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.

Study No.: MEA114092
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.
Rationale: Mepolizumab is under development for the treatment of severe asthma with eosinophilic inflammation. The purpose of this study was to evaluate the exposure-response (pharmacokinetics [PK]/pharmacodynamics [PD; blood eosinophils]) relationship of repeat doses of mepolizumab administered via the subcutaneous (SC) and intravenous (IV) routes of administration to asthmatic subjects with elevated blood eosinophil levels.
Phase: IIa
Study Period: 21 February 2011–07 March 2012.
Study Design: Multicentre, randomised, parallel group, repeat dose, open label, dose ranging.
Centres: Eleven centres in four countries.
Indication: Asthma.
Treatment: Subjects received three once-monthly administrations of either SC mepolizumab 12.5 mg or 125 mg or 250 mg, or IV mepolizumab 75 mg. The duration of IV administration was approximately 30 to 60 minutes.
Objectives: The primary objective was to demonstrate that the PK/PD relationship between the exposure of SC administered mepolizumab and a marker of response, blood eosinophils, is comparable to that observed following IV administration.
Primary Outcome/Efficacy Variables: The primary endpoint of this study was 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 (Emax), time to maximum change in blood eosinophil levels ($Tmax_{eos}$), time to 50% eosinophil repletion (Trep); area under the plasma concentration-time curve (AUC), maximum plasma concentration (Cmax), time to Cmax (Tmax) and terminal half-life ($t_{½}$) of mepolizumab.
Secondary Outcome/Efficacy Variables: AUC and Cmax of mepolizumab for bioavailability assessment; levels of anti-mepolizumab antibodies; adverse events (AEs), vital signs, electrocardiograms (ECGs) and clinical laboratory values.
Statistical Methods: The PD Population was defined as all subjects randomised to treatment who received at least one dose of study medication and who also had a baseline PD measurement and at least one post-treatment PD measurement. Both linear and non-linear inhibition (Imax) dose-response models were fitted to the change from baseline in log_{10}-transformed blood eosinophil levels at Week 12 (Day 84), incorporating all regimens. Blood eosinophil PD parameters were also derived. The PK Population was defined as all subjects randomised to treatment who received at least one dose of study treatment and who had at least one PK sample taken and analysed. Population modelling techniques using non-linear mixed effects methods were used to estimate individual and population PK parameters for mepolizumab. The absolute bioavailability of the SC route of administration based on AUC was derived from the post-hoc individual clearance estimates obtained after SC and IV administration. The ratios of dose-normalised Cmax between the SC and IV routes of administration after the first and third dose were also derived from the individual Cmax estimates obtained after SC and IV administration. Log-transformed clearance and log-transformed dose-normalised Cmax were analysed using analysis of variance models. A population PK/PD model was used to estimate population PK/PD parameters for blood eosinophil inhibition. The Safety Population was defined as all subjects randomised to treatment who received at least one dose of study medication. This was the primary population for assessing safety and was also used for the majority of the study population displays. In each population, subjects were classified by the actual study treatment they received.
Study Population: Male and female subjects with asthma aged 18–65 years, inclusive, having been on a stable dose of their current asthma medications for 12 weeks prior to screening. Subjects had forced expiratory volume in 1 second ≥45% and <90 % of predicted normal value and evidence of airway reversibility with inhalation of albuterol, or airway hyper-responsiveness to methacholine/histamine. Subjects had documented evidence of eosinophilia within 12 months of screening and evidence of eosinophilia at screening (>0.3 cells 10^9/L or ≥0.2 cells 10^9/L following protocol amendment 1). The allocation ratio for the study was 4:3:4:2 (12.5 mg SC, 125 mg SC, 250 mg SC, 75 mg IV). Since data on 75 mg IV was available, the sample for this group was smaller.

Number of Subjects:	Mepo SC 12.5 mg	Mepo SC 125 mg	Mepo SC 250 mg	Mepo IV 75 mg	Total
Planned, N	20	15	20	10	65
Randomised, N	21	15	23	11	70
Completed, n (%)	20 (95)	14 (93)	21 (91)	11 (100)	66 (94)
Total Number Subjects Withdrawn, N (%)	1 (5)	1 (7)	2 (9)	0	4 (6)
Withdrawn due to adverse events n (%)	1 (5)	0	0	0	1 (1)
Withdrawn due to protocol deviation n (%)	0	0	1 (4)	0	1 (1)
Withdrawn at Investigator discretion[a] n (%)	0	0	1 (4)	0	1 (1)
Withdrew consent n (%)	0	1 (7)	0	0	1 (1)
Demographics					
N	21	15	23	11	70
Females : Males	13 : 8	5 : 10	14 : 9	5 : 6	37 : 33
Mean Age, years (SD)	43.1 (11.53)	37.0 (17.80)	43.9 (13.42)	44.8 (12.55)	42.3 (13.83)
Mean Weight, kg (SD)	73.86 (18.16)	72.81 (13.74)	74.81 (22.92)	83.85 (23.25)	75.52 (19.83)
White, n (%)	20 (95)	14 (93)	21 (91)	11 (100)	66 (94)
Baseline Blood Eosinophils in GI/L, Mean (range)	0.583 (0.19–1.70)	0.461 (0.15–1.18)	0.586 (0.22–2.42)	0.348 (0.19–0.55)	-

IV=intravenous; SC=subcutaneous.

a. Subject left the country and did not return before Day 140.

Primary Outcome Results: The analysis of change from baseline in log_{10}-transformed blood eosinophil levels at Week 12 (Day 84): non-linear (Imax) dose-response model results are presented below.

Proportion of Baseline Blood Eosinophils remaining at Week 12 (Day 84)	N	Estimate	SE (Log)	95% CI
Mepolizumab SC 12.5 mg	20	0.43	0.067	0.31, 0.58
Mepolizumab IV 75 mg	11	0.14	0.040	0.12, 0.17
Mepolizumab SC 125 mg	14	0.14	0.041	0.11, 0.17
Mepolizumab SC 250 mg	21	0.12	0.048	0.10, 0.15
Minimum		0.11	0.058	0.08, 0.14
Dose (mg) inducing half maximal reduction in log_{10}-transformed blood eosinophils	-	11.02	2.921	5.19, 16.85

CI=confidence interval. Mepolizumab IV 75 mg was assumed to equate with 100 mg SC within the model. Baseline adjustment incorporated into the model.

Dose (mg) inducing 90% of maximal reduction in log_{10}-transformed blood eosinophils attributable to the drug at week 12 was 99 mg (95% CI=47-152)

Derived blood eosinophil parameters are summarised by treatment group below.

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
$AUEC_{eos(0–Day\ 84)}$ (GI.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
Max_{eos} (GI/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[a]	n (%)	8 (38)	1 (7)	2 (9)	1 (9)

a. The planned endpoint was time to 50% repletion. However, as few subjects reached ≥50% repletion by Day 140 (last visit) the number of subjects who achieved ≥50% repletion was reported instead.

$AUEC_{eos(0–Day\ 84)}$=area under the absolute blood eosinophil time curve to Day 84 determined using the linear trapezoidal rule, for subset of subjects with blood eosinophil data to Day 84; Geo=geometric; proportional inhibition $AUEC_{eos(0–Day\ 84)}$=area above the absolute blood eosinophil time curve to Day 84 as a proportion of the total area under the baseline blood eosinophil level to Day 84, for subset of subjects with blood eosinophil data to Day 84; Max_{eos}=maximum reduction from baseline in blood eosinophils (between Day 0 and last quantifiable measurement); $Tmax_{eos}$=time to first occurrence of maximum reduction from baseline in blood eosinophil levels (between Day 0 and last quantifiable measurement); CI=confidence interval.

Mepolizumab population PK parameter estimates from the IV and SC population PK analyses are presented below.

Parameters (IV)	Estimate (95% CI)	BSV
CL (L/day)	0.210 (0.189, 0.232)	23.3%
V1 (L)	3.60 (3.19, 4.05)	17.2%
K12 (/day)	0.280 (0.214, 0.367)	60.6%
K21 (/day)	0.283 (0.233, 0.344)	NA
RESIDUAL	0.214 (0.142, 0.286)	

CL=plasma clearance; V1=volume of the central compartment; K12=rate constant (from central to peripheral compartment); K21= rate constant (from peripheral to central compartment); NA=not applicable; CI=confidence interval; BSV=between-subject variability.

Parameters (SC)	Estimate (95% CI)	BSV
CL/F (L/day)	0.310 (0.275, 0.349)	57.7%
V2/F (L)	4.57 (4.02, 5.20)	59.3%
K23 (/day)	0.280	NA
K32 (/day)	0.283	NA
KA (/day)	0.194 (0.155, 0.242)	87.2%
RESIDUAL	0.333 (0.279, 0.387)	

CL/F=apparent clearance; V2/F=apparent volume of the central compartment; K23=rate constant (from central to peripheral compartment); K32= rate constant (from peripheral to central compartment); NA=not applicable; CI=confidence interval; BSV=between-subject variability.

Individual mepolizumab PK parameters were obtained by using the post-hoc Bayesian predictions from the population PK model. Derived PK parameters for mepolizumab (geometric mean [95% CI] for $AUC_{(0-\tau)}$ and Cmax), (median (range) for Tmax and arithmetic mean [95% CI] for t½) are presented below.

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 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 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 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)

The population concentration associated with 50% of the maximal blood eosinophils inhibitory effect (IC_{50}) and the maximum blood eosinophils inhibitory effect (Imax) estimates from the population PKPD model were 1.26 μg/mL [95% CI: 0.878–1.81 μg/mL] and 0.928 [95% CI: 0.875–0.959], respectively.

Secondary Outcome Variables: The absolute bioavailability estimate of the SC route of administration in the upper

arm was 74% (90% CI= 54%-102%) and the estimated dose normalised Cmax ratio (SC/IV) after the first and third dose administered was 42% [90% CI: 30%–58%] and 54% [90% CI: 39%–74%], respectively.

Eight subjects out of 70 (11%) tested positive for anti-drug antibodies (ADAs) at one or more sampling time-points, of which 7 subjects had ADAs during treatment. Thirteen samples out of 201 (6%) had confirmed positive ADA results, of which 11 were post-dosing samples. Incidence of immunogenicity was low, with generally low titres. The samples with a confirmed positive ADA result were also tested for neutralizing antibodies; all results were negative.

Safety Results: Adverse event and serious adverse event (SAE) data were collected and recorded on the electronic case report form from the administration of the first dose of study medication until the final follow-up contact. Any AE that occurred in more than one subject in any one dose group is presented below.

	Mepo SC 12.5 mg N=21	**Mepo SC 125 mg N=15**	**Mepo SC 250 mg N=23**	**Mepo SC All doses N=59**	**Mepo IV 75 mg N=11**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	14 (67)	7 (47)	12 (52)	33 (56)	6 (55)
Injection site reaction[a]	3 (14)	3 (20)	1 (4)	7 (12)	0
Asthma	4 (19)	1 (7)	1 (4)	6 (10)	1 (9)
Nasopharyngitis	3 (14)	1 (7)	2 (9)	6 (10)	1 (9)
Arthralgia	1 (5)	0	0	1 (2)	2 (18)
Cough	2 (10)	0	0	2 (3)	0
Headache	0	0	2 (9)	2 (3)	0

a. Six of the seven subjects experiencing a local injection site reaction reported pain after receiving either mepolizumab diluted with water for injection (WFI) or WFI as placebo.

Serious Adverse Events - On-Therapy
n (%) [n considered by the Investigator to be related to study medication]

	Mepo SC 12.5 mg N=21	**Mepo SC 125 mg N=15**	**Mepo SC 250 mg N=23**	**Mepo SC All doses N=59**	**Mepo IV 75 mg N=11**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Subjects with any SAE(s), n(%)	1 (5) [0]	0	0	1 (2) [0]	0
Bladder papilloma	1 (5) [0]	0	0	1 (2) [0]	0

Conclusion: A dose-response relationship for the change from baseline in $\log_{10}$-transformed blood eosinophil levels at Week 12 (Day 84) was observed. The SC dose estimated to provide 50% and 90% of the maximal inhibition of blood eosinophils attributable to the drug at week 12 were 11 mg (95% CI=5, 17) and 99 mg (95% CI=47-152), respectively. The estimated minimal proportion of baseline blood eosinophils remaining at Week 12 accounting for the mean baseline eosinophils across dose groups was 0.11 (95% CI= 0.08, 0.14). Route of administration does not affect the mepolizumab eosinophil concentration response relationship. The estimated absolute bioavailability of SC mepolizumab in the upper arm was 74% (90% CI= 54%-102%). The estimated dose normalised Cmax ratio (SC/IV) after the first and third dose administered was 42% [90% CI: 30%–58%] and 54% [90% CI: 39%–74%], respectively.

Subjects reporting AEs after SC and IV dosing were similar: 56% and 55%, respectively. In the 12.5 mg mepolizumab SC group, 14 (67%) subjects reported an AE; injection site reaction, asthma, nasopharyngitis and cough were the most frequently reported. In the 125 mg mepolizumab SC group, seven (47%) subjects reported an AE; injection site reaction was the most frequently reported. In the 250 mg mepolizumab SC group, 12 (52%) subjects reported an AE; nasopharyngitis and headache were the most frequently reported. In the 75 mg mepolizumab IV group, six (55%) subjects reported an AE; arthralgia was the most frequently reported. One non-fatal SAE of bladder papilloma was reported in the 12.5 mg mepolizumab SC group. No non-fatal SAE were reported in the 125 mg or 250 mg mepolizumab SC groups or the 75 mg mepolizumab IV group. No fatalities were reported during the study. All samples were negative for neutralising antibodies.