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.: A4M105038
Title: A Randomised, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study to Investigate the MRI Efficacy and the Safety of Six Months' Administration of Firategrast (150 - 1200mg twice daily) in Subjects with Relapsing-Remitting Multiple Sclerosis
Rationale: Multiple sclerosis (MS) is a debilitating, progressive neurological disease characterised by inflammation of the central nervous system (CNS). Although the cause of MS remains unknown, convergent lines of genetic, immunological, and epidemiological evidence suggest that tissue injury results from a misdirected immune response triggered by "non-self" antigens that mimic constitutive peptides of myelin. The $\alpha4\beta1$ and $\alpha4\beta7$ integrins play an important role in the initiation and perpetuation of localised inflammation as demonstrated by the use of $\alpha4$-integrin inhibitors in a number of disease models [Brodie, 1999; Socha-Urbanek 1998; Tsukamoto, 1995; Ebihara, 1999; Lin, 1999; Murai, 2003]. Natalizumab, a monoclonal antibody acting against $\alpha4$ integrins, has been shown to reduce relapse rates and disability progression in Phase III MS trials [Polman, 2006] There is a considerable unmet need for orally administered therapies in MS. Firategrast is an oral antagonist of $\alpha_4\beta_1/\alpha_4\beta_7$ integrins effective in a number of animal models of inflammation, including the relapsing remitting Biozzi mouse EAE model.
Phase: Phase II
Study Period: 21Dec2006 – 31 May 2010 (up to end of Extended Follow-Up Phase)
Study Design: This was a multi-centre, randomised, double-blind, placebo-controlled, dose-ranging study, consisting of a core 40 week period that included a Screening visit, a 4 week Run-In Phase, a 24 week Treatment Phase and a 12 week Core Follow-Up Phase. In addition subjects continued follow-up for up to 12 months after receiving their last dose of investigational product (Extended Follow-Up Phase).
Centres: 78 centres in 13 countries (18 centres in Germany, 8 centres in Spain, 7 centres each in France and Russia, 6 centres in the Netherlands, 5 centres each in Canada, Italy, Norway, and the UK, 4 centres each in Australia and Poland, 3 centres in New Zealand, and 1 centre in Austria)
Indication: Relapsing-Remitting Multiple Sclerosis
Treatment: Firategrast was provided as white, round, film coated tablets in two active strengths, 150 mg and 300 mg and a single matched placebo tablet.
Objectives: The primary objective was to assess the efficacy of firategrast, using magnetic resonance imaging (MRI), following 24 weeks of treatment in subjects with relapsing-remitting Multiple Sclerosis (MS). Dose-response and evaluation of individual firategrast doses versus placebo were evaluated.
Primary Outcome/Efficacy Variable: The primary endpoint was the cumulative number of new gadolinium-enhancing lesions on monthly MRI scans during the Treatment Phase i.e. Weeks 0-24.
Secondary Outcome/Efficacy Variables: The protocol-defined secondary endpoints were: Cumulative volume of new gadolinium-enhancing lesions on monthly MRI scans, cumulative number of persistent gadolinium-enhancing lesions on monthly MRI scans, cumulative number of total enhancing lesions on monthly MRI scans: the sum of new and persistent gadolinium-enhancing lesions, cumulative number of new/enlarging T2 lesions on Month 3, Month 6 and end of Core Follow-Up MRI scans, cumulative number of new T1 hypointense lesions on Month 3, Month 6 and end of Core Follow-Up MRI scans, number of relapses during treatment, and change from Baseline in Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores.
Statistical Methods: The required sample size of 301 evaluable subjects with an allocation of 43, 86, 86,and 86 subjects to 150 mg, 600 mg, 900/1200 mg (females/males) and placebo respectively was prospectively determined to be sufficient to detect a treatment difference of 3.5 new enhancing lesions (i.e. a clinically relevant 50% treatment difference) between each of the two highest firategrast doses (600 mg and 900/1200 mg [females/males]) and placebo. This calculation assumed a two-sided test, with 90% power and a 5% level of significance, a placebo mean of 7 lesions and a standard deviation of seven. The sample size additionally provided at least 90% power to detect a significant dose response relationship across all treatment groups in a model-based analysis. The planned sample size of 350 allowed for an attrition rate of 14% between randomisation and the end of the 24-week Treatment Phase. The Intent-to-Treat (ITT) population, utilised for analysis of the efficacy variables, consisted of all subjects randomised to treatment who took at least one dose of investigational product and who had at least one post-baseline MRI

assessment.

The Per Protocol (PP) population consisted of all subjects in the ITT population who had no major protocol violations and was used in analysis of the primary endpoint only.

The Safety population consisted of all randomised subjects who took at least one dose of investigational product.

The primary endpoint was prospectively defined to be analysed using a parametric analysis of covariance with dose fitted as a continuous variable to assess dose-response, and an imputed missing values (IMV) approach to allow for missing data. A linear test for trend was to be performed to assess dose-response. The assumptions underlying this analysis did not hold and hence an alternative pre-specified model (a generalized linear model with underlying negative binomial distribution and log link) was utilised in which all evaluable scans during the treatment phase contributed to the analysis. Each dose group was compared with placebo in a model where dose was fitted as a categorical variable and pairwise comparisons were conducted for each dose group (150 mg, 600 mg and 900/1200 mg) versus placebo.

Secondary endpoints for MRI lesion data were analysed using the same model as for the pair-wise comparisons of the primary efficacy endpoint. The rate of relapse over the 24-week treatment period was analysed using maximum likelihood based analysis, assuming the Poisson distribution.

Study Population: Male or female subjects aged 18 to 65 years, inclusive; with a diagnosis of relapsing-remitting MS with dissemination in time and space were eligible.

Subjects were required to have an Expanded Disability Status Scale (EDSS) of between 0 and 6.0 inclusive at the Screening visit, occurrence of at least two relapses in the previous 24 months with at least one relapse or documented evidence of gadolinium-enhancement on MRI (prior to Screening) in the previous 12 months, and a minimum of five T2 lesions on brain MRI at Visit 2 (end of Screening) as determined by the central MRI analysis reader.

Subjects who had a relapse within 4 weeks prior to Screening were excluded, along with subjects who had received specific therapies affecting the immune system or for treatment of MS within specified periods of the Screening visit. Those subjects with a CD4 count <500, CD4:CD8 <1.0, JC viremia detected in plasma or white cells, idiopathic CD4/CD8 lymphopenia or secondary lymphopenia at Screening were also excluded.

	Placebo	**Firategrast**		
		150mg bid	**600mg bid**	**900mg/1200mg bid**
Number of Subjects:				
Planned, N	100	50	100	100
Randomized, N	99	49	95	100
Completed, n (%)				
Completed to Week 24	83 (84)	42 (88)	79 (84)	85 (87)
Completed to Week 36	82 (83)	41 (85)	79 (84)	84 (86)
Total Number Subjects Withdrawn through Week 36, n (%)	16 (16)	6 (13)	15 (16)	13 (13)
Withdrawn due to Adverse Events through Week 36, n (%)	5 (5)	1 (2)	7 (7)	6 (6)
Withdrawn due to Lack of Efficacy through Week 36, n (%)	0	1 (2)	1 (1)	0
Withdrawn for other reasons through Week 36, n (%)	11 (11)	4 (8)	7 (7)	7 (7)
Entered Extended Follow-Up, (n%)	93 (94)	43 (90)	89 (95)	92 (94)

Completed Extended Follow-Up (having entered Extended Follow-Up), (n%)	88 (95)	40 (93)	84 (94)	85 (92)
Total Number of Withdrawn during Extended Follow-Up, (n%)	5 (5)	3 (7)	5 (6)	6 (7)
Withdrawn due to Adverse Events during Extended Follow-Up, n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy during Extended Follow-Up, n (%)	0	0	0	0
Withdrawn for other reasons during Extended Follow-Up, n (%)	5 (5)	3 (7)	5 (6)	6 (7)
Demographics	**Placebo**	**Firategrast**		
		150mg bid	**600mg bid**	**900mg/1200mg bid**
N (ITT)	99	48	94	98
Females: Males	66:33	32:16	63:31	67:31
Mean Age, years (SD)	38.8 (10.73)	37.0 (10.61)	38.6 (9.92)	40.7 (11.05)
White, n (%)	98 (99)	48 (100)	94 (100)	98 (100)

Primary Efficacy Results: Cumulative number of new gadolinium-enhancing lesions on monthly MRI scans during the Treatment Phase i.e. Weeks 0-24.

	Placebo	**Firategrast**		
	N=99	**150mg bid N=48**	**600mg bid N=94**	**900mg/1200mg bid N=98**
n (number of subjects contributing to the analysis)	90	47	86	92
Mean rate (cumulative number of new gadolinium-enhancing lesions per 24 weeks)	5.31	9.51	4.12	2.69
Ratio (firategrast/placebo)	--	1.79	0.78	0.51
95% Confidence Interval	--	(1.041, 3.081)	(0.497, 1.213)	(0.324, 0.788)
p-value	--	0.0353	0.2657	0.0026

Secondary Outcome Variable(s):

	Placebo	**Firategrast**		
	N=99	**150mg bid N=48**	**600mg bid N=94**	**900mg/1200mg bid N=98**
n (number of subjects contributing to the analysis)	90	47	86	92
Cumulative volume of new gadolinium-enhancing lesions on monthly MRI scans to Week 24				
Mean rate (cumulative volume of new gadolinium-enhancing lesions per 24 weeks)	734.56	896.31	1002.53	405.74
Ratio (firategrast/placebo)	--	1.22	1.25	0.55
95% Confidence Interval	--	(0.484, 3.078)	(0.636, 2.929)	(0.261, 1.171)
Cumulative number of persistent gadolinium-enhancing lesions on monthly MRI scans to Week 24				
Mean rate (cumulative number of persistent gadolinium-enhancing lesions per 24 weeks)	2.05	1.65	1.78	1.02
Ratio (firategrast/placebo)	--	0.80	0.87	0.50
95% Confidence Interval	--	(0.432, 1.497)	(0.521, 1.442)	(0.293, 0.837)
Cumulative number of total enhancing lesions on monthly MRI scans: the sum of new and persistent gadolinium-enhancing lesions to Week 24				
Mean rate (cumulative number of persistent gadolinium-enhancing lesions per 24 weeks)	6.99	10.70	5.15	3.43
Ratio (firategrast/placebo)		1.53	0.74	0.49
95% Confidence Interval		(0.890, 2.635)	(0.469, 1.157)	(0.313, 0.768)
Cumulative number of new T1 hypointense lesions on MRI scans to Week 24				

n (number of subjects contributing to the analysis)	87	43	82	90
Mean rate (cumulative number of new lesions per 24 weeks)	2.18	2.08	2.85	1.33
Ratio (firategrast/placebo)	--	0.96	1.31	0.61
95% Confidence Interval		(0.483, 1.893)	(0.754, 2.267)	(0.352,1.056)
Cumulative number of new/newly enlarging T2 lesions on MRI scans to Week 24				
Mean rate (cumulative number of new lesions per 24 weeks)	7.25	7.25	9.44	3.54
Ratio (firategrast/placebo)		1.00	1.30	0.49
95% Confidence Interval		(0.521, 1.920)	(0.755,0.811)	((0.294, 0.811)
Cumulative volume of new/newly enlarging T2 lesions on MRI scans to Week 24				
n (number of subjects contributing to the analysis)	59	33	64	67
Least Squares Mean	-827.8	-113.5	-148.7	-1257.4
Difference (firategrast-placebo)		714.29	679.13	-429.50
95% Confidence Interval		(-922.63, 2351.22)	(-688.21, 2046.47)	(-1753.6, 894.559)
Relapses Occurring during the On-Treatment Phase				
n (number of subjects contributing to the analysis)	99	49	95	100
Mean relapse rate (per 24 weeks from Poisson model)	0.41	0.35	0.32	0.30
Ratio (firategrast/placebo)		0.86	0.78	0.73
95% Confidence Interval		(0.494, 1.482)	(0.482, 1.255)	(0.461, 1.169)
Change from Baseline in EDSS scores.				
n (number of subjects contributing to the analysis)	74	37	72	79
Improved, n (%)	14 (19)	4 (11)	6 (8)	12 (15)
Unchanged, n (%)	54(73)	30 (81)	57 (79)	60 (76)
Worsened, n (%)	6 (8)	3 (8)	9 (13)	7 (9)
Change from Baseline in MSFC scores.				
n (number of subjects contributing to the analysis)	73	37	70	79
Mean Baseline	0.111	-0.022	-0.018	-0.049
Adjusted Mean Change From Baseline	0.021	0.012	-0.112	-0.059
Difference vs. Placebo	--	-0.010	-0.134	-0.080
95% CI for Treatment Difference	--	(-0.2887, 0.2697)	(-0.3658, 0.0984)	(-0.3050, 0.1444)
Safety Results: If the adverse event (AE) or serious adverse event (SAE) onset date is any date from the date of initiation of investigational product to the date investigational product was permanently discontinued + 3 days (inclusively) then it was considered 'On-treatment'.				

	Placebo	Firategrast		
	N=99	150mg bid N=49	600mg bid N=95	900mg/1200mg bid N=100
Most Frequent AEs – On-Therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Event	86 (87)	42 (86)	76 (80)	81 (81)
Headache	39 (39)	18 (37)	37 (39)	35 (35)
Nasopharyngitis	19 (19)	13 (27)	7 (7)	26 (26)
UTI	4 (4)	4 (8)	12 (13)	14 (14)
Diarrhoea	8 (8)	2 (4)	4 (4)	8 (8)
Abdominal pain upper	7 (7)	3 (6)	2 (2)	9 (9)
Back pain	6 (6)	4 (8)	3 (3)	7 (7)
Nausea	6 (6)	2 (4)	4 (4)	8 (8)
Dizziness	7 (7)	3 (6)	2 (2)	6 (6)
Upper RTI	4 (4)	1 (2)	9 (9)	4 (4)
Fatigue	8 (8)	1 (2)	3 (3)	5 (5)
Influenza	4 (4)	3 (6)	5 (5)	3 (3)
Vertigo	6 (6)	4 (8)	2 (2)	2 (2)
Pain in extremity	3 (3)	3 (6)	3 (3)	3 (3)
Pharyngitis	2 (2)	0	5 (5)	5 (5)
Abdominal pain	3 (3)	0	3 (3)	5 (5)
Pyrexia	3 (3)	3 (6)	1 (1)	4 (4)
Bronchitis	2 (2)	5 (10)	2 (2)	1 (1)
Dyspepsia	0	2 (4)	6 (6)	2 (2)
Vomiting	0	0	2(2)	7 (7)
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**				
	Placebo	**Firategrast**		
	N=99	**150mg bid N=49**	**600mg bid N=95**	**900mg/1200mg bid N=100**
Subjects with non-fatal SAEs, n (%)	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Any SAE	4 (4) [1]	0	4 (4) [2]	1 (1) {0]
Back pain	0	0	1 (1) [0]	0
Dehydration	1 (1) [1]	0	0	0
Gastritis erosive	1 (1) [0]	0	0	0
Hypertransaminasaemia	0	0	1 (1) [1]	0
Lip and/or oral cavity cancer	1 (1) [0]	0	0	0
Multiple sclerosis relapse	2 (2) [0]	0	0	1 (1) [0]
Ovarian cyst	0	0	1 (1) [0]	0
Urinary tract infection	0	0	0	1 (1) [0]
Uterine leiomyoma	0	0	1 (1) [1]	0
Subjects with fatal SAEs, n (%)	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Any event	0	0	0	0
Conclusion: The efficacy of 6-months of oral administration of firategrast twice daily in subjects with relapsing-remitting MS was established for the 900/1200 mg dose group by a clinically relevant and statistically significant difference from placebo in the primary efficacy endpoint. Four (4%) subjects in the placebo group reported an SAE while 4 (4%) subjects in the 600 mg group and 1 (1%) subject in the 900mg group reported SAEs. There were no deaths reported in this study. There was no evidence of PML in follow-up to one year after the last dose of firategrast.				
Publications: None				