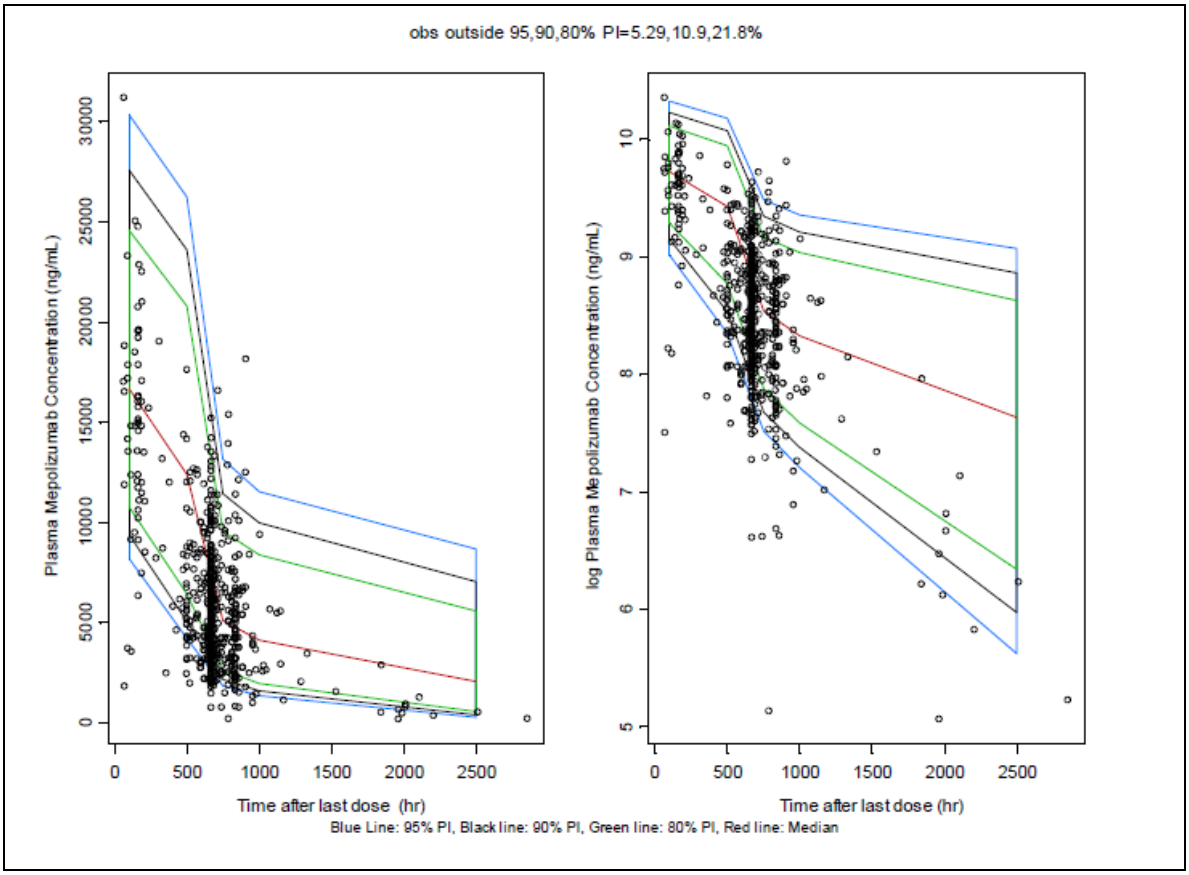
$V2 = EXP(\theta 4_2 + \theta_7 * LOG(WT/70) + \eta_4)$

Residual error model:

$Y = F + F * \theta_8 * (\varepsilon_1)$

Source: Model MEA588IV032.res

Figure 2: Visual predictive check for final IV PK model



Sources: Page 1368

2.1.2 Population PK after SC administration

Of the 194 subjects randomised to the SC treatment group, 189 mepolizumab-treated subjects contributed 621 concentrations to the analysis. About 60% (113/189) of mepolizumab-treated subjects included in the analysis were female. The median (range) age was 54 (12-81) years. The median (range) bodyweight at baseline was 73 (45-140) kg. The median (range) baseline calculated (using the Cockcroft-Gault formula) creatinine clearance (CRCL) was 102 (46-242) mL/min. The median (range) albumin at baseline was 45 (37-53) g/L. Based on subject's baseline calculated creatinine clearance, no subjects had severe renal impairment, one subject (<1%) had moderate impairment, 35 (19%) had mild renal impairment. The remaining majority, 81% (153/189), had normal renal function.

Table 2. Final Subcutaneous Population PK Model

Parameter [Units]	NONMEM Estimates					
	Final Estimate	%RSE	Theta Estimate	SE	95% CI	
CL/F [L/Day]	0.280	0.604	-4.45 [L/hr]	0.00269	0.267-0.295	
V2/F [L]	4.44	2.27	1.49 [L]	0.00338	4.14-4.76	
Ka [Day^{-1}]	0.289	3.57	-4.42 [hr^{-1}]	0.158	0.212-0.394	
K23 [Day^{-1}]	0.280 FIX	--	-4.45 FIX [hr^{-1}]	--	--	
K32 [Day^{-1}]	0.283 FIX	--	-4.44 FIX [hr^{-1}]	--	--	
CL/F~WT	0.75 FIX	--	0.75 FIX	--	--	
V2/F~WT	1.0 FIX	--	1.0 FIX	--	--	
CL/F~ALB	0.480 FIX	--	-0.733 FIX	--	--	
CL/F~CRCL	1.18	44.7	0.164	0.0733	1.02-1.36	
Inter-individual variability						CV%
$\omega^2_{CL/F}$	0.0825	12.4	--	0.00102	0.0625-0.102	28.7
Residual variability						CV%
σ^2_{prop}	0.241	3.50	0.241	0.00843	0.224-0.258	24.1

NONMEM Subroutine ADVAN4 TRANS1, FOCEI method and nonmem_v1_exclpredose.csv dataset was used in the model development. Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate *100; 95% CI= 95% confidence interval on the parameter; CL/F = apparent clearance, V2/F = apparent volume of central compartment, Ka = absorption rate constant; K23 = rate constant from central to peripheral compartment, K32 = rate constant from peripheral to central compartment; $\omega^2_{CL/F}$ = variance of random effect of CL/F; σ^2prop = proportional component of the residual error model; CV = coefficient of variation of proportional error (=[σ^2prop]*100), SE=Standard error of the estimate, WT=Body weight, ALB=Albumin, CRCL=Creatinine clearance

Final Model description:

$CL/F = EXP(\theta_1 + \theta_7 * LOG(WT/70) + \theta_9 * LOG(ALB/45)) + \theta_{10} * LOG(CRCL/102) + \eta_1)$

$V2/F = EXP(\theta_2 + \theta_8 * LOG(WT/70) + \eta_2)$

$Ka = EXP(\theta_3 + \eta_3)$

$K23 = EXP(\theta_4 + \eta_4)$

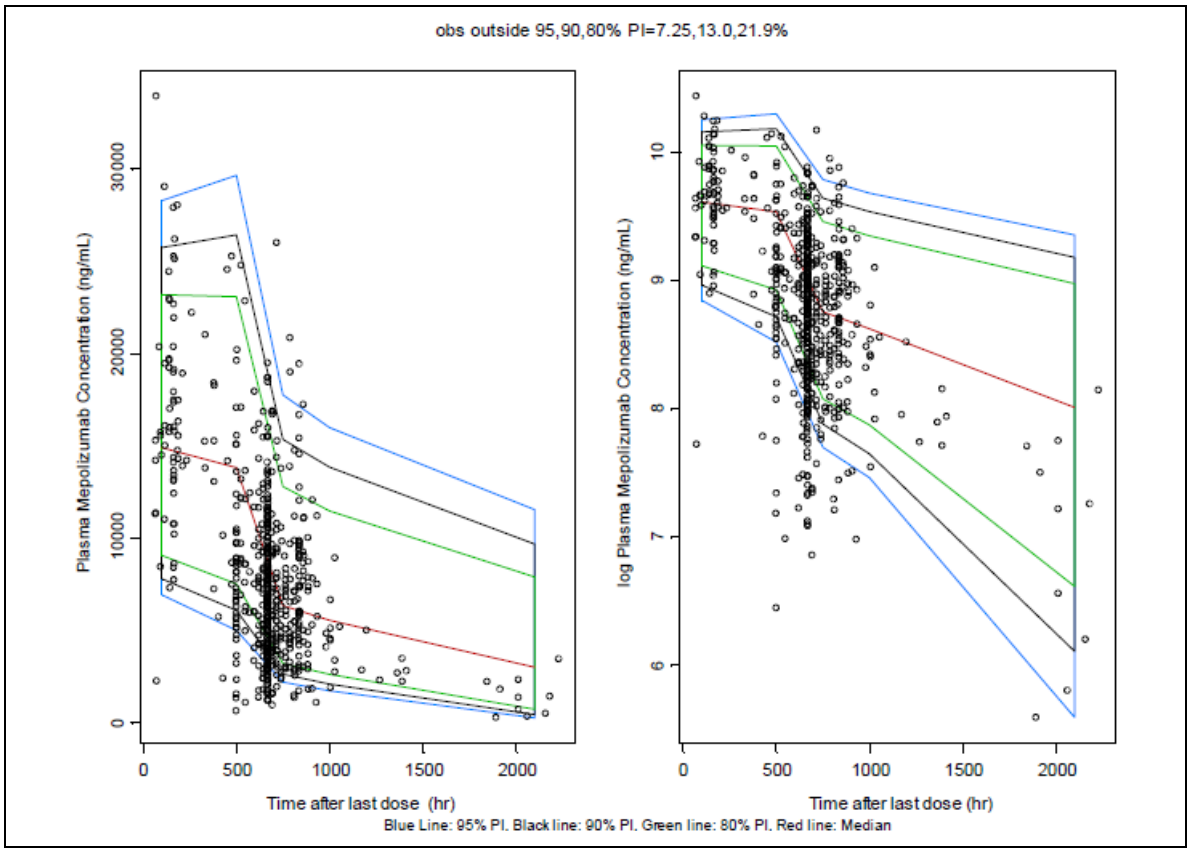
$K32 = EXP(\theta_5 + \eta_5)$

Residual error model:

$Y = F + F * \theta_6 * (\varepsilon_1)$

Source: Model MEA588SC061.res

Figure 3: Visual predictive check for final SC PK model



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Summary of findings based on population PK analysis:

1. The population PK models (2 compartment model) can describe adequately the observed PK data after IV and SC administration.
2. Body weight, albumin and creatinine clearance were identified as covariates for mepolizumab PK, although none were deemed clinically significant. No dose adjustments are necessary with respect to these covariates.
3. The absolute bioavailability of the subcutaneous route was assessed and estimated to be 80% [90% CI: 76%–84%]. This is consistent with the previous estimates of approximately 75% in studies SB-240563/018 and MEA114092.
4. Mepolizumab showed approximately two-fold accumulation (accumulation ratio was calculated as the ratio of individual predicted Ctrough at steady state divided by the individual predicted Ctrough at Week 4) and steady-state was achieved by Week 16 following dosing every four weeks, regardless of administration route.

Reviewer's Comments:
1. It is expected that body weight is a covariate for the PK of mepolizumab as monoclonal antibody is degraded by proteolysis throughout the body. Mepolizumab shows conventional allometric scaling typically seen for protein drugs.
2. The effect of creatinine clearance and albumin is not considered meaningful for the following reasons:
(a) Creatinine clearance and albumin are related to renal and hepatic function. However, renal or hepatic elimination pathways are not expected to contribute significantly to the clearance of mepolizumab as stated previously.

(b).Inclusion of these two covariates in the model in addition to body weight resulted in marginal reductions in between-subject variability in clearance (IV PK model: CV% reduced from 22.0% to 20.8%; SC PK model: CV% reduced from 29.5% to 28.7%).

(c). The magnitude of the effects of these two covariates on PK are minimal: For a creatinine clearance range of 46–242 ml/min, a 12 % decrease to a 15% increase for clearance relative to a typical subject (creatinine clearance of 102 ml/min) is expected. For albumin range of 37–53 g/L, a 15 % increase to a 11% decrease for clearance relative to a typical subject (albumin of 45g/L) is expected. Therefore, these two covariates have no meaningful clinical impact.

Population PK analysis in other studies

All available PK data from 327 subjects in six studies (Study MHE100185, Study SB-240563/001, Study SB-240563/006, Study SB-240563/018 (IV arm), Study SB-240563/035, and Study MEE103226) were combined for population pharmacokinetic analysis. The descriptions of each of these studies are following:

MHE100185: Mepolizumab was administered as nine monthly 30-minute intravenous infusions at 750 mg to adult subjects with hypereosinophilic syndrome (HES).
Study SB-240563/001: Mepolizumab (0.05, 0.5, 2.5, or 10 mg/kg) or placebo was administered as a single 30-minute intravenous infusion to adult subjects with asthma.
Study SB-240563/006: Mepolizumab 250 or 750 mg or placebo was administered as three monthly 30-minute intravenous infusions in adult subjects with asthma.
Study SB-240563/018 (IV arm): Mepolizumab was administered as a single 30-minute intravenous infusion at 250 mg in adult healthy subjects.
Study SB-240563/035: Mepolizumab (0.5, 2.5, or 10 mg/kg) or placebo was administered as a single 30-minute intravenous infusion in adult subjects with asthma.
Study MEE103226: Mepolizumab was administered as a 30-minute intravenous infusion at 750 mg Days 0 and 7 and at 1500 mg Weeks 5 and 9 to subjects with eosinophilic espohagitis.

The pharmacokinetics of mepolizumab was best described by a two-compartment model. Various covariates, including body weight, height, age, sex, race, country of study site, disease state, creatinine clearance, and liver function, were evaluated in the model. Body weight was identified as the only statistically significant covariate for CL and V1. Similarly, the magnitude of this effect was not considered to be clinically significant. There is no significant difference in PK across different diseases. But CL and V1 were approximately 30% lower in healthy subjects compared to patients. This finding should be interpreted with caution due to the limited data in healthy subjects (12 individuals in one study). The model developed herein was also adequate to describe the PK data in subjects with severe refractory asthma in a phase 3 Study MEA112997 without further refinement.

2.3 E-R analysis for efficacy

2.3.1 E-R analysis for exacerbation rate

The rate of clinically significant exacerbations was analysed using generalised linear and nonlinear (sigmoid Emax) exposure-response models. A model considering treatment as a class or binary effect was included. For comparison, different models were compared using the Bayesian Information Criteria (BIC), with lower values denoting better model fit. Subjects with missing average concentration or other covariates were excluded from all analyses to make comparisons valid. For the nonlinear model the following Emax model is used:

Log(Number of exacerbations) = ß0 + ß1*Cav**Slope /(exp(ß2)**Slope + Cav**Slope),

Where ß0 is an intercept, ß1 is the maximal response attributable to mepolizumab and ß2 is the logarithm of the EC50; the average concentration providing half-maximal drug effect. Slope was fixed to unity. The number of clinically significant exacerbations was assumed to follow a negative binomial probability distribution. The logarithm of time on treatment was used as an offset variable to account for differing times on study. The model also included a covariate for study. Other covariates included in the models were baseline maintenance OCS therapy (OCS vs. no OCS), geographical region, number of exacerbations in the year prior to the study (as an ordinal variable), log(baseline blood eosinophil count) – with imputed values of LLQ/2 = 0.005 for zero, and baseline disease severity (as % predicted FEV1). Analysis was conducted using SAS and proc genmod and proc nlmixed.

The Bayesian Information Criterion of the models for exacerbation rate is shown in

Table 3 . Linear and nonlinear negative binomial models were fitted to the combined Phase III datasets with adjustment for region, baseline FEV1 as a marker of disease severity, previous exacerbation history, oral steroid usage, study and log(baseline blood eosinophil count). The effects of mepolizumab were evaluated by model comparison with the Phase III primary analysis model of treatment as a class effect. Note that in previously reported analyses no adjustment was made for baseline blood eosinophil count. For comparative purposes, the same linear model was also fitted using proc nlmixed, before modification to a nonlinear Emax(Cav) model which retained all other covariates. Model comparisons are based on Bayesian Information Criteria (BIC), which incorporates a penalised likelihood, based on the number of model parameters, and lower values denote better model fit.

Table 3: Summary (Negative binomial) model fit statistics for exacerbation count data

Model	Proc	Treatment	BIC	DBIC	Notes
Linear	genmod	Class	3265.0	0.0	Primary analysis model with further adjustment for eosinophils
Linear	nlmixed	Class	3265.0	0.0	Primary analysis model with further adjustment for eosinophils
Linear	genmod	Mepo/Plac	3245.9	-19.1	Mepolizumab or Placebo (binary treatment)
Linear	genmod	Q(Cav)	3264.5	-0.4	Exposure-response Quartiles(Cav)
Nonlinear	nlmixed	Emax(Cav)	3253.0	-12.0	Exposure response: Emax(Cav)

Table **3** shows that when average concentration is treated as a categorical variable, Q(Cav) (i.e., concentration quartile), there is no improvement in BIC; essentially the quartile of Cav is a very good proxy for treatment due to the wide separation of IV doses (10-fold). `Figure 2.` shows the absence of exposure response graphically. There is a reduction of 12 points when a nonlinear Emax(Cav) model is used. Unfortunately, although the model converges, estimation of EC50 is not possible and the standard error is approximately 800%.

Reviewer's comments: A very wide confidence interval of EC50 in Emax model reflected the lack of information about the declining part of E-R curve in the observed exposure range in phase 3 studies.

2.3.2 E-R analysis for exacerbation as binary outcome

The number of subjects with N or more exacerbations per year (N = 1 to 6) was calculated. Since subjects remained on study for different periods (recall the two studies are of different duration), an offset of

logtime was again used to annualise probabilities. The dichotomous probability Prob(>=N) was then subject to linear and nonlinear logistic regression. For the nonlinear model the following Emax model was used:

Logit = ß0 + ß1 Cav**Slope /(exp(ß2)**Slope + Cav**Slope),

Where all parameters are denoted as before. Covariates were maintained from the exacerbation rate analysis. All analyses were again conducted using SAS proc genmod and proc nlmixed, with model comparisons based on Bayesian Information Criteria with lower values implying better model fit.

Figure 4: Odds ratio of N or more exacerbations compared with placebo (N=1 to 6)

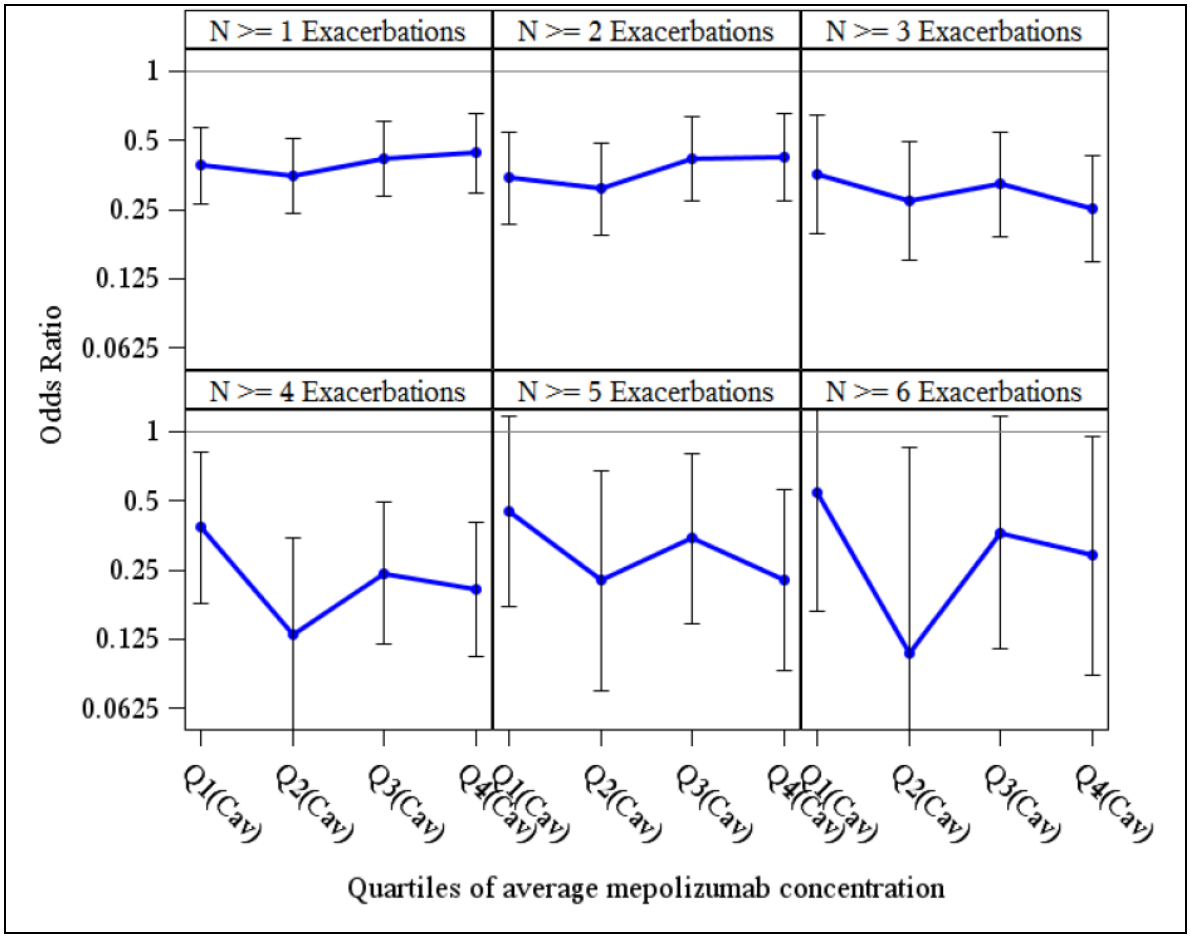
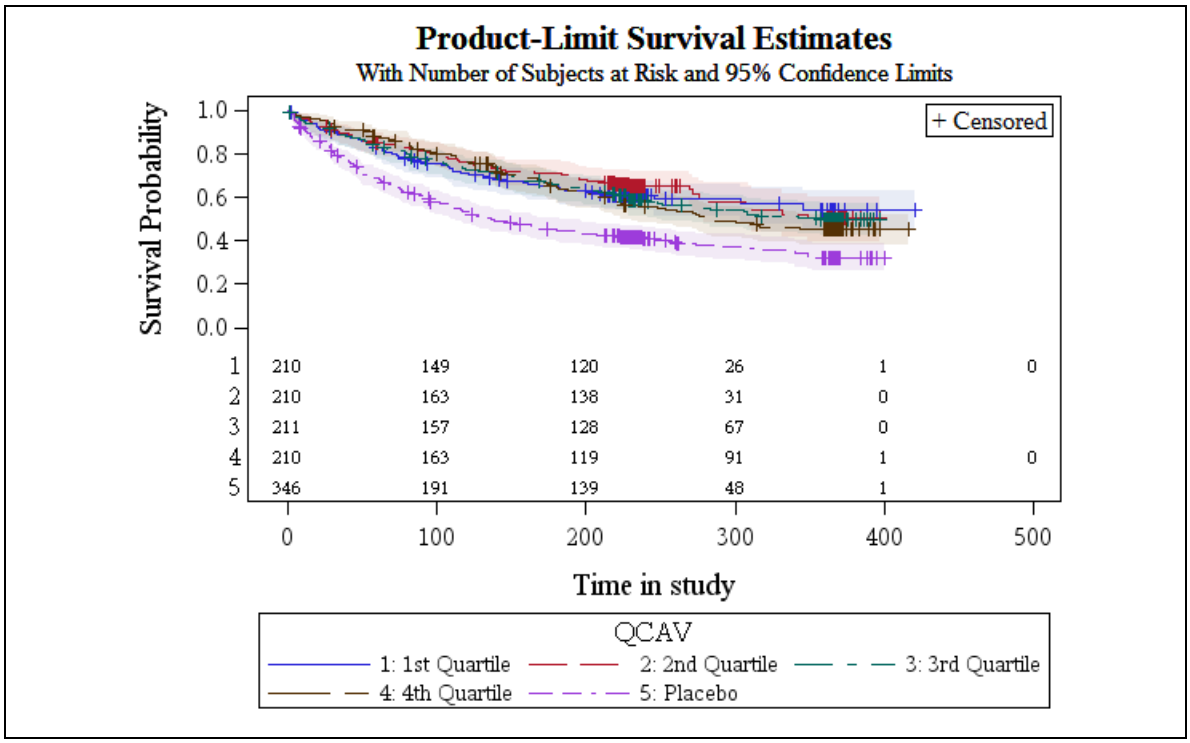


Figure 4 shows the adjusted mean odds ratio by quartile of exposure for each dichotomised frequency of exacerbation. There is no clear evidence that patients in the lowest exposure quartile (Q1) have a higher odds ratio than other patients. The 95% confidence interval increases with increasing N reflecting the reduced number of patients falling into subsequent categories.

2.3.3 E-R analysis for time to first exacerbation

Non-parametric survival curves are shown in Figure 5 for the combined Phase III data considering treatment as quartiles of exposure. Although there is clear separation between placebo and other treatments, there is no separation between quartiles of average exposure. The large number of censored observations at 224 days is due to the 32 week trial duration for study MEA115588.

Figure 5: Kaplan-Meier survival curve for mepolizumab by quartile of average exposure



For completeness, Parametric survival model with a weibull distribution and Cox proportional hazards models were fitted to the data .All covariates were included in the models as before, and similarly there is no evidence of exposure response.

Reviewer's Comments: All E-R analyses for different endpoint of clinical interest reached consistent conclusion that when average mepolizumab concentration is treated as a categorical variable (concentration quartile), or as a continuous variable, there is no evidence of exposure response for efficacy after adjustment for multiple covariates.

4.2 Appendix – New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**125526**	**Brand Name**	**Nucala**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Mepolizumab**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Anti-IL-5 antibody**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	**add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 1) 150 cells/µL at initiation of treatment, or, 2) 300 cells/µL in the past 12 months**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Lyophilized powder for injection**
Other discipline reviewers	**Jingyu Yu Ph.D. Liang Zhao Ph.D.**	**Dosing Regimen**	**100 mg once every 4 weeks**
Date of Submission	**11/4/2014**	**Route of Administration**	**Subcutaneous injection**
Estimated Due Date of OCP Review	**9/15/2015**	**Sponsor**	**GlaxoSmithKline**
PDUFA Due Date	**11/4/2015**	**Priority Classification**	**Standard 351 (a)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			Electrochemiluminescent Immunoassay, Fluorescent Immunoassay, Chemiluminescent Immunoassay, ELISA
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**	**2**	Study SB-240563/018 and MEA115705
multiple dose:				
Patients-				
single dose:	**X**	**2**	**2**	Study SB-240563/001and SB-240563/035
multiple dose:	**X**	**4**	**3**	Study SB-240563/017, SB-240563/036, MEA114092 and MEE103219 (irrelevant indication)

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**1**	**1**	Study MEA115705
gender:				
pediatrics:	**X**	**1**	**0**	MEE103219 (irrelevant indication)
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**5**	**3**	Study SB-240563/001, SB-240563/035, SB-240563/017, SB-240563/045 (irrelevant indication) and MEE103219 (irrelevant indication)
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**	**3**	Study SB-240563/036, MEA115705 and MEA114092,
Phase 3 clinical trial:	**X**	**3**	**3**	MEA112997, MEA115588, and MEA115575
Population Analyses -				
Meta-analysis:				
Data sparse:	**X**	**4**	**3**	MEA112997, MEA115588, MEA115575, and MEE103219 (irrelevant indication)
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	Study SB-240563/018
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**13**	**11**	

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

/s/

YUNZHAO REN
07/02/2015

JINGYU YU
07/02/2015

YANING WANG
07/02/2015

PING JI
07/03/2015

SURESH DODDAPANENI
07/05/2015

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**125526**	**Brand Name**	**Nucala**
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Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Anti-IL-5 antibody**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	**add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 1) 150 cells/µL at initiation of treatment, or, 2) 300 cells/µL in the past 12 months**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Lyophilized powder for injection**
Other discipline reviewers	**Jingyu Yu Ph.D. Liang Zhao Ph.D.**	**Dosing Regimen**	**100 mg once every 4 weeks**
Date of Submission	**11/4/2014**	**Route of Administration**	**Subcutaneous injection**
Estimated Due Date of OCP Review	**9/15/2015**	**Sponsor**	**GlaxoSmithKline**
PDUFA Due Date	**11/4/2015**	**Priority Classification**	**Standard 351 (a)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			Electrochemiluminescent Immunoassay, Fluorescent Immunoassay, Chemiluminescent Immunoassay, ELISA
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**	**2**	Study SB-240563/018 and MEA115705
multiple dose:				
Patients-				
single dose:	**X**	**2**	**2**	Study SB-240563/001and SB-240563/035
multiple dose:	**X**	**4**	**3**	Study SB-240563/017, SB-240563/036, MEA114092 and MEE103219 (irrelevant indication)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**1**	**1**	Study MEA115705
gender:				
pediatrics:	**X**	**1**	**0**	MEE103219 (irrelevant indication)
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**5**	**3**	Study SB-240563/001, SB-240563/035, SB-240563/017, SB-240563/045 (irrelevant indication) and MEE103219 (irrelevant indication)
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**	**3**	Study SB-240563/036, MEA115705 and MEA114092,
Phase 3 clinical trial:	**X**	**3**	**3**	MEA112997, MEA115588, and MEA115575
Population Analyses -				
Meta-analysis:				
Data sparse:	**X**	**4**	**3**	MEA112997, MEA115588, MEA115575, and MEE103219 (irrelevant indication)
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	Study SB-240563/018
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**13**	**11**	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The drug substance changing strategy (250 mg/vial to 100 mg/vial) was acceptable in accordance with CMC EOP2 meeting held on 11/7/2012
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	Not applicable to antibody products
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference			X	This is a 505(b)(1) submission

	product for a 505(b)(2) application?				
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
13	Is the appropriate pharmacokinetic information submitted?	X			
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
17	Are the pediatric exclusivity studies adequately	X			The PSP was agreed

	designed to demonstrate effectiveness, if the drug is indeed effective?				(DARRTS date 6/12/2014 under IND 006971)
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
20	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA

Regulatory History

GSK opened mepolizumab first IND 006971 on 12/20/1996. (b) (4) the current indication is focused on severe eosinophilic asthma. (b) (4)

The major interactions with the Agency during an 18-year drug development for IND 006917 were focused on disease characterization, target patient population selection, patient selection criteria, and selection of endpoints.

An EOP2 meeting with FDA was held on 05/04/2009. The summary of clinical pharmacology-related discussions and comments are listed as following:

1) Dose selection and dosing regimen in Phase 3 trials
   The Sponsor proposed 75 mg iv and 100 mg sc every 4 weeks in Phase 3 pivotal trails. The 100 mg sc dosing regimen was never tested in Phase 2 trials.
   FDA Response: We are unable to agree at this time. While the 75 mg IV dose appears reasonable for further study, the overall dose selection for Phase 3 is risky from several perspectives:
   - *Based on the results of MEA112997, we note that lower doses of mepolizumab may also be efficacious. Should a safety signal be identified in the clinical program, the adequacy of the dose-ranging will be a review issue.*
   - *We generally recommend that pivotal dose-ranging be conducted with the to-be-marketed formulation. There are no efficacy data to support selection of the 100 mg SC dose. The clinical relevance of serum eosinophilia, the pharmacodynamic parameter used to relate the 100 mg SC dose to the 75 mg IV dose, is unknown.*
   - *Likewise, we expect replicate trials of efficacy with the to-be-marketed product. The proposed bridging between the 75 mg IV and 100 mg SC dose may be adequate to support the SC dose; however, any differences in efficacy or safety that are observed in MEA115588 between the two formulations will jeopardize this approach. If the proposed bridging strategy fails, then the clinical program will lack replication for the to-be-marketed formulation.*

2) Sponsor proposed not to identify the isotype of the neutralizing antibody
   FDA Response: We concur with your plan to not determine the isotype of neutralizing antibodies unless there is a correlation with clinically relevant findings.

3) Sponsor proposed not to further evaluate the hepatocyte induction (CYP3A4)
   FDA Response: Agency is unable to concur at this time that no further evaluation is needed prior to BLA submission. This is an evolving area and we suggest that you follow developments in this area and make an appropriate decision regarding further DDI assessment. We suggest that you refer to the revised draft drug-drug interaction guidance published on February 18, 2012 for current thinking at this time;
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

The mepolizumab drug product, at 3 strengths (50 mg/vial, 250 mg/vial, and 100 mg/vial), was manufactured to supply pre-clinical, clinical, and proposed commercial presentation. The qualitative composition and the dosage form of mepolizumab drug product were maintained for all three product strengths. However, there were small changes in the quantitative formulation and manufacturing process. The initial clinical batches of mepolizumab for Injection, 250 mg/vial were manufactured at pilot scale prior to the transfer of the MDP1 (mepolizumab drug product 1) manufacturing process to the proposed commercial facility, GSK Manufacturing, Parma. MDP1 (250 mg/vial) was used for Phase II study MEA114092, pivotal Phase III clinical studies (MEA112997, MEA115588, MEA115575) and initiation of the OLE studies (MEA115666, and MEA115661). MDP2 (250 mg/vial) was used in all ongoing clinical studies, including the two OLE studies (MEA115661 and MEA115666). MDP2 is proposed for marketing. Based on the demonstrated biochemical comparability, no pre-clinical pharmacology, PK or toxicology studies were deemed necessary and no formal human bioequivalence studies were conducted. This strategy was reviewed and endorsed by the FDA at the Type B EOP2 CMC meeting held on 11/07/2012:

Question 1: Does the Agency consider that the proposed strategy and anticipated data package are sufficient to demonstrate drug substance comparability between (b) (4)?
FDA Response: The strategy to demonstrate mepolizumab (b) (4) comparability is largely acceptable. We note that the IL5 neutralization assay is not included in this comparability assessment although it was included in the previous comparability studies. We recommend that you include this method in the (b) (4) comparability protocol.

In addition, provide a description of the design of IL5 kinetic binding method by surface plasmon resonance (mepolizumab on the chip or as analyte, etc.) and a rationale for its use. Since IgG mAbs are bivalent, the mAb is typically coupled to the chip and the ligand is the analyte in order to assess binding affinities and kinetics. However, we note that IL5 exists as a dimer, so whether mepolizumab or IL5 are coupled to the chip, it is not clear what will be measured by this method.

Please submit (b) (4) viral clearance validation data to the IND in advance of use of (b) (4) derived drug product in clinical trials.

The Sponsor held pre-BLA meeting with FDA on 01/15/2014. The summary of clinical pharmacology-related discussions and comments are listed as following:

Question 8: The data which will be available to characterize Immunogenicity of mepolizumab administered IV and SC at the time of BLA submission is described in the briefing document. Does the Agency agree this characterization is sufficient to support registration of mepolizumab dosed SC?
FDA Response: The proposed clinical assessment of immunogenicity appears reasonable. We also request that you submit analyses of any association between immunogenicity and efficacy and adverse event rates.

Question 9: Based on available guidance (including: Revised Draft Guidance: Drug Interaction Studies UCM292362, February 18, 2012), GSK believe that the clinical pharmacology package for mepolizumab outlined in this briefing document is complete and no additional clinical pharmacology studies are needed for registration.
FDA Response: Yes, we agree that no additional clinical pharmacology studies are needed to support registration of mepolizumab. The adequacy of the data will be a review issue.

The Agency agreed Sponsor's initial pediatric study plan (iPSP) on 06/12/2014. The Sponsor proposed a Phase 2 PK/PD study in pediatric population aged 6 to 11 years old with severe eosinophilic asthma. Mepolizumab will be administered sc every 4 weeks for 12 weeks. The study initiation date will be no later than June 2015.

Clinical Pharmacology Studies

In total, the sponsor submitted 11 studies containing PK and/or PD components in healthy or asthmatic patients (Table 1). In addition, the Sponsor also submitted a popPK meta-analysis report by pooling PK data from iv administration.

Table 1 Summary of Trials Including PK or PD evaluation in Healthy or Asthmatic Patients

Stud ID	Phase	Objective	Subjects	Treatments	Dosing Regimen[#]
001	2	PK, PD	38 male with mild asthma	0.05 mg/kg, IV 0.5 mg/kg, IV 2.5 mg/kg, IV 10 mg/kg, IV Placebo, IV	SD (9.4 – 210 ml/30min)
006	2	PK, efficacy	362 patients with asthma	250 mg IV 750 mg IV placebo IV	3 doses, q4w (150 ml/30min)
017	2	PK, PD	16 patients with asthma	250 mg SC placebo SC	3 doses, w1, 6,8
018	1	PK	60 Healthy subjects	250 mg SC, 3 different sites 250 mg IM 250 mg IV	SD (100 ml/30min)
035	1	PK, PD	18 males with mild asthma	0.5 mg/kg, IV 2.5 mg/kg, IV 10 mg/kg, IV Placebo, IV	SD (96-157 ml, 30 min)
036	2	PD	24 patients with atopic asthma	750 mg, IV Placebo, IV	3 doses, q4w (150 ml/30min)
MEA112997*	2b/3	Efficacy, safety, PK, PD	616 patients with severe eosinophilic asthma	75 mg, IV 250 mg, IV 750 mg, IV Placebo, IV	q4w for 48 weeks (100 ml/30min)
MEA114092	2	PK, PD	70 asthmatic patients with eosinophilia	12.5 mg, SC 125 mg, SC 250 mg SC 75 mg, IV	3 doses, q4w (30 min)
MEA115575*	3	Efficacy, safety, PK	135 patients with severe refractory asthma	100 mg SC Placebo SC	q4w for 24 weeks
MEA115705	1	PK, PD	35 healthy Japanese male	10 mg, IV 75 mg, IV 250 mg, IV 750 mg, IV Placebo, IV	SD (30 min)
MEA115588*	3	Efficacy, safety, PK	576 patients with severe eosinophilic asthma	75 mg IV + Placebo SC 100 mg SC + Placebo IV Placebo IV + Placebo SC	8 doses, q4w (30 min)

All trials were conducted in a randomized, parallel group design.
*** Pivotal trial**
[#] The volume and time of iv infusion is included in the parenthesis

The study designs and major PK conclusions are as follows:

- Study 001 was a Phase 2a double-blind, placebo-controlled, single-dose, dose ranging, parallel group study to assess safety, PK and effect on the early and late phase response to allergen challenge of mepolizumab in 38 male patients with mild asthma. A total of 4 single iv doses ranging from 0.05 mg/kg to 10 mg/kg were investigated. PK samples were collected at pre-dose, 15 min, 30 min, 35 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h post-dose on Day 1, on the morning of Day2, 3, 4, 5, 8, 15, 29 and at Week 6, 8, 10, 12 and 16. No deaths, withdrawals due to adverse experiences (AEs) or serious AEs were reported in the study. Mepolizumab exhibited dose-proportional PK. The elimination half-life was approximately 19 days, which was independent of dose. Plasma clearance and steady-state volume of distribution were relatively constant across the dose range studied. After 10 mg/kg mepolizumab, mean levels of blood eosinophil counts were reduced from 0.3 x 10^9/L at baseline (Day 14) to 0.06 x 10^9/L on Day 29. The sputum eosinophil counts were also reduced from 13.1% (Day 13) to 1.4% (Day 30).

- Study 006 was a Phase 2 double-blind, placebo-controlled, 3-doses of 250 mg or 750 mg iv, parallel group study to assess safety, efficacy and PK in 362 patients with moderate asthma (approximately 120 patients per arm). Two intravenous doses of mepolizumab at 250 and 750 mg were tested. The drug was given once every 4 weeks for 12 weeks. Five PK samples were collected from all randomized patients at the following times: Day 1 (immediately after the end of infusion), Week 1, Week 2, Week 4 (prior to administration of the second dose) and Week 8. The most commonly reported AE was upper respiratory tract infection which was higher in the 750 mg group than in the placebo and 250 mg treatment groups. No significant differences were observed in mean change from baseline in morning domiciliary PEFR between the placebo group and both the 250 mg and the 750 mg treatment groups at Week 12, Week 20 or as primary endpoint. Blood eosinophil counts significantly decreased at Week 4 and persisted to Week 20 for both mepolizumab treatments. Sputum eosinophil counts only significantly reduced in the 250 mg treatment group. Mepolizumab exhibited dose-proportional PK.

- Study 017 was a Phase 2 double-blind, placebo-controlled, three 250 mg subcutaneous doses, parallel group study to assess safety and PK of mepolizumab in 16 male patients with mild asthma (8 subjects received mepolizumab treatment). There were 6 weeks between the first 2 doses and 2 weeks between the second and third doses. PK samples were collected at pre-dose, 15 min, 30 min, 35 min, 1 h, 2 h, 4 h, 8 h, 12 h post-dose on Day 1, on the morning of Day 2, 3, 4, 5, 8, 15, 29 and at Week 6, 8, 10, 12 and 16. There were no deaths or serious adverse events reported in this study. The PK results were similar to Study 001. No obvious relationship was observed between mepolizumab concentration and percent change in FEV1 from baseline. A persistent and dose dependent reduction in peripheral eosinophil count relative to baseline was observed in the majority of patients who received any dose of mepolizumab. The maximum decrease relative to baseline (just prior to dose administration) was observed by study Day 4 or later, whilst maximum concentration occurred approximately at the end of the i.v. infusion time or shortly thereafter on Day 1.

- Study 018 was a Phase 1 open-label, randomized, single-dose, parallel group study to assess the bioavailability following administration at 3 subcutaneous sites (abdomen, arm and thigh) and 1 intramuscular site relative to intravenous administration of single 250 mg doses of mepolizumab to 60 healthy volunteers (12 subjects per arm). PK samples were collected at pre-dose, 10 min, 15

min, 30 min, 35 min, 1 h, 2 h, 4 h, 6 h, 8 h post-dose on Day 1, on the morning of Day2, 3, 4, 5, 6, and at Week 2, 3, 4, 6, 8 and 12. There were no deaths or serious adverse events in this study. The Tmax following subcutaneous injection ranged from 2 to 14 days. The average T1/2 of 3 administrations ranged from 17.9 days to 20.4 days. The bioavailability of subcutaneous injection was 71%, 80% and 77% with injection site as abdomen, arm and thigh, respectively. A reduction in peripheral blood eosinophils was observed in the healthy subjects.

- Study 035 was a Phase 1 double-blind, placebo-controlled, single-dose, dose ranging, parallel group study to assess safety, PK and PD of mepolizumab in 18 patients with asthma. 3 single iv doses were tested: 0.5 mg/kg, 2.5 mg/kg, and 10 mg/kg. PK samples were collected at pre-dose, 15 min, 30 min, 35 min, 1 h, 2 h, 4 h, 8 h, 12 h post-dose on Day 1, on the morning of Day2, 3, 4, 5, 8, 15, 29 and at Week 6, 8, 10, 12 and 16. There were no deaths or serious adverse events in this study. The most commonly reported adverse events were related to respiratory infections. The PK results were similar to Study 001. No obvious relationship was observed between mepolizumab concentration and percent change in FEV1 from baseline. A persistent and dose dependent reduction in peripheral eosinophil count relative to baseline was observed in the majority of patients who received any dose of mepolizumab. The maximum decrease relative to baseline (just prior to dose administration) was observed by study Day 4 or later, whilst maximum concentration occurred approximately at the end of the i.v. infusion time or shortly thereafter on Day 1.

- Study 036 was a Phase 2 double-blind, placebo-controlled, three 750 mg iv doses, parallel group study to assess safety and PD of mepolizumab in 24 patients with asthma (11 subjects received mepolizumab treatment). Three 750 mg doses were administered by infusion at 4-week intervals. One serious AE, pneumonitis (a reaction to the bronchial alveolar lavage), was reported 13 days after the final infusion of placebo. At Week 9 there was a statistically significant reduction in the number of eosinophils in bone marrow, blood and the bronchial mucosa biopsy in subjects in the mepolizumab group, relative to placebo. However, the change from baseline in the number of eosinophils in the bronchial alveolar lavage fluid at Week 9, following dosing with mepolizumab, was not significantly different from placebo.

- MEA112997 was a Phase 2b/3 double-blind, placebo-controlled, dose ranging intravenous dose, parallel group study to determine the effect of mepolizumab on exacerbation rates in 616 subjects with severe uncontrolled refractory asthma. Three intravenous doses of mepolizumab at 75, 250 and 750 mg were administered q4w for 52 weeks. The primary efficacy endpoint of this study, frequency of clinically significant exacerbations of asthma, was statistically significant ($p<0.001$) in all mepolizumab groups compared with the placebo group (Table 2). PK sampling was performed pre-dose at the first dose, pre-dose and within 30 minutes after the end of the infusion at Week 20, and at the end of Week 56 or early withdrawal. Numbers of subjects reporting on-treatment AEs were similar in all four treatment groups. Three subjects died during the study. Two subjects received mepolizumab 250 mg: of these one experienced two fatal SAEs (pancreatitis acute and septic shock) and the other subject died from a fatal acute asthma attack. The third subject, who received mepolizumab 750 mg, died from suicide (reported as asphyxia). The PK data in this severe uncontrolled refractory asthma population were consistent with those derived in previous patient studies. The PK/PD model estimated that the IC_{50} of blood eosinophil counts was 226 ng/mL (95% CI: 100 – 508 ng/mL). The post-baseline positive rate of ADA was the same (1%) for mepolizumab treated group and placebo group. None of the subjects receiving mepolizumab tested positive in the neutralizing antibody assay.

Table 2 Reduction of Asthma Exacerbation Rate by Mepolizumab in Study 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

- MEA114092 was a Phase 2a open-label, dose ranging, three doses, parallel group study to assess PK and PD of mepolizumab in 70 adult asthmatic subjects with elevated blood eosinophil levels. Four dosing levels of mepolizumab at 12.5 mg (sc), 125 mg (sc), 250 mg (sc), and 75 mg (iv) were tested. Dosing occurred on three occasions with dosing interval as 4 weeks. Dosing day PK samples were collected at pre-dose, 0.5 h, 1 h and 2 h. Other PK samples were collected on Day 1, 3, 7, 28, 56, 70, 84, 112, and 140 The most frequently reported AEs were injection site reaction, asthma and nasopharyngitis. The clearance of 75 mg iv was 0.210 L/day. The clearance of sc route was 0.310 L/day. The estimated absolute bioavailability for all sc cohorts ranged from 64% to 82%. There appeared a relationship between the blood eosinophil counts and mepolizumab plasma concentrations (Fig.1). No clear relationship was observed between serum total IL-5 and mepolizumab plasma concentrations (Fig. 2). No clear relationship was observed between doses and FEV1 change from baseline (Table 3). The ADA was detected in 2/69 (3%) patients on Day 1 and 6/65 patients (9%) on Day 112. None of the ADAs us neutralization antibody.

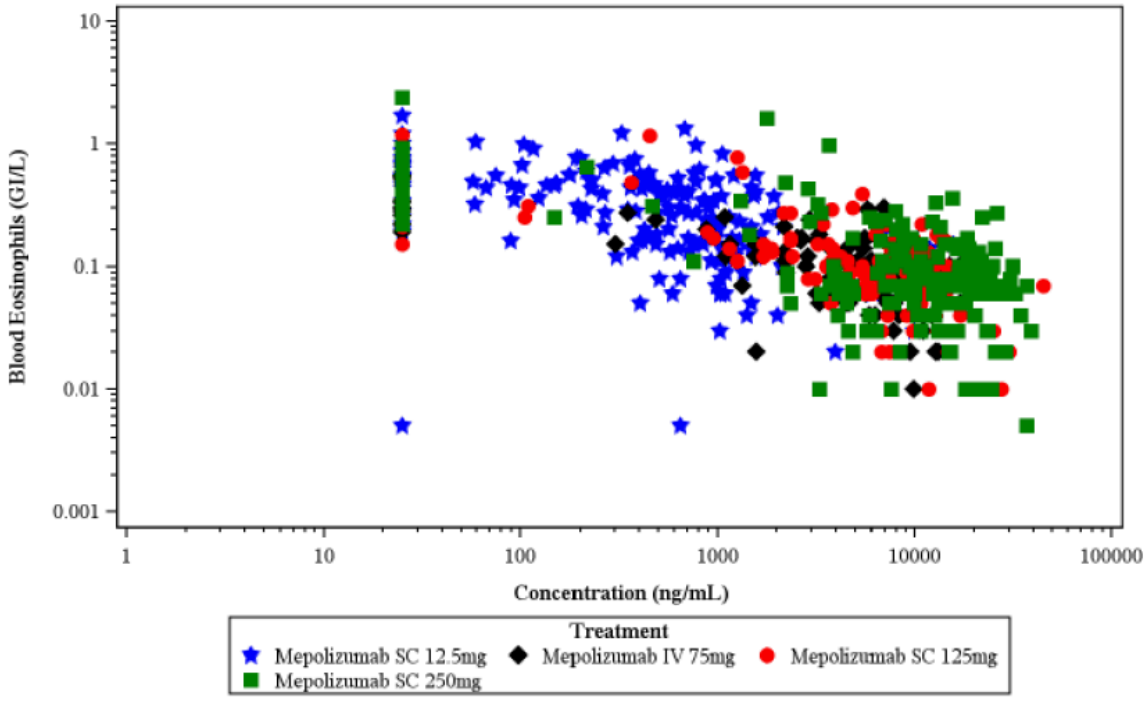

Fig.1 Blood eosinophil counts versus mepolizumab plasma concentration following three doses of mepolizumab treatments.

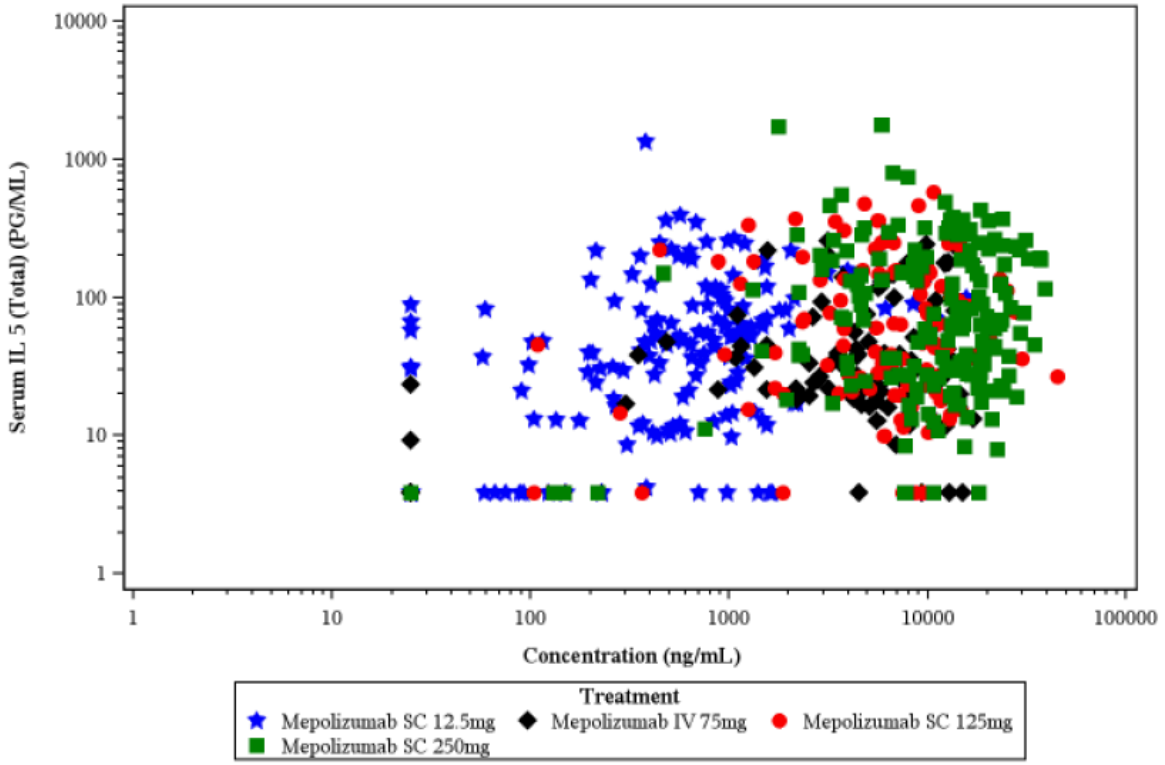

Fig.2 Serum total IL-5 concentrations versus mepolizumab plasma concentration following three doses of mepolizumab treatments.

Table 3 Change of FEV1 (L) from Baseline Following Three Doses Mepolizumab Treatments from Study 114092

	12.5 mg sc	125 mg sc	250 mg sc	75 mg iv
Screening	2.375 (N=21, SD=0.848)	2.593 (N=15, SD=0.572)	2.102 (N=23, SD=0.611)	2.411 (N=11, SD=0.674)
Day 112	2.570 (N=20, SD=0.922)	2.731 (N=14, SD=0.748)	2.479 (N=21, SD=0.831)	2.498 (N=11, SD=0.676)
Change from Baseline	0.165 (N=20, SD=0.437)	0.146 (N=14, SD=0.347)	0.433 (N=21, SD=0.567)	0.087 (N=11, SD=0.510)

- MEA115575 was a Phase 3a double-blind, placebo-controlled, subcutaneous 100 mg dose (q4w), parallel group study to determine the effect of mepolizumab to reduce oral cortical steroid (OSC) use in 135 subjects (66 in placebo group and 69 on mepolizumab treatment) with severe refractory asthma. Subjects who completed the 24-week double-blind treatment period, and met the eligibility criteria, were offered the opportunity to participate in a 12-month open-label extension (OLE) study (MEA115661). Subjects who were not eligible for the OLE study, or who chose not to enter the OLE study, were requested to return for a follow-up Visit 12 weeks after their last dose of double-blind study treatment (Week 32). PK samples were collected on Day 1, Week16 following the dose, and 12 weeks post-last dose for OLE study (4 weeks post-last dose for subjects not entering OLE study). The primary efficacy endpoint was met. Subjects treated with mepolizumab were able to achieve greater reductions in daily OCS dose, while maintaining asthma

control, compared with subjects treated with placebo (p=0.008) (Table 4). The overall incidence of AEs during treatment was higher in the placebo group (92%) compared with the mepolizumab group (83%). Numbers of subjects reporting on-treatment AEs were similar in all four treatment groups. Three subjects died during the study. One death (placebo group) occurred during the study due to gastrointestinal hemorrhage and aspiration. Thirteen subjects (12 in the placebo group and 1 in the mepolizumab group) experienced non-fatal serious AEs (SAEs) during the study. Based on individual predicted C_{trough} measurements, an approximately 2-fold accumulation between Week 4 and Week 20/24 was observed, consistent with the half-life of mepolizumab (3 weeks). Steady-state was achieved by Week 20. Adjusted mean ratios of blood eosinophil counts to baseline were statistically significant in favor of mepolizumab at every time point during the study (p<0.001). 6 of 135 subjects (4%) tested positive ADA in their post-baseline samples; one of them was positive on neutralizing antibody.

Table 4 Reduction of OCS Use Following Mepolizumab Treatments in Study MEA 115575

	Number (%) of Subjects	
Percent OCS Reduction from Baseline Weeks 20-24	**Placebo N=66**	**Mepolizumab 100 mg SC N=69**
n	66	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

- MEA115705 was a Phase 1 single blind, placebo-controlled, single ascending intravenous dose, parallel group study to assess safety, PK, and PD of mepolizumab in 35 healthy Japanese patients (26 subjects received mepolizumab treatment). Four intravenous single doses of mepolizumab at 10, 75, 250 and 750 mg were tested. PK samples were collected at pre-dose, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h post-dose on Day 1, on the morning of Day2, 3, 5, 8, 15, 29, 43, 57 and 85. The most common drug-related AE was headache. A dose-proportional PK profile was observed. The clearance of 75 mg iv was 0.152 L/day. Half-reduction of mean peripheral eosinophil counts was observed post dosing in each mepolizumab treatment group, but not in placebo, by 24 hours. At baseline, serum total IL-5 levels were below the LOQ in all except three subjects. In the placebo group, serum total IL-5 levels remained essentially unchanged till Day 43. In contrast, in mepolizumab groups, mean serum total IL-5 levels increased from baseline post-dosing in a dose dependent manner. The increase trend was observed till Day 43 for all the doses. The free IL-5 serum level remained relatively unchanged for all the groups till Day 43. The anti-mepolizumab binding antibodies (ADA) were detected in five subjects from mepolizumab treatment groups on Day 8, but not from placebo group. None of the subjects were ADA-positive during the later phase of the study (from Day 85 to Day 151).

- MEA115588 was a Phase 3 double-blind, double-dummy, placebo-controlled, parallel group study of efficacy and safety of mepolizumab adjunctive therapy in 576 patients (~ 190 subjects per arm) with severe uncontrolled refractory asthma. 2 dosage forms, 75 mg iv or 100 mg sc was administered as q4w for total 8 doses. PK samples were collected on Day 1, Week 3 and Week 8 following the first dose. The primary efficacy endpoint was met. Mepolizumab 75 mg iv and 100 mg sc produced a statistically significant ($p<0.001$) greater reduction in the frequency of exacerbations compared with placebo (Table 5). More SAEs of asthma worsening were reported for subjects treated with placebo (14%) compared with subjects treated with either dose of mepolizumab (5% and 3% with 75 mg IV and 100 mg SC, respectively). Five subjects (4 in the placebo group and 1 in the mepolizumab 100 mg SC group) were prematurely withdrawn due to AEs/SAEs. Four of these subjects (3 in the placebo group and 1 in the mepolizumab 100 mg SC group) were withdrawn due to SAEs: acute hypersensitivity reaction (placebo), epileptic seizure (placebo), a fatal traffic accident (placebo) and atrial flutter (mepolizumab 100 mg SC). Mepolizumab showed approximately two-fold accumulation when dosed every four weeks. The absolute bioavailability of the the SC route was estimated to be 80% (90% CI: 76%–84%) in this study. Blood eosinophil counts were similar across the treatment groups at baseline and treatment with mepolizumab produced a marked decrease in blood eosinophil level by Week 4 (80% for both mepolizumab groups compared to placebo, $p<0.001$), which was maintained throughout the treatment period (Fig.3). Positive immunogenicity values post-baseline were low: 3 subjects (2%) in the placebo group, 7 subjects (4%) in the mepolizumab 75 mg iv group and 9 subjects (5%) in the mepolizumab 100 mg sc group. The neutralizing antibody assay was negative for all three treatment arms.

Table 5 Reduction of Asthma Exacerbation Rate by Mepolizumab in Study 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[1]		<0.001	<0.001
Adjusted p-value[2]		<0.001	<0.001

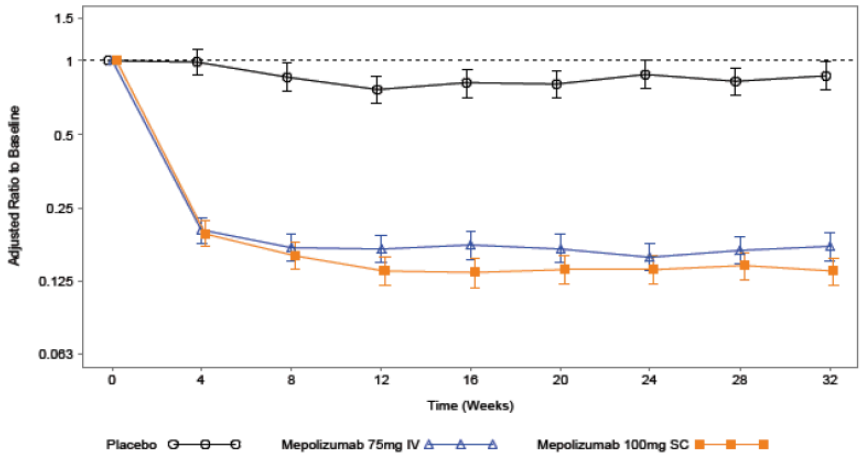

Fig.3 Time course of ratios of blood eosinophil counts to baseline in study 115588

Acceptance of these findings will be a review issue.

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

/s/

YUNZHAO REN
12/30/2014

SATJIT S BRAR
12/30/2014