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.: MEA112997

Title: A multicentre, randomised, 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.

Rationale: The purpose of this study was to evaluate the efficacy, safety and pharmacodynamics of three doses (75 mg, 250 mg and 750 mg) of mepolizumab administered intravenously (IV) every 4 weeks compared with placebo in subjects with severe uncontrolled refractory asthma over a 52 week treatment period.

Phase: IIb/III

Study Period: 09 November 2009–05 December 2011.

Study Design: Multicentre, randomised, double-blind, placebo-controlled, parallel group, dose-ranging.

Centres: Eighty-one centres in 13 countries enrolled subjects.

Indication: Asthma.

Treatment: Mepolizumab IV 75 mg, 250 mg and 750 mg and placebo IV given every 4 weeks for 48 weeks (giving 52 weeks of exposure to investigational product).

Objectives: To evaluate the dose response, based on efficacy and safety of three 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.

Primary Outcome/Efficacy Variable: The primary endpoint of this study was the frequency (rate) of clinically significant asthma exacerbations over the 52-week treatment period. Exacerbations were defined as worsening of asthma which in the investigator's opinion required use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. For subjects on maintenance oral corticosteroids (OCS), an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing maintenance dose for at least 3 days.

Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints included: frequency of exacerbations requiring hospitalization or emergency department visit; mean change from baseline in clinic pre and post-bronchodilator FEV_1; mean change from baseline in Asthma Control Questionnaire (ACQ) score; mean change in Asthma Quality of Life Questionnaire (AQLQ) score from baseline.

Statistical Methods: Significance tests were performed at the two sided 0.05 level. Analyses were conducted on the Intent-to-Treat Population of all subjects randomized who received treatment. The frequency of clinical significant exacerbations (rate) was compared across treatment groups using a generalised linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a 'log link' function. The model included covariates for treatment group, use of maintenance OCS, region, number of exacerbations in the year prior to the study and baseline % predicted FEV_1. FEV_1, ACQ and AQLQ were analysed using mixed model repeated measures methods, including covariates as above plus baseline value, visit and interaction terms for visit by baseline and visit by treatment group.

Study Population: Male or female non-smoking subjects with severe refractory asthma, aged ≥12 years, weighing ≥45 kg, with a requirement for regular treatment with high dose inhaled corticosteroids, with or without maintenance OCS, in the 12 months prior to Visit 1. Subjects required additional controller medication, e.g., long-acting beta-$_2$ receptor agonist, leukotriene receptor antagonist or theophylline. Subjects had persistent airflow obstruction as indicated by a pre-bronchodilator FEV_1 <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 documented asthma exacerbations requiring treatment with oral or systemic corticosteroids in the 12 months prior to Visit 1.

Number of Subjects:	**Placebo**	**Mepolizumab 75 mg**	**Mepolizumab 250 mg**	**Mepolizumab 750 mg**
Planned, N	151	151	151	151
Randomized, N	155	153	152	156
Completed, n (%)	127 (82)	129 (84)	131 (86)	133 (85)
Total Number Subjects Withdrawn, N (%)	28 (18)	24 (16)	21 (14)	23 (15)
Withdrawn due to:				
Adverse Events n (%)	6 (4)	5 (3)	8 (5)	9 (6)
Lack of Efficacy n (%)	8 (5)	6 (4)	4 (3)	4 (3)
Other reasons n (%)	14 (9)	13 (8)	9 (6)	10 (6)
Demographics				

N	155	153	152	156
Females: Males	97:58	104:49	93:59	93:63
Age in years, mean (SD)	46.4 (11.3)	50.2 (10.8)	49.4 (11.6)	48.6 (11.1)
White (%)	140 (90)	139 (91)	135 (89)	140 (90)
Hispanic or Latino (%)	16 (10)	15 (10)	14 (9)	16 (10)
Primary Efficacy Results: Frequency of clinically significant exacerbations of asthma up to Week 52				
	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
Key Secondary Outcome Variables:				
Rate of exacerbations requiring hospitalisation or ED visits				
n	155	153	152	156
Exacerbation rate/year	0.43	0.17	0.25	0.22
Comparison vs. placebo				
Rate ratio (mepolizumab/placebo)	-	0.40	0.58	0.52
95% CI	-	(0.19, 0.81)	(0.30, 1.12)	(0.27, 1.02)
Mean change from baseline pre-bronchodilator FEV_1 at week 52				
n	127	129	129	132
LS mean change (SE)	60 (37.7)	121 (37.6)	140 (37.3)	115 (36.9)
Comparison vs. placebo				
Difference	-	61	81	56
95% CI	-	(-39, 161)	(-19, 180)	(-43, 155)
Mean change from baseline post-bronchodilator FEV_1 at week 52				
n	126	128	129	130
LS mean change (SE)	-9 (36.7)	36 (36.4)	80 (36.1)	69 (35.6)
Comparison vs. placebo				
Difference	-	45	89	78
95% CI	-	(-50, 139)	(-6, 184)	(-16, 172)
Mean change from baseline in ACQ score at week 52				
n	121	127	126	129
LS mean change (SE)	-0.59 (0.087)	-0.75 (0.087)	-0.87 (0.086)	-0.80 (0.086)
Comparison vs. placebo				
Difference	-	-0.16	-0.27	-0.20
95% CI	-	(-0.39, 0.07)	(-0.51, -0.04)	(-0.43, 0.03)
Mean change from baseline in AQLQ score at week 52				
n	123	128	127	129
LS mean change (SE)	0.71 (0.090)	0.80 (0.089)	0.77 (0.088)	0.93 (0.088)
Comparison vs. placebo				
Difference	-	0.08	0.05	0.22
95% CI	-	(-0.16, 0.32)	(-0.19, 0.29)	(-0.02, 0.46)

Safety Results: On-therapy AEs and SAEs were defined as an AE or SAE with onset between the start date of investigational product and the last dose of investigational product plus 28 days.

	Placebo N=155	**Mepolizumab 75 mg N=153**	**Mepolizumab 250 mg N=152**	**Mepolizumab 750 mg N=156**
Most Frequent Adverse Events – On-Therapy, n (%)				
Subjects with any AE(s), n (%)	119 (77%)	126 (82%)	124 (82%)	122 (78%)

Headache	27 (17%)	32 (21%)	32 (21%)	32 (21%)
Nasopharyngitis	24 (15%)	34 (22%)	33 (22%)	29 (19%)
Asthma	24 (15%)	14 (9%)	26 (17%)	16 (10%)
Sinusitis	16 (10%)	10 (7%)	10 (7%)	12 (8%)
Upper respiratory tract infection	15 (10%)	10 (7%)	18 (12%)	19 (12%)
Bronchitis	15 (10%)	17 (11%)	13 (9%)	13 (8%)
Back pain	11 (7%)	11 (7%)	7 (5%)	15 (10%)
Infusion-related reaction	10 (6%)	8 (5%)	12 (8%)	19 (12%)
Subjects with Any SAE, n (%)	**Placebo N=155**	**Mepolizumab 75 mg N=153**	**Mepolizumab 250 mg N=152**	**Mepolizumab 750 mg N=156**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**

Any event	25 (16%) [0]	20 (13%) [0]	24 (16%) [1]	19 (12%) [1]
Asthma	17 (11%) [0]	11 (7%) [0]	16 (11%) [0]	9 (6%) [0]
Cerebrovascular accident	2 (1%) [0]	0	0	0
Nephrolithiasis	2 (1%) [0]	0	0	0
Lobar pneumonia	1 (<1%) [0]	2 (1%) [0]	0	0
Tendon rupture	1 (<1%) [0]	0	0	1 (<1%) [0]
Haematoma infection	1 (<1%) [0]	0	0	0
Infection	1 (<1%) [0]	0	0	0
Pleuritic pain	1 (<1%) [0]	0	0	0
Post-procedural infection	1 (<1%) [0]	0	0	0
Viral upper respiratory tract infection	1 (<1%) [0]	0	0	0
Atrial flutter	1 (<1%) [0]	0	0	0
Overdose	1 (<1%) [0]	0	0	0
Peritoneal haemorrhage	1 (<1%) [0]	0	0	0
Cervicobrachial syndrome	1 (<1%) [0]	0	0	0
Haematuria	1 (<1%) [0]	0	0	0
Liver function test abnormal	1 (<1%) [0]	0	0	0
Pneumonia	0	1 (<1%) [0]	0	2 (1%) [0]
Myocardial ischaemia	0	1 (<1%) [0]	0	1 (<1%) [0]
Hypertension	0	1 (<1%) [0]	0	1 (<1%) [0]
Post-procedural haemorrhage	0	1 (<1%) [0]	0	0
Nasal septum deviation	0	1 (<1%) [0]	0	0
Bacteraemia	0	1 (<1%) [0]	0	0
Bronchitis	0	1 (<1%) [0]	0	0
Cholecystitis infective	0	1 (<1%) [0]	0	0
Infected skin ulcer	0	1 (<1%) [0]	0	0
Acute myocardial infarction	0	1 (<1%) [0]	0	0
Coronary artery thrombosis	0	1 (<1%) [0]	0	0
Malignant hypertension	0	1 (<1%) [0]	0	0
Venous thrombosis limb	0	1 (<1%) [0]	0	0
Chest pain	0	1 (<1%) [0]	0	0
Cholecystitis acute	0	1 (<1%) [0]	0	0
Anaphylactic reaction (to nuts)	0	1 (<1%) [0]	0	0
Diabetes mellitus inadequate control	0	1 (<1%) [0]	0	0
Diabetes ketoacidosis	0	1 (<1%) [0]	0	0
Abortion spontaneous	0	1 (<1%) [0]	0	0
Upper respiratory tract infection	0	0	1 (<1%) [0]	0
Sinusitis	0	0	1 (<1%) [0]	0
Meningitis viral	0	0	1 (<1%) [0]	0
Decubitus ulcer	0	0	1 (<1%) [0]	0
Coronary artery insufficiency	0	0	1 (<1%) [0]	0
Concussion	0	0	1 (<1%) [0]	0
Spinal compression fracture	0	0	1 (<1%) [0]	0
Abdominal pain lower	0	0	1 (<1%) [0]	0
Thrombosis mesenteric vessel	0	0	1 (<1%) [0]	0
Pancreatitis acute	0	0	1 (<1%) [0]	0
Distributive shock	0	0	1 (<1%) [0]	0
Urinary retention	0	0	1 (<1%) [0]	0
Urinary tract obstruction	0	0	1 (<1%) [0]	0
Microlithiasis	0	0	1 (<1%) [0]	0
Reticulocyte count decreased	0	0	1 (<1%) [1]	0
Endometrial hyperplasia	0	0	1 (<1%) [0]	0
Leukopenia	0	0	1 (<1%) [0]	0
Uterine cancer	0	0	1 (<1%) [0]	0
Suicide[a]	0	0	0	1 (<1%) [0]

Herpes zoster ophthalmic	0	0	0	1 (<1%) [0]
Lung infection pseudomonal	0	0	0	1 (<1%) [0]
Staphylococcal infection	0	0	0	1 (<1%) [0]
Streptococcal bacteraemia	0	0	0	1 (<1%) [0]
Tonsillitis	0	0	0	1 (<1%) [0]
Atrial fibrillation	0	0	0	1 (<1%) [0]
Myocardial infarction	0	0	0	1 (<1%) [0]
Supraventricular tachycardia	0	0	0	1 (<1%) [1]
Colitis	0	0	0	1 (<1%) [0]
Cranial nerve disorder	0	0	0	1 (<1%) [0]
Ovarian cyst	0	0	0	1 (<1%) [0]
Subjects with fatal SAEs, n (%)				
Any event	0	0	2 (1%)	1 (<1%)
Suicide[a]	0	0	0	1 (<1%)
Asthma	0	0	1 (<1%)	0
Pancreatitis acute	0	0	1 (<1%)	0
Septic shock	0	0	1 (<1%)	0

NOTE: One subject experienced two fatal adverse events (pancreatitis acute and septic shock).

a. Reported as asphyxia.

Conclusion: Compared with placebo, 75, 250 and 750 mg of mepolizumab monthly for 12 months reduced the rate of clinically significant exacerbations by 48% (95% CI: 31%, 61%; p<0.001), 39% (19%, 54%; p<0.001), and 52% (36%, 64%; p<0.001) respectively. In the placebo arm, 119 subjects reported an adverse event, with the most frequently reported being headache, nasopharyngitis and asthma. In the mepolizumab 75mg group, 126 subjects reported an adverse event, with the most frequently reported being headache and nasopharyngitis. In the mepolizumab 250mg group, 124 subjects reported an adverse event, with the most frequently reported being headache and nasopharyngitis. In the mepolizumab 750mg group, 122 subjects reported an adverse event, with the most frequently reported being headache and nasopharyngitis. In the placebo arm, 25 subjects reported a serious adverse event, with the most frequently reported being asthma, cerebrovascular accident and nephrolithiasis. In the mepolizumab 75mg group, 20 subjects reported a serious adverse event, with the most frequently reported being asthma and lobar pneumonia. In the mepolizumab 250mg group, 24 subjects reported a serious adverse event, with the most frequently reported being asthma. In the mepolizumab 750mg group, 19 subjects reported a serious adverse event, with the most frequently reported being asthma and pneumonia. There were no fatalities in the placebo, no fatalities in the 75mg group, 2 fatalities in the 250mg group and 1 fatality in the 750mg group.