The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: mepolizumab (SB240563)

Study No.: MHE100901

Title: An Open-label Extension Study to Study MHE100185, to Evaluate Long-term Safety, Efficacy and Optimal Dosing Frequency of 750 mg Intravenous Mepolizumab in Subjects with Hypereosinophilic Syndrome (Final Report)

Rationale: To evaluate data on the long-term safety and efficacy of mepolizumab in the treatment of subjects with HES. This study was also intended to explore the optimal mepolizumab dosing frequency based on individual patient requirements for management of their disease in a clinical setting.

Phase: III

Study Period: 30 September 2004 through 29 September 2010

Study Design: Multicenter, open-label, long-term safety study

Centres: A total of 23 centers enrolled subjects in the study: 9 in the United States, 3 each in Belgium, Canada, and Germany, 2 each in Australia and France, and 1 in Italy.

Indication: Hypereosinophilic syndrome (HES)

Treatment: Mepolizumab 750 mg IV, dosing regimen was individually optimized (maximum dosing frequency one infusion per month)

Objectives: The primary objective was to evaluate the long-term safety of mepolizumab 750 mg intravenous (IV) infusion at maximum dosing frequency of once every month in subjects with hypereosinophilic syndrome (HES). Secondary objectives were to: Investigate the durability of response with mepolizumab 750 mg IV infusion in maintaining the prednisone dose level of those subjects who completed the 9-month treatment period in Study MHE100185 and achieved a daily prednisone dose of <=10 mg; characterize the durability of response with mepolizumab 750 mg IV infusion in reducing blood eosinophil count; gain further information on potential dosing frequency of mepolizumab 750 mg IV infusion in HES subjects using blood eosinophil count as a dosing marker in a clinical practice setting; investigate the clinical efficacy of mepolizumab 750 mg IV infusion beyond 9 months treatment in subjects with various HES clinical manifestations; and gain further information on quality of life (QoL) measures in HES subjects treated with mepolizumab 750 mg IV infusion.

Primary Outcome/Safety Variable: Frequency of all adverse events (AEs)

Secondary Outcome/Efficacy Variables: endpoints

Proportion of subjects achieving a prednisone level of $\leq$10 mg (as sole background therapy) at the end of the study

Proportion of subjects maintaining a daily dose of $\leq$10 mg prednisone for at least 3 months ($\geq$12 weeks) for those subjects who entered Stage 2 directly from Study MHE100185 with a prednisone level of $\leq$10 mg

Proportion of subjects achieving a daily dose of $\leq$10 mg prednisone for at least 3 months ($\geq$12 weeks) for those subjects who entered Stage 1 from Study MHE100185 with a prednisone level of >10 mg

Proportion of subjects achieving an eosinophil count <600 cells/μL at the end of the study

Blood eosinophil count (with consideration of a subject's HES background therapy) during each stage of treatment

Proportion of subjects by dosing frequency groups (defined as 2-week dosing ranges greater than a 4-week interval) at the end of Stage 2

Pruritus Visual Analogue Scale (pVAS) and total erythema/edema score at 3 months after the start of the study and every 6 months thereafter.

Quality of life and current health status were assessed based on SF-12v2 scores at 3 months after the start of the study and every 6 months thereafter.

Statistical Methods: The Intent-to-Treat (ITT) Population was defined as all subjects who received at least one infusion of mepolizumab in Study MHE100901 and was used for analysis of safety, efficacy, and health outcomes data. If a subject was enrolled into Study MHE100901 $\leq$1 month of the final assessments for Study MHE100185, the last observed values from Study MHE100185 were used as the baseline values for Study MHE100901. If a subject was enrolled into Study MHE100901 >1 month after the final assessments for Study MHE100185, baseline assessments were recorded at the Baseline Visit.

Adverse events (AEs) and serious adverse events (SAEs) recorded on the case report form (CRF) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and within SOC by preferred term. AEs and SAEs were summarized by descending incidence.

The duration of exposure to mepolizumab and intervals between infusions were calculated. The proportion of subjects with a total daily dose of ≤10 mg prednisone as sole background HES therapy at selected timepoints were summarized. Blood eosinophil counts, assessed at Baseline and various timepoints throughout the study, were summarized.

Study Population: All subjects who either completed 9 months of treatment or withdrew from Study MHE100185 after receiving at least two infusions of study medication could be enrolled into Study MHE100901. At entry into the extension study, subjects could not have any life-threatening or other serious illness or clinical manifestation deemed inappropriate for inclusion in the study per the principal investigator.

	Mepolizumab 750 mg
Number of Subjects:	78
Completed, n (%)	N/A-study terminated
Total Number Subjects Withdrawn, N (%)	5 (6)
Withdrawn due to Adverse Events, n (%)	10 (13)
Withdrawn due to Lack of Efficacy, n (%)	6 (8)
Withdrawn for other reasons, n (%)	1 (1)
Demographics	
N (ITT)	78
Females: Males	42:36
Mean Age, years (SD)	49.2 (14.89)
White, n (%)	67 (86)

Efficacy Results:

Subjects Achieving Specified Daily Prednisone Dose for Defined Time Period

Time Period	**≤10mg n (%)**	**0mg [1] n (%)**
≥ 24 weeks	61 / 71 (86)	44 / 71 (62)
≥ 48 weeks	56 / 65 (86)	40 / 65 (62)
≥ 72 weeks	49 / 63 (78)	35 / 63 (56)
≥ 96 weeks	44 / 60 (73)	33 / 60 (55)
≥ 120 weeks	39 / 59 (66)	29 / 59 (49)
≥ 144 weeks	32 / 59 (54)	24 / 59 (41)
≥ 168 weeks	27 / 59 (46)	21 / 59 (36)
≥ 192 weeks	23 / 58 (40)	17 / 58 (29)
≥ 216 weeks	16 / 54 (30)	14 / 54 (26)
≥ 240 weeks	10 / 39 (26)	9 / 39 (23)

1. The 0 mg group is a subset of subjects from the ≤10mg group.

Summary of Subjects Corticosteroid-Free over Time (as Sole Background Therapy)

Time Point	**Stage 1 Entry N=37**	**Stage 2 Entry N=41**
MHE100901 Baseline	2/37 (5%)	22/41 (54%)
Week 12	8/34 (24%)	22/40 (55%)
Week 24	15/32 (47%)	19/38 (50%)
Week 48	16/29 (55%)	21/35 (60%)
Week 96	15/27 (56%)	19/33 (58%)
Week 144	16/26 (62%)	17/33 (52%)
Week 192	18/26 (69%)	20/32 (62%)
End of Study	53/78 (68%)	

Proportion of Subjects Achieving an Eosinophil Level of <600 cells/uL (in addition to the Lowest Background Therapy [1]) at End of Study (MHE100901 ITT population)			
Stage at Entry: Overall	**Previous Placebo**	**Previous Mepo**	**Total**
Total number of subjects achieving endpoint	23 / 38 (61)	23 / 40 (58)	46 / 78 (59)
Eosinophil level/background therapy for those subjects not achieving the endpoint:			
<600 cell/uL at end of study with increase in background therapy	4 / 38 (11)	8 / 40 (20)	12 / 78 (15)
≥600 cell/uL at end of study with no increase in background therapy	9 / 38 (24)	4 / 40 (10)	13 / 78 (17)
≥600 cell/uL at end of study with increase in background therapy	0 / 38	1 / 40 (3)	1 / 78 (1)
Unknown	2 / 38 (5)	4 / 40 (10)	6 / 78 (8)
1. Lowest background therapy is defined as the prednisone or equivalent daily dose, and number of additional HES medications, being taken of the day of the first stage 2 infusion			

Safety Results: AEs and SAEs were collected from study start through study termination.

Most Frequent Adverse Events – On-Therapy	**Mepolizumab 750 mg N=78**
Subjects with any AE(s), n,(%)	76 (97)
Cough	26 (33)
Fatigue	24 (31)
Headache	23 (29)
Upper respiratory tract infection	23 (29)
Sinusitis	22 (28)
Bronchitis	21 (27)
Arthralgia	19 (24)
Nausea	18 (23)
Diarrhea	18 (23)
Dyspnea	18 (23)
Nasopharyngitis	18 (23)

Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**	
	Mepolizumab 750 mg
Subjects with non-fatal SAEs, n (%) [related]	38 (49) [1] [0]
Pneumonia	4 (5) [0]
Pyrexia	3 (4) [0]
Cardiac failure	2 (3) [0]
Cholecystitis acute	2 (3) [0]
Diarrhea	2 (3) [0]
Eosinophilia [2]	2 (3) [0]
Dyspnea	2 (3) [0]
Prostate cancer	2 (3) [0]
1. There were 40 subjects with SAEs on-treatment or follow-up. However, subjects 200 and 221 died (with no other SAEs); therefore only 38 subjects had non-fatal SAEs. 2. As a sign of HES (i.e., elevated eosinophil counts due to lack of efficacy or disease progression)	
Subjects with fatal SAEs, n (%) [related]	4 (5) [1]
Cardiac failure; Sepsis; Multi-organ failure	1 (1) [0]
Aspiration pneumonia; Respiratory failure	1 (1) [0]
Sudden death[1]	1 (1) [0]
Angioimmunoblastic T-cell lymphoma; Cardiopulmonary failure	1 (1) [1]
1. Reported as myocardial infarction in a prior interim analysis, but SAE was clarified as 'sudden death' on follow-up	

Conclusion: Four deaths occurred during this long-term extension study. Of the SAEs leading to the deaths, one event (angioimmunoblastic T-cell lymphoma) was considered possibly related to study drug by the investigator though the investigator also reported the relationship as unlikely. Mepolizumab was effective in reducing or eliminating prednisone requirement with more than half the subjects achieving steroid-free status. Overall, no significant safety concerns were attributable to treatment with mepolizumab.