Synopsis

Study Number: MEE103219

Title: A randomized, double-blind, parallel group clinical trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous (IV) mepolizumab (SB-240563) (0.55mg/kg, 2.5mg/kg or 10mg/kg) in pediatric subjects with eosinophilic esophagitis, aged 2 to 17 years (Study MEE103219)

Investigators: Multicenter study

Study centers: This was a global study sponsored by GlaxoSmithKline (GSK); 20 centers randomized subjects to treatment: one in Australia, three in Canada, three in the UK and 13 in the US; and eight centers enrolled subjects in the Observational Cohort (ObC): one in Australia, one in Canada, two in the UK and four in the US.

Publications: None at the time of this report.

Study Period: 11 September 2006 to 25 November 2008

Phase of Development: I/II

Objectives: The primary objectives of this study were to investigate safety and tolerability, pharmacokinetics, and the ability to reduce esophageal eosinophil counts to within normal limits (highest count of eosinophils per high power field [HPF] for all esophageal sites biopsied to lower than 5 cells per HPF at X400 magnification), of IV mepolizumab (0.55mg/kg, 2.5mg/kg or 10mg/kg) over 12 weeks in pediatric subjects with eosinophilic esophagitis.

The secondary objectives were to obtain dose-response information for design of subsequent studies. To explore the relationship between dose and clinical symptoms:

- Frequency and severity of the cardinal symptoms at Week 12 and Week 24:
  - eosinophilic esophagitis-related pain,
  - regurgitation,
  - vomiting,
  - swallowing disorders,
  - feeding difficulties,

Swallowing and feeding difficulties were investigated separately for solid foods ("did you eat any solid foods") and liquid foods ("did you have anything to drink"). Subjects who were fed by enteral tube could still take some fluids orally and they were asked to rate the swallowing difficulties related to their oral intake of fluids.

- Time to relapse in subjects who responded at Week 12 as defined by histopathological confirmation of a peak eosinophil count (highest count of eosinophils per HPF in one or more of esophageal sites biopsied) of >20 in

esophageal biopsy specimens at Week 24 and, to investigate the relationship between pharmacodynamic parameters (e.g., counts of circulating eosinophils, histopathology parameters, including eosinophil counts, clinical endpoints) and pharmacokinetics.

The exploratory objectives were to assess the effect of treatment on pathological features (including counts of eosinophils in blood and in esophageal biopsy specimens; to explore the relationship between dose and clinical response [e.g., symptoms, growth] in subgroups of subjects [e.g., according to subgroups of diet, medication, allergic background]; to explore the effect of mepolizumab on eosinophilic esophagitis-related biomarkers:

- biomarkers of eosinophil activation/degranulation (e.g., eosinophil-derived neurotoxin [EDN]) in esophageal tissue,
- biomarker of eosinophil activation (EDN) in stools,
- biomarker of eosinophil activation (EDN) and cytokine levels (interleukin-5 [IL-5]) in peripheral blood.

and, to explore the natural history of eosinophilic esophagitis in the ObC by observing during the 24-week observation period:

- the pattern of daily symptoms (same symptom questionnaire as the active groups),
- diet and medications,
- the pattern and results of investigations during the 24-week observation period (e.g., hematology, biochemistry, histopathology parameters whenever possible).

Methodology: This was a randomized, double-blind, stratified, parallel group Phase I/II clinical trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamic, of mepolizumab (SB-240563) administered intravenously at 0.55mg/kg, 2.5mg/kg or 10mg/kg in pediatric subjects (aged 2 to 17 years) with active eosinophilic esophagitis.

The study population consisted of two cohorts: a Treatment Cohort and an Observational Cohort. In the Treatment Cohort, a 12-week Treatment Phase was followed by a 12-week Follow-Up Phase of no treatment (Weeks 13 to 24) and a 10-week Long-Term Follow-Up Phase of no treatment (Weeks 25 to 34). During the Treatment Phase, subjects had infusions at Day 1, Week 4, and Week 8. During the Screening, Treatment and Follow-Up Phases, subjects recorded their eosinophilic esophagitis symptoms (stomach pain, chest/throat pain, regurgitation, vomiting, feeling of something stuck in throat, difficulties eating and drinking) daily using a hand held personal digital assistant (PDA). Subjects underwent an esophagogastroduodenoscopy (EGD) with biopsies at Screening and at Weeks 12 and 24. Blood samples were taken at Day 1 and Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 34 for determination, at relevant time points, of mepolizumab concentrations and blood eosinophils. A urine pregnancy test was performed on females of childbearing potential at Screening, Day 1, Weeks 4, 8, 12, and 24. The total duration from the start of Screening to the Long-Term Follow-Up visit was 36 weeks.

Additionally, subjects with eosinophilic esophagitis who met the key inclusion/exclusion criteria but chose not to enter the treatment arm of the study were enrolled into an ObC for the purpose of providing natural history information on the disease throughout 24 weeks. The ObC was not used to make comparisons to the Treatment Cohort in this study. In the ObC, subjects underwent an EGD with biopsies at Screening and had a blood sample taken for hematology including blood eosinophil counts. Subjects recorded their eosinophilic esophagitis symptoms (stomach pain, chest/throat pain, regurgitation, vomiting, feeling of something stuck in throat, difficulties eating and drinking) daily using a hand held PDA throughout the 24 weeks of observation. No other investigations were mandated, but the eosinophilic esophagitis-related events (e.g., adverse events, medications, diet, laboratory test results) were collected.

Number of subjects: In the Treatment Cohort, 54 subjects (18 per treatment arm) were planned and 59 (19 in the 0.55mg/kg treatment arm and 20 each in the 2.5 and 10mg/kg treatment arms) were randomized to treatment. Subjects were to be randomized to one of the three treatment groups within two separate strata, according to the subject's age (age groups: 2 to 7 years old, 8 to 17 years). In the ObC, 18 subjects were planned and enrolled.

Diagnosis and main criteria for inclusion: For inclusion in this study, male or female subjects had to be between 2 to 17 years of age, had to weigh ≤ 84.9kg (males)/ ≤ 72.5kg (females), and had a body mass index (BMI) between 5% and 85% for age. To be eligible for entry in the treatment group of the study, a female subject had to be not pregnant or nursing, of non-childbearing potential, or of childbearing potential with a negative urine pregnancy test at the Screening visit.

Eligible subjects had a diagnosis of eosinophilic esophagitis and current evidence on biopsy of active disease defined as peak esophageal eosinophil counts of 20 or more eosinophils in a minimum of one HPF at 400X magnification on histology of esophageal biopsies from distal and mid-esophagus within two weeks of commencing study medication, as determined by the central histopathologist. Subjects were also required to have an inadequate response to, or be intolerant of, therapy for eosinophilic esophagitis.

A subject was not eligible for inclusion in this study if there was evidence of eosinophilic gastrointestinal enteropathy (EGID) other than isolated eosinophilic esophagitis, evidence of gastroesophageal reflux disease (GERD), or other causes of esophagitis which in the investigator's opinion was the predominant cause of the subject's esophageal eosinophilia, or presence or history of hypereosinophilic syndromes, collagen, vascular disease, vasculitis, allergic drug reaction as the cause of the peripheral eosinophilia, graft-versus host disease, chronic idiopathic inflammatory bowel disorders, celiac disease, or active *H. pylori* infection.

Treatment administration: Mepolizumab for injection, 250mg per vial, was presented as a sterile, lyophilized formulation in a 10mL clear glass, stoppered vial. The drug was supplied by GSK as a single-use vial and was not formulated with a preservative. The mepolizumab lots used globally in this study were: 041019480, 041037464, and 041051118.

A total of 54 subjects (18 per treatment arm) with eosinophilic esophagitis were to be randomized to the treatment groups in the study. Each eligible subject was randomized to one of three treatment groups:

- nominal dose level 0.55mg/kg
- nominal dose level 2.5mg/kg
- nominal dose level 10mg/kg

Subjects were randomized with equal allocation to one of the three treatment groups within two separate strata according to the subject's age (age groups: 2 to 7 years or 8 to 17 years). A minimum number of 15 subjects were to be randomized in each of the age groups to ensure sufficient subjects for pharmacokinetics.

Additionally, 18 subjects who met the inclusion/exclusion criteria but chose not to enter the blinded study were to be enrolled into an ObC and observed throughout the study.

The volume of mepolizumab dosing solution to be administered by IV infusion was determined by the subject's weight band (weight bands ranged from 5 to 5.9kg to 80 to 84.9kg). All subjects within a given weight band were to receive the same volume of infusate regardless of treatment group. Within each weight band, the subject received a dose based on the middle weight of the weight band, which meant that subjects received between 90% and 113% of their nominal dose.

Criteria for evaluation:

The Screening visit occurred 2 weeks before the 1st study medication administration to confirm that the subjects met the entrance criteria for the study. Informed consent and assent were obtained according to the IRB/IEC guidelines, and prior to performance of any protocol specific procedures. The following procedures were performed at the Screening visit: complete medical history; prior eosinophilic esophagitis therapy history (3 months); physical examination; allergic profile; vital signs; 12-lead electrocardiogram (ECG); clinical laboratory tests (hematology, chemistry, immunoglobulin E [IgE] level, urinalysis); urine pregnancy test (female subjects of childbearing potential), EGD and biopsy, and collection of samples for biomarker testing.

Study assessments obtained during the study consisted of adverse events (AEs), concurrent medications, diet history, physical examination, vital signs, 12-lead ECGs, clinical laboratory tests (hematology, chemistry, IgE levels, urinalysis), urine pregnancy test (female subjects of childbearing potential), pharmacokinetic sampling, assessment of clinical symptoms, anti-mepolizumab antibodies, biomarkers, and EGD and biopsy.

Statistical methods: A total sample size of 54 subjects (i.e., 18 per group) provides 80% power at a 5% 2-sided significance level to detect a difference of 50% for the pairwise comparisons between the low dose versus the middle and high dose treatment groups in the response rates for the primary PD endpoint of <5 eosinophils/HPF at Week 12. Response rates of 30% in the mepolizumab 0.55mg/kg arm and 80% in the mepolizumab 2.5mg/kg and 10mg/kg arms were assumed. For the primary endpoint, the difference in the response rates between treatment groups was analyzed by exact logistic regression

with terms for treatment group and age group; the difference was presented as an odds ratio, along with the corresponding 95% confidence intervals and p-value. The study was not powered for statistical inference on the secondary endpoints; therefore, results of statistical testing for the secondary endpoints were considered descriptive. No adjustment was made for multiple comparisons. Exploratory endpoints were evaluated using descriptive statistics.

The primary population of interest for presentation of efficacy and safety was the **Intention-to-treat (ITT) population** (defined as all subjects in the Treatment Cohort who gave informed consent, were randomized, and received at least one dose of medication). The **pharmacokinetic population** included any subject having received study medication and for whom a mepolizumab sample was obtained and analyzed. The **pharmacodynamic population** included any subject having received study medication and for whom a pharmacodynamic variable (blood eosinophils and/or tissue eosinophils) was obtained.

Summary:

Demographics and Baseline:

Treatment Cohort: A total of 59 subjects were enrolled in the Treatment Cohort and included in the ITT population (19 subjects in the 0.55mg/kg treatment arm and 20 subjects each in the 2.5 and 10mg/kg treatment arms). Most (52 of 59 subjects, or 88%) subjects in the ITT population completed the study.

Demographics (ITT Population)

	Number (%) of Subjects		
	Mepolizumab 0.55mg/kg (N=19)	Mepolizumab 2.5mg/kg (N=20)	Mepolizumab 10mg/kg (N=20)
Age (yrs)			
Mean (SD)	10.4 (4.28)	10.5 (5.15)	10.4 (4.66)
Min-Max	3-17	2-17	2 -17
Sex, n (%)			
Female	3 (16)	6 (30)	3 (15)
Male	16 (84)	14 (70)	17 (85)
Ethnicity, n (%)			
Hispanic/Latino	2 (11)	0	1 (5)
Not Hispanic/Latino	17 (89)	20 (100)	19 (95)
Race and racial combinations			
n	18	20	20
White	18 (100)	19 (95)	17 (85)
African American/ African heritage	0	1 (5)	2 (10)
Asian	0	0	1 (5)
BMI, kg/m^2			
Mean (SD)	17.9 (4.07)	19.6 (3.40)	19.1 (3.45)

BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation

Observational Cohort: A total of 18 subjects were included in the ObC. Two of these subjects were prematurely withdrawn from the study: one was lost to follow-up and one decided to withdraw. The mean age for subjects in the ObC was 10.3 years. Most subjects were male and all but one were white.

Safety:

Treatment Cohort: During the Treatment Phase, AEs were reported in 86% (51/59) of subjects with the lowest incidence of AEs (16 of 20 subjects, or 75%) reported in the 2.5mg/kg mepolizumab group. The system organ classes (SOC) with the highest incidence of AEs during the Treatment Phase were gastrointestinal disorders and infections and infestations. During the Treatment Phase, the most common AEs (reported in >5 subjects overall) were nasopharyngitis, vomiting, cough, diarrhea, headache, oropharyngeal pain, upper abdominal pain, and pyrexia. No cardiac or ECG-related adverse events were reported in any subjects during the Treatment Phase of the study. No AEs appeared to be dose-related.

Adverse Events During the Treatment Phase Occurring in ≥5% of Subjects Overall (ITT Population)

	Number (%) of Subjects [number of events]		
	Mepolizumab 0.55mg/kg (N=19)	Mepolizumab 2.5mg/kg (N=20)	Mepolizumab 10mg/kg (N=20)
Any event	18 (95) [104]	15 (75) [62]	18 (90) [70]
Nasopharyngitis	5 (26) [6]	1 (5) [1]	4 (20) [4]
Vomiting	5 (26) [5]	3 (15) [5]	2 (10) [3]
Cough	7 (37) [8]	1 (5) [1]	0 [0]
Diarrhea	3 (16) [3]	4 (20) [4]	1 (5) [1]
Headache	2 (11) [6]	2 (10) [2]	4 (20) [4]
Oropharyngeal pain	4 (21) [5]	1 (5) [2]	2 (10) [2]
Upper abdominal pain	3 (16) [3]	2 (10) [3]	1 (5) [1]
Pyrexia	4 (21) [5]	0 [0]	2 (10) [3]
Abdominal pain	2 (11) [2]	0 [0]	3 (15) [3]
Nasal congestion	1 (5) [1]	3 (15) [3]	1 (5) [1]
Nausea	4 (21) [7]	0 [0]	1 (5) [1]
Asthma	3 (16) [6]	1 (5) [2]	0 [0]
Dizziness	1 (5) [2]	0 [0]	2 (10) [2]
Ear infection	1 (5) [1]	1 (5) [1]	1 (5) [1]
Influenza	1 (5) [1]	2 (10) [2]	0 [0]
Streptococcal pharyngitis	1 (5) [1]	1 (5) [1]	1 (5) [1]
Pruritus	3 (16) [3]	0 [0]	0 [0]
Sinusitis	2 (11) [2]	0 [0]	1 (5) [4]
Throat irritation	1 (5) [1]	1 (5) [1]	1 (5) [1]
Upper respiratory tract infection	1 (5) [1]	1 (5) [1]	1 (5) [1]

Thirteen of 59 subjects (32% in the 0.55mg/kg group, 20% in the 2.5mg/kg group, and 15% in the 10mg/kg mepolizumab group) experienced AEs during the Treatment Phase that were assessed as drug-related by the investigator. Pruritus and back pain were the only drug-related AEs occurring in more than one subject; both events were reported in two subjects each.

There were no verbatim reports of hypersensitivity or infusion reactions in the ITT population. Pruritus and back pain were the only AEs reported in more than one subject within 24 hours of an infusion.

No subject died during the study. Three subjects reported SAEs during the Treatment Phase. These events were chest discomfort, esophageal injury (occurred during EGD study procedure), and food stuck in throat. One subject reported an SAE of eosinophilic esophagitis of moderate intensity in the Follow-Up Phase and one subject reported two SAEs (sinusitis and asthma) during the Long-Term Follow-Up Phase. All the SAEs resolved or were resolving at last contact and all were assessed as unrelated to mepolizumab by the investigator. [redacted]

[redacted] Two subjects withdrew from the Follow-Up Phase due to AEs of eosinophilic esophagitis.

ECG data from this study show no clinically relevant trends related to prolongation of the QT/QTc interval. There were no clinically relevant changes in vital sign or clinical laboratory results in any of the three treatment groups.

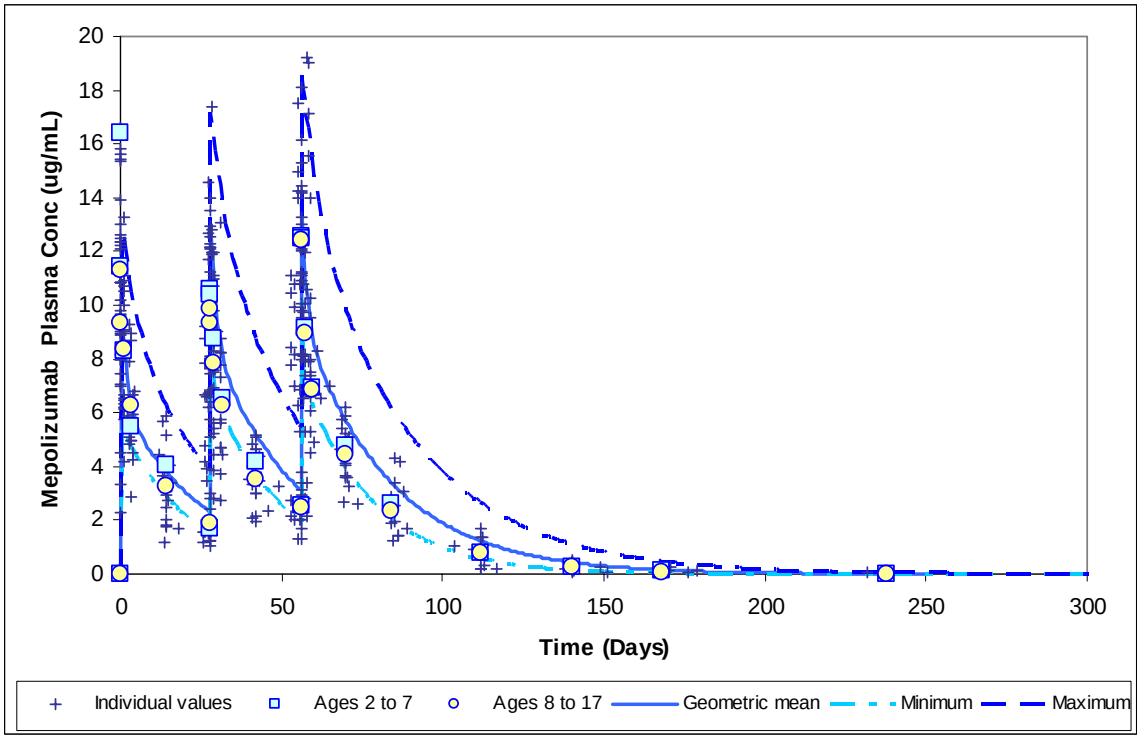
Observational Cohort: Three subjects in the ObC reported four AEs: vomiting, upper respiratory tract infection, depression, and dyspnea. No subject in the ObC died, experienced a non-fatal SAE, or had an AE that led to withdrawal from the study.

Pharmacokinetic Results: Mean mepolizumab plasma concentrations were similar at the 0.55mg/kg dose between subjects whose age ranged from 2 to 7 years and those whose age ranged from 8 to 17 years. At the 2.5mg/kg and 10mg/kg doses, mean mepolizumab plasma concentrations were slightly higher in the older than younger children at the majority of time points while ranges overlapped between the two age groups.

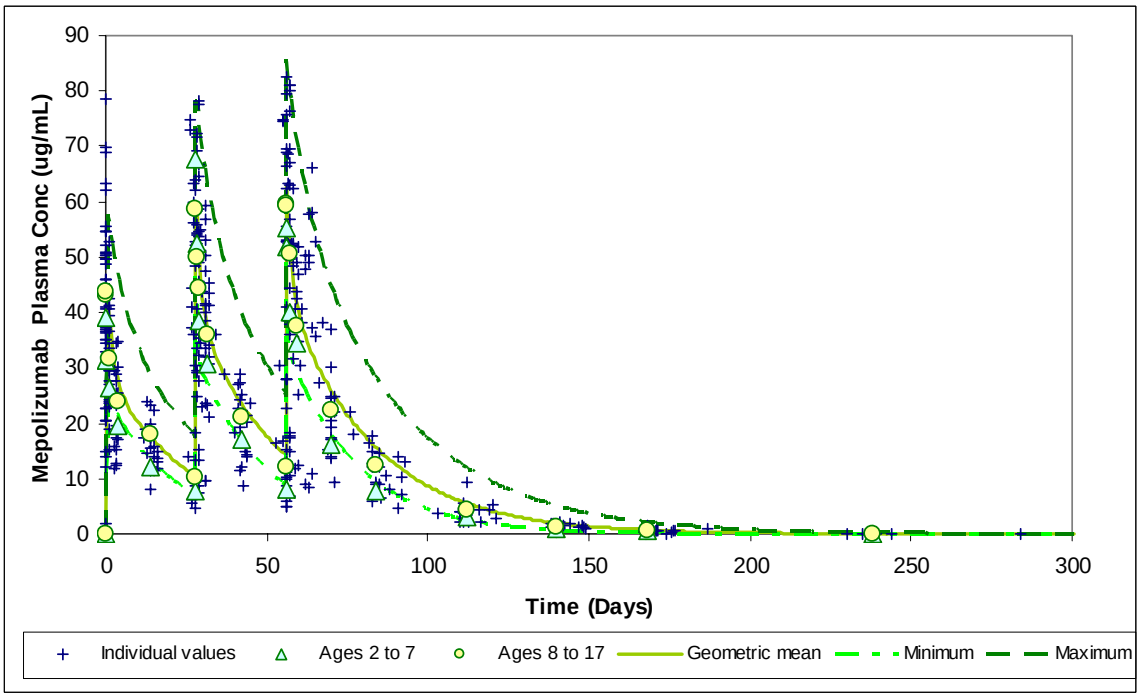
Mepolizumab plasma concentration-time data from this study were visually compared with data from previous adult single-dose studies (SB-240563/Study 001 and SB-240563/Study 035) in which similar doses were administered and a full-sampling schedule for pharmacokinetics was used. In the visual comparison, plasma concentrations from MEE103219 were similar to mepolizumab plasma concentrations from the previous studies.

As a limited pharmacokinetic sampling schedule was used in this study, full-profile pharmacokinetic analysis was not possible. To determine if the concentration values obtained in this study were consistent with the previously observed pharmacokinetic behavior after single doses in adult subjects with mild asthma (SB-240563/Study 001, SB-240563/Study 035, and SB-240563/Study 001 and SB-240563/Study 035 combined), population estimates based on a two-compartment IV infusion model along with doses and dosing schedule in MEE103219 were used to predict multiple-dose mepolizumab concentrations. Predictions using a range of pharmacokinetic estimates previous single-dose analyses accounted for most of the individual concentrations. Simulated data appeared to fit the individual and mean data. The predictions from SB-240563/Study 001 appeared to best fit the individual and mean data. Simulations from SB-240563/Study 001 are presented below along with mean an actual data from MEE103219 for 0.55mg/kg, 2.5mg/kg, and 10mg/kg.

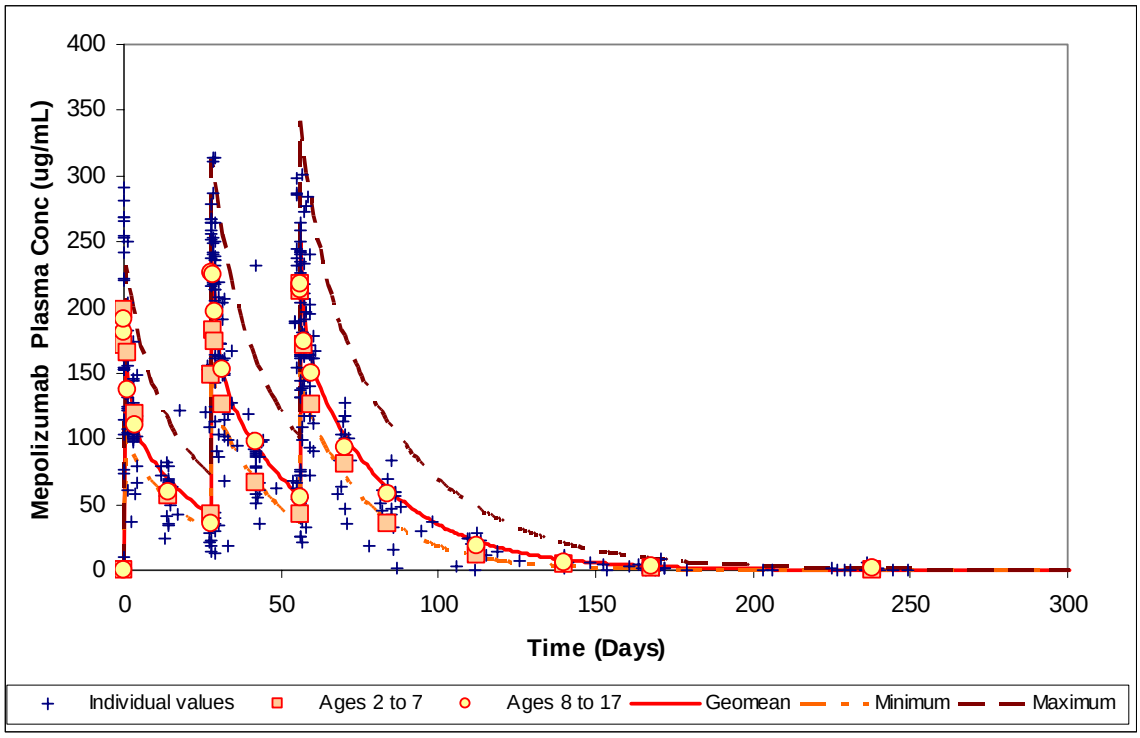
Individual and Mean Mepolizumab Plasma Concentrations Overlaid with a Range of Simulated Data – 0.55mg/kg



Individual and Mean Mepolizumab Plasma Concentrations Overlaid with a Range of Simulated Data – 2.5mg/kg



Individual and Mean Mepolizumab Plasma Concentrations Overlaid with a Range of Simulated Data – 10mg/kg



Efficacy Results:

Treatment Cohort: The primary efficacy endpoint was the proportion of subjects who responded to treatment, where response was defined as achieving a reduction in esophageal eosinophils to <5 cells per HPF at Week 12. Five (three in the 0.55mg/kg group and two in the 2.5mg/kg group) of the 59 subjects in this study were responders. There were no statistical differences between the treatment groups.

Histopathological Response of < 5 Cells/HPF at Week 12 - (ITT Population)

	Number (%) of Subjects		
	Mepolizumab 0.55mg/kg (N=19)	Mepolizumab 2.5mg/kg (N=20)	Mepolizumab 10mg/kg (N=20)
Age Group: Overall, n (%)			
n	17	20	20
Responders[a]	3 (17.6)	2 (10.0)	0
Odds Ratio[b]		0.55	0.21
95% CI of Odds Ratio		(0.04, 5.44)	(<0.01, 2.07)
p-value[c]		0.865	0.190
Age Group: 2-7 years old, n (%)			
n	3	6	6
Responders[a]	0	1 (16.7)	0
Age Group: 8-17 years old, n (%)			
n	14	14	14
Responders[a]	3 (21.4)	1 (7.1)	0

a. Worst case (non-response) assumed for missing data occurring due to lack of efficacy or adverse event. Missing data occurring due to other reasons was not imputed.
b. Odds ratio and p-value are from the exact logistic regression model adjusted for age group.
c. p-value is based on a pairwise comparison to 0.55mg/kg group.

An evaluation was also made of responses defined as reductions in peak eosinophils to levels of 5 to <10 cells/HPF, 10 to <15 cells/HPF, 15 to <20 cells/HPF, and ≥20 cells/HPF achieved. Overall, 18/59 (31%) subjects achieved the pre-defined response level of <20 eosinophils per HPF at Week 12 whereas 39/59 (66%) subjects did not respond (i.e., peak eosinophils remained ≥20 cells/HPF at Week 12.

Mean esophageal eosinophil counts were decreased at Week 12 for all three treatment groups compared to baseline results. These decreases were not sustained at Week 24 (off-treatment since Week 12) for the two lowest dose groups but mean esophageal eosinophil counts were still decreased from baseline in the 10mg/kg group.

Peak esophageal eosinophil counts decreased at Week 12 for all three treatment groups. These decreases were not sustained at Week 24 (off-treatment since Week 12) for the two lowest dose groups but peak esophageal eosinophil counts were still decreased from baseline in the 10mg/kg group.

Among the five subjects who achieved a response of <5 cells/HPF at Week 12 (based on a worst case analysis), three relapsed and two maintained a response of <20 cells/HPF at Week 24.

Mean blood eosinophil counts were at the high end of the normal range (0.6 GI/L) at the Screening and baseline (Day 1) assessments for all three mepolizumab treatment groups. A marked decrease in blood eosinophils was observed in the mepolizumab-treated subjects as early as 24 hours after the start of treatment and remained low through the Week 12 assessment.

The most predominant macroscopic abnormalities at Screening (reported in more than 50% of the subjects) included the presence of white exudates, the subjective mucosal change of edema, furrows or vertical lines, and loss of vascular pattern. The presence of white exudates was reported as resolved in more than half of subjects at Week 12 (67%) and Week 24 (58%), whereas resolution of edema, furrows or vertical lines, and loss of vascular pattern was reported in fewer subjects. While other esophageal mucosal abnormalities were reported in fewer subjects, marked improvement was observed in terms of the number of subjects achieving resolution of many of these abnormalities at the end of treatment. In particular, resolution of nodules, exudate plaques, mucosal friability and fragility, crepe paper mucosa, circular folds and corrugated rings were reported for 40% to 79% of subjects. For most abnormalities, there were a few subjects who had the abnormality absent at Screening but developed it at Week 12 or 24.

At Screening, the majority of subjects were able to drink and eat solid foods daily (mean proportion of days 92.2% for eating solid food and 99.49% for drinking) with mean pain severity and difficulty scores ranging between none and a little. Although there were trends towards improvement observed for almost all of the clinical symptoms, the low baseline severity and frequency of symptoms limited the capacity for changes of substantial magnitude.

Observational Cohort: The mean (SE) esophageal eosinophil count at Screening for the ObC was 35.54 (5.633). The most common esophageal macroscopic findings were furrows or vertical lines, loss of vascular pattern, and edema.

Four of the ObC subjects (22%) had no symptoms at Screening, seven subjects (39%) had one or two symptoms, and seven subjects (39%) had three or more symptoms. Generally, the proportion of days with symptoms and the severity of the symptoms were low during the first week and remained so during the study. Subjects ate solid foods and drank liquids on all days during Week 1.

Pharmacokinetic/Pharmacodynamic Results: In the Treatment Cohort, blood or esophageal tissue eosinophil data were variable (coefficient of variation [CV%] ranged 36% to 267%) during the study, but eosinophil counts in both decreased from baseline after dosing with mepolizumab. As there were more frequent sampling times for blood eosinophils (n= 18) than for tissue eosinophils (n=3), the effect of mepolizumab concentrations on blood eosinophils was better defined than the effect on tissue eosinophils. Therefore, the decrease in blood eosinophils occurred after the first dose and for tissue eosinophils it was observed at the time of the second biopsy (Week 12). The timing and magnitude of decreases in tissue eosinophils following any of the three doses are unknown.

Due to the paucity of esophageal tissue biopsies, the mepolizumab concentration correlating with low eosinophil levels could not be determined as accurately but the general tendency was still seen. Mepolizumab concentrations were greater than 4.0μg/mL (value selected from previous studies) for a longer time in a dose-proportional manner; therefore, esophageal tissue and blood eosinophils remained decreased for a longer time at the higher doses. In addition, there was a tendency for a greater rate of increase in blood or tissue eosinophils when mepolizumab concentrations were <1μg/mL.

Biomarker Results: At Week 12 mean values for extracellular EDN deposition and EDN eosinophil infiltration were decreased from baseline at the distal and mid sites across all three mepolizumab treatment groups. Week 24 mean values were higher than those noted at Week 12 but generally for the two higher doses still represented decreases from baseline.

Serum EDN results were similar to those obtained from eosinophils in esophageal tissue with decreases from baseline noted at Week 12 in all three mepolizumab groups. At Week 24 mean EDN had returned to near baseline levels or above in the two lower dose groups, but sustained an approximate 50% decrease from baseline in the 10mg/kg dose group.

Based on the mean changes, there were possible trends toward a decrease from Screening to Week 12; however, the data were quite variable and therefore no clear interpretation can be made. At Week 24, change from baseline in mean (SD) stool EDN concentrations were slightly decreased in the 0.55mg/kg group and increased in the 2.5mg/kg and 10mg/kg groups, and were highly variable.

Serum IL-5 concentrations were available for less than half of the subjects thus making it difficult to draw conclusions regarding any changes in free-IL5 levels.

At Weeks 12 and 24, mean IgE levels tended to increase from baseline; however, the data were highly variable and therefore no clear interpretation can be made.

Immunogenicity Results: Forty-six (46) of 59 subjects (78%) who were dosed with mepolizumab developed anti-mepolizumab antibodies. Out of these 46 positives, 25 subjects developed detectable antibodies at > two time points with only 13 of them persisting until Week 34. Twenty-one (21) subjects developed transient antibodies (detectable antibodies at a single time point, but negative for antibodies at all other time points) that had disappeared by the end of the study. The titer values in most of positive subjects (85%) at Week 34 were < 20. The presence of anti-mepolizumab was not associated with any specific AEs, SAE or clinically significant laboratory abnormalities.

Conclusions:

- All doses of mepolizumab were well tolerated in the pediatric eosinophilic esophagitis subjects included in this study. The most common AEs (reported in >5 subjects overall) during the Treatment Phase were nasopharyngitis, vomiting, cough, diarrhea, headache, oropharyngeal pain, upper abdominal pain, and pyrexia; no AEs appeared to be dose-related. ECG data showed no clinically relevant trends related to prolongation of the QT/QTc interval; no cardiac or ECG-related adverse events were reported. No clinically relevant trends in vital signs or laboratory data were observed.
- At Week 12 (end of treatment), the primary efficacy endpoint (peak eosinophil count of <5 cells per HPF) was achieved in 5/59 (8%) subjects (three in 0.55mg/kg, two in 2.5mg/kg group). There were no statistical differences between the 0.55mg/kg compared to 2.5mg/kg or 10mg/kg groups with respect to this endpoint. At

Week 24, two of these five subjects maintained a response below the entry criteria of <20 cells per HPF.

- Treatment with mepolizumab was associated with a pronounced pharmacodynamic effect characterized by a marked reduction of eosinophils in both esophageal tissue and the blood.
- There was a low frequency and severity of symptoms in most subjects at baseline. The study was not powered for the assessment of clinical symptoms; trends toward improvement were observed but the clinical relevance of these results is unclear.
- Plasma mepolizumab concentrations were similar in subjects 2 to 7 years old compared with 8 to 17 years old. Concentrations were also similar when comparing this study population of subjects 2 to 17 years old with adults dosed on a mg/kg basis.
- Plasma mepolizumab concentrations appeared dose-proportional and concentrations across doses were associated with decreases in mean and peak esophageal and blood eosinophil counts. The mean reductions in esophageal and blood eosinophil counts were somewhat similar among the three dose groups but remained decreased for a longer time in the higher dose groups where plasma concentrations were higher for longer.
- Assessments of the relationship between dose and various clinical responses were secondary and exploratory objectives, and these assessments did not reveal any clear dose-response relationship.
- A high positive incidence was observed from the anti-mepolizumab binding antibody assay when using a sensitive ECL assay; however, these results were unable to be confirmed for their neutralizing activity. Most of the positive results were transient with low titers. Furthermore, positive results were not associated with the clinical adverse events and did not impact on the pharmacokinetic and pharmacodynamic profiles. These findings indicate low risks and/or concerns associated with the immunogenicity profile.

Date of Report: 26 June 2009