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.: SB-683699/003
Title: A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Investigate the MRI Efficacy and Safety of Three Months' Administration of SB-683699 (150 – 1200mg twice daily) in Subjects with Relapsing Multiple Sclerosis
Rationale: SB-683699 is an orally available antagonist of $\alpha4\beta1/\alpha4\beta7$ integrin mediated cell adhesion that has shown to be active in a number of models of inflammation. A monoclonal antibody directed against $\alpha4$-integrin, natalizumab, has been shown to be effective in multiple sclerosis (MS). The purpose of this study was therefore to evaluate the safety and efficacy of SB-683699 in the treatment of subjects with relapsing MS.
Phase: II
Study Period: Study start-11 November 2004 Study termination (due to FDA clinical hold on all $\alpha4$-integrin antagonists in clinic) – 14 March 2005 Last subject assessment – 21 Jul 2006
Study Design: Multi-centre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging
Centres: 47 centres in 10 countries
Indication: Relapsing Multiple Sclerosis
Treatment: Subjects entered a 4 week run-in phase (Week 0 – Week 4) during which no treatment was administered, after which they were randomised to receive SB-683699 150mg, 450mg, 750mg, 900mg (females), 1200mg (males) or placebo, twice daily, for 12 weeks (Week 4 – Week 16). Study medication was provided in combinations of 150mg and 300mg tablet strengths. All subjects were originally to be followed up for 8 weeks after the end of treatment, however following the FDA clinical hold, all randomised subjects were followed up for 6 months post-cessation of treatment with subjects who received SB-683699 being followed up to one year after their last dose.
Objectives: The primary objective was to investigate the MRI efficacy of three months administration of SB-683699 in subjects with relapsing MS.
Primary Outcome/Efficacy Variable: **-** Cumulative number of new gadolinium enhancing lesions
Secondary Outcome/Efficacy Variable(s): **MRI efficacy endpoints:** - number of persistent gadolinium-enhancing lesions on monthly scans: - number of total enhancing lesions on monthly scans - number of new/enlarging T2 lesions at Baseline, end of Treatment and end of Follow-up - number of new active lesions on monthly scans - number of new T1 hypointense lesions at Baseline, end of Treatment and end of Follow-up **Pharmacodynamic endpoints:** **-** circulating lymphocytes **-** circulating neutrophils **Pharmacokinetic endpoints:** - pharmacokinetic profile of SB-683699 - pharmacokinetic profile of the metabolite GW786375X
Statistical Methods: The primary comparison of interest was the effect of SB-683699 compared with placebo on the cumulative number of new gadolinium-enhancing lesions at the end of the 12-week treatment period (Week 16) for the intent-to-treat population (subjects who completed run-in, received at least one dose of study treatment and had one post baseline MRI assessment). Due to the low subject numbers at Week 16, data at Week 12 (after 8 weeks of treatment) and at Week 8 (after 4 weeks of treatment) were also analysed. Profiles over time and analyses at intermediate time points were performed as supportive analyses. Analysis of covariance was used to determine treatment effects on the primary endpoint. The analysis was conducted on the intent-to-treat population using the imputed missing values dataset, where missing numbers of lesions were imputed and was repeated using the observed case dataset. Non-parametric analyses were also performed using the Wilcoxon rank sum test. Secondary efficacy endpoints were analysed using the same approach as for the primary endpoint. All statistical tests were

performed with significance interpreted at a nominal 5% significance level, since no adjustment was made for multiple comparisons. All subjects randomised who took at least one dose of study medication were included in the safety population.

Study Population: Males or females, aged 18 to 65 years with a diagnosis of MS (as per McDonald criteria), with dissemination in time and space and an Expanded Disability Status Scale (EDSS) of between 0 and 6.5 inclusive. Subjects were to have had at least one clinical attack in the previous 12 months, but no relapse within the 4 weeks prior to Screening.

Number of Subjects:	**Placebo**	**SB-683699**				
		150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Planned, N	50	50	50	50	40	20
Randomised, N	36	37	38	38	30	12
Completed, n (%)	4 (11)	7 (19)	5 (13)	6 (16)	4 (13)	1 (8)
Total Number Subjects Withdrawn, N (%)	32 (89)	30 (81)	33 (87)	32 (84)	26 (87)	11 (92)
Withdrawn due to Adverse Events n (%)	0	0	0	1 (3)	1(3)	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0	0	0
Withdrawn for other reasons n (%) (includes due to study termination)	32 (89)	30 (81)	33 (87)	31[a] (82)	25(83)	11(92)

a. one subject had primary reason for withdrawal recorded as other but had AE leading to withdrawal also

Demographics	**Placebo**	**SB-683699**				
		150mg	**450mg**	**750mg**	**900mg**	**1200mg**
N (ITT)	36	34	33	37	28	12
Females: Males	24:12	22:12	22:11	25:12	28:0	0:12
Mean Age, years (SD)	38.1 (9.65)	42.7 (8.96)	35.8 (10.15)	38.2 (9.94)	38.1 (9.19)	42.2 (10)
White/Caucasian, n (%)	33 (92)	34 (100)	31 (94)	34 (92)	28 (100)	12 (100)

Primary Efficacy Results:
Number of New Gadolinium-Enhancing Lesions (ITT Population).

	SB-683699				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Week 8	**N=24**	**N=25**	**N=27**	**N=20**	**N=11**
Estimated difference vs placebo (95% CI)	-0.2 (-1.1, 0.7)	0.9 (-0.0, 1.8)	0.0 (-0.9, 0.9)	-0.6 (-1.6, 0.4)	-0.2 (-1.4, 1.1)
Week 12	**N=14**	**N=19**	**N=16**	**N=14**	**N=7**
Estimated difference vs placebo (95% CI)	0.3 (-2.1, 2.8)	2.8 (0.5, 5.1)	-0.0 (-2.4, 2.3)	-0.2 (-3.8, 1.5)	0.0 (-3.2, 3.2)
Week 16	**N=7**	**N=6**	**N=5**	**N=6**	**N=1**
Estimated difference vs placebo (95% CI)	-1.1 (-4.8, 2.6)	3.4 (-0.6, 7.4)	-0.4 (-4.4, 3.6)	-0.2 (-4.1, 3.8)	-0.4 (-7.3, 6.5)

Note: Week 8 = 4 weeks of treatment, Week 12 = 8 weeks of treatment and Week 16 = 12 weeks of treatment

Secondary MRI Outcome Variable(s): ITT Population

Number of persistent Gadolinium-Enhancing Lesions	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Estimated difference vs placebo (95% CI)	0.2 (-0.4, 0.7)	0.1 (-0.5, 0.7)	0.0 (-0.6, 0.6)	-0.3 (-0.9, 0.3)	-0.2 (-0.9, 0.6)
Week 12					
Estimated difference vs placebo (95% CI)	0.7 (-1.5, 2.9)	0.2 (-1.8, 2.3)	0.7 (-1.4, 2.9)	-1.0 (-3.3, 1.4)	-0.4 (-3.3, 2.5)
Week 16					

Estimated difference vs placebo (95% CI)	0.7 (-1.0, 2.5)	0.2 (-1.7, 2.1)	-0.5 (-2.4, 1.5)	-0.5 (-2.4, 1.4)	-0.4 (-3.7, 3.0)
Number of Total Gadolinium-Enhancing Lesions	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Estimated difference vs placebo (95% CI)	0.0 (-1.2, 1.2)	1.00 (-0.2, 2.2)	0.0 (-1.2, 1.2)	-0.9 (-2.3, 0.5)	-0.3 (-3.0, 1.4)
Week 12					
Estimated difference vs placebo (95% CI)	1.1 (-2.7, 4.9)	3.0 (-0.6, 6.6)	0.7 (-3.0, 4.4)	-2.1 (-6.2, 2.0)	-0.3 (-5.3, 4.7)
Week 16					
Estimated difference vs placebo (95% CI)	-0.4 (-4.2, 3.4)	3.6 (-0.5, 7.7)	-0.9 (-4.9, 3.2)	-0.7 (-4.7, 3.4)	-0.8 (-7.8, 6.3)
New/newly Enlarging T2 Lesions @ Week 16	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Estimated difference vs placebo (95% CI)	-0.4 (-1.4, 0.5)	0.1 (-0.9, 1.0)	-0.2 (-1.2, 0.7)	-0.2 (-1.3, 0.8)	-0.2 (-1.5, 1.1)
Number Active Lesions ´Week 16	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Estimated difference vs placebo (95% CI)	-0.6 (-3.0, 1.7)	0.3 (-2.1, 2.7)	-0.4 (-2.8, 2.0)	-0.3 (-2.8, 2.3)	-0.3 (-3.7, 3.0)
Number of New Hypointense T1 Lesions @ Week 16	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
Estimated difference vs placebo (95% CI)	-0.3 (-0.7, 0.1)	-0.1 (-0.5, 0.3)	-0.3 (-0.7, 0.1)	-0.2 (-0.6, 0.2)	0.0 (-0.6, 0.5)

Pharmacodynamic results (ITT Population)					
Lymphocyte Counts (10^9/L)					
Treatment regimen	**Visit**	**Time**	**N**	**Mean**	**SD**
Placebo	Week 8	Pre-dose	23	1.80	0.470
		1 hr post-dose	22	1.80	0.544
		2 hr post-dose	21	1.86	0.578
		4 hr post-dose	21	2.04	0.716
	Week 12	Pre-dose	15	1.89	0.526
		1 hr post-dose	14	1.87	0.484
		2 hr post-dose	14	1.94	0.586
		4 hr post-dose	14	2.07	0.642
	Week 16	Pre-dose	4	2.14	0.248
		1 hr post-dose	4	2.22	0.290
		2 hr post-dose	4	2.28	0.472
		4 hr post-dose	4	2.27	0.480
SB-683699 150mg	Week 8	Pre-dose	22	2.11	0.732
		1 hr post-dose	19	2.49	0.931
		2 hr post-dose	21	2.56	0.688
		4 hr post-dose	20	2.51	0.619
	Week 12	Pre-dose	10	2.01	0.839
		1 hr post-dose	10	2.40	0.614
		2 hr post-dose	10	2.48	0.689
		4 hr post-dose	10	2.63	0.659
	Week 16	Pre-dose	7	1.79	0.369
		1 hr post-dose	7	2.23	0.521
		2 hr post-dose	7	2.56	0.599
		4 hr post-dose	7	2.31	0.551
SB-683699 450mg	Week 8	Pre-dose	22	1.93	0.464
		1 hr post-dose	22	2.47	0.470
		2 hr post-dose	22	2.67	0.482
		4 hr post-dose	23	2.70	0.500
	Week 12	Pre-dose	17	1.98	0.561
		1 hr post-dose	15	2.43	0.524
		2 hr post-dose	16	2.75	0.648
		4 hr post-dose	16	2.75	0.539
	Week 16	Pre-dose	5	2.19	0.625
		1 hr post-dose	5	2.71	0.560
		2 hr post-dose	5	3.02	0.529
		4 hr post-dose	5	2.70	0.365
SB-683699 750mg	Week 8	Pre-dose	23	2.50	0.756
		1 hr post-dose	24	3.09	0.763
		2 hr post-dose	23	3.15	0.707
		4 hr post-dose	22	3.12	0.677
	Week 12	Pre-dose	13	2.49	0.829
		1 hr post-dose	13	3.26	0.950
		2 hr post-dose	14	3.39	0.673
		4 hr post-dose	12	3.22	0.594
	Week 16	Pre-dose	5	1.80	0.698
		1 hr post-dose	4	2.73	0.718
		2 hr post-dose	4	2.95	0.775
		4 hr post-dose	4	2.97	0.826
SB-683699 900mg	Week 8	Pre-dose	19	2.29	0.682

		1 hr post-dose	18	2.95	1.067
		2 hr post-dose	18	3.28	1.108
		4 hr post-dose	18	3.13	1.182
	Week 12	Pre-dose	13	2.42	0.636
		1 hr post-dose	13	2.83	0.859
		2 hr post-dose	13	3.26	1.061
		4 hr post-dose	13	3.11	0.788
	Week 16	Pre-dose	5	1.91	0.442
		1 hr post-dose	5	2.61	0.800
		2 hr post-dose	5	2.85	0.856
		4 hr post-dose	5	2.59	1.062
SB-683699 1200mg	Week 8	Pre-dose	10	2.18	0.434
		1 hr post-dose	10	2.75	0.344
		2 hr post-dose	10	2.99	0.439
		4 hr post-dose	9	2.82	0.614
	Week 12	Pre-dose	7	1.85	0.417
		1 hr post-dose	6	2.78	0.585
		2 hr post-dose	6	2.85	0.669
		4 hr post-dose	6	2.87	0.700
	Week 16	Pre-dose	1	2.27	-
		1 hr post-dose	1	2.86	-
		2 hr post-dose	1	2.91	-
		4 hr post-dose	1	2.98	-
Neutrophil Counts (10^9/L)					
Treatment regimen	**Visit**	**Time**	**N**	**Mean**	**SD**
Placebo	Week 8	Pre-dose	23	4.15	2.020
		1 hr post-dose	22	4.21	2.114
		2 hr post-dose	21	4.46	2.102
		4 hr post-dose	21	4.34	1.672
	Week 12	Pre-dose	15	3.96	2.068
		1 hr post-dose	14	4.09	1.869
		2 hr post-dose	14	4.15	1.770
		4 hr post-dose	14	4.22	1.672
	Week 16	Pre-dose	4	3.96	1.419
		1 hr post-dose	4	3.93	1.558
		2 hr post-dose	4	4.02	1.201
		4 hr post-dose	4	3.83	1.465
SB-683699 150mg	Week 8	Pre-dose	22	4.09	1.799
		1 hr post-dose	19	4.32	2.048
		2 hr post-dose	21	4.44	1.724
		4 hr post-dose	20	4.57	1.672
	Week 12	Pre-dose	10	4.35	1.836
		1 hr post-dose	10	4.47	1.776
		2 hr post-dose	10	4.55	1.705
		4 hr post-dose	10	4.36	1.803
	Week 16	Pre-dose	7	3.13	1.002
		1 hr post-dose	7	3.27	1.122
		2 hr post-dose	7	3.45	1.166
		4 hr post-dose	7	3.31	1.172
SB-683699 450mg	Week 8	Pre-dose	22	3.74	1.429
		1 hr post-dose	22	3.82	1.549
		2 hr post-dose	22	4.34	1.438

		4 hr post-dose	23	4.39	1.492
	Week 12	Pre-dose	17	3.61	1.435
		1 hr post-dose	15	3.79	1.192
		2 hr post-dose	16	4.09	1.101
		4 hr post-dose	16	4.18	0.812
	Week 16	Pre-dose	5	2.79	1.154
		1 hr post-dose	5	2.97	1.198
		2 hr post-dose	5	3.32	1.408
		4 hr post-dose	5	2.80	1.386
SB-683699 750mg	Week 8	Pre-dose	23	4.28	1.643
		1 hr post-dose	24	4.57	1.644
		2 hr post-dose	23	4.82	1.512
		4 hr post-dose	22	4.54	1.454
	Week 12	Pre-dose	13	3.86	0.951
		1 hr post-dose	13	4.23	1.198
		2 hr post-dose	14	4.53	1.245
		4 hr post-dose	12	4.43	1.492
	Week 16	Pre-dose	5	5.86	1.600
		1 hr post-dose	4	6.58	2.408
		2 hr post-dose	4	6.61	2.327
		4 hr post-dose	4	6.55	2.707
SB-683699 900mg	Week 8	Pre-dose	19	3.72	1.565
		1 hr post-dose	18	4.13	1.690
		2 hr post-dose	18	4.68	2.306
		4 hr post-dose	18	4.38	1.800
	Week 12	Pre-dose	13	4.48	1.966
		1 hr post-dose	13	4.78	1.989
		2 hr post-dose	13	5.06	1.806
		4 hr post-dose	13	4.72	1.508
	Week 16	Pre-dose	5	3.86	1.422
		1 hr post-dose	5	4.36	1.441
		2 hr post-dose	5	5.53	3.542
		4 hr post-dose	5	5.28	2.704
SB-683699 1200mg	Week 8	Pre-dose	10	3.95	0.833
		1 hr post-dose	10	4.36	1.182
		2 hr post-dose	10	4.49	1.563
		4 hr post-dose	9	4.41	1.113
	Week 12	Pre-dose	7	3.71	1.135
		1 hr post-dose	6	3.68	1.608
		2 hr post-dose	6	3.86	1.356
		4 hr post-dose	6	3.60	0.942
	Week 16	Pre-dose	1	3.28	-
		1 hr post-dose	1	3.88	-
		2 hr post-dose	1	4.37	-
		4 hr post-dose	1	4.87	-

Pharmacokinetic results: Summary of PK Parameters @ Week 8

Geometric Mean (CVb%)	**SB-683699**				
	150mg	**450mg**	**750mg**	**900mg**	**1200mg**
SB-683699					
n	23	24	25	18	10
Cmax (μg/mL)	1.51 (57.6%)	9.61 (54.7%)	20.7 (48.5%)	32.3 (51.3%)	32.8 (54.8%)
AUC $_{0\text{-}12}$ (μg.h/mL)	14.0 (15.6%)	35.6 (33.4%)	64.1 (42.4%)	93.4 (40.6%)	104 (46.1%)

GW786375X					
n	23	24	25	18	10
Cmax (μg/mL)	0.21 (76.5%)	0.79 (53.2%)	1.29 (43.2%)	1.65 (73.8%)	1.60 (46.3%)
AUC $_{0\text{-}12}$ (μg.h/mL)	3.12 (18.8%)	5.62 (32.3%)	7.46 (26.1%)	9.36 (43.8%)	9.04 (33.6%)

Safety Results:

On-treatment AEs were defined as occurring from the first dose until the end of the treatment phase. Serious AEs (SAEs) related to study participation were collected from the beginning of the run-in phase. Originally all other SAEs were collected from randomisation to the end of the study, however following the early termination of the study only SAEs related to SB-683699 were collected during the extended follow-up period.

NB: discuss with CIP during approval process the need to include additional information on extended follow up assessments

Most frequent AEs on-treatment	Treatment group					
	Placebo (N=36)	SB-683699				
		150mg (N=37)	450mg (N=38)	750mg (N=38)	900mg (N=30)	1200mg (N=12)
Any event	16 (44%)	22 (59%)	20 (53%)	20 (53%)	20 (67%)	7 (58%)
Headache	6 (17%)	0	5 (13%)	9 (24%)	8 (27%)	2 (17%)
Nasopharyngitis	2 (6%)	3 (8%)	5 (13%)	4 (11%)	4 (13%)	1 (8%)
Cough	2 (6%)	4 (11%)	0	1 (3%)	3 (10%)	0
Abdominal pain upper	5 (14%)	1 (3%)	2 (5%)	0	1 (3%)	0
Dyspepsia	1 (3%)	2 (5%)	3 (8%)	1 (3%)	1 (3%)	0
Influenza	1 (3%)	2 (5%)	1 (3%)	2 (5%)	2 (7%)	0
Nausea	1 (3%)	0	2 (5%)	3 (8%)	2 (7%)	0
Diarrhoea	1 (3%)	0	1 (3%)	1 (3%)	2 (7%)	1 (8%)
Back pain	1 (3%)	2 (5%)	1 (3%)	0	1 (3%)	0
Pain in extremity	2 (6%)	1 (3%)	1 (3%)	0	1 (3%)	0
Pharyngolaryngeal pain	1 (3%)	0	0	2 (5%)	2 (7%)	0
Pyrexia	2 (6%)	0	1 (3%)	2 (5%)	0	0
Urinary tract infection	1 (3%)	0	0	3 (8%)	1 (3%)	0
Fatigue	0	0	2 (5%)	0	2 (7%)	0
Paraesthesia	0	1 (3%)	1 (3%)	0	2 (7%)	0
Rash	0	0	2 (5%)	1 (3%)	1 (3%)	0
Sinusitis	0	2 (5%)	1 (3%)	0	1 (3%)	0
Vertigo	1 (3%)	1 (3%)	0	0	2 (7%)	0
ALT increased	2 (6%)	0	0	0	1 (3%)	0
Arthralgia	2 (6%)	0	1 (3%)	0	0	0
AST increased	2 (6%)	0	0	0	1 (3%)	0
Influenza-like illness	0	2 (5%)	1 (3%)	0	0	0
Acne	0	0	2 (5%)	0	0	0
Chills	0	0	0	0	2 (7%)	0
Muscle fatigue	0	0	0	0	0	2 (17%)
Nasal congestion	0	0	2 (5%)	0	0	0
Tonsilitis	2 (6%)	0	0	0	0	0

Serious Adverse Events On therapy
N (%) [n considered by the investigator to be related to study medication]

	Treatment group					
	Placebo (N=36)	SB-683699				
		150mg (N=37)	450mg (N=38)	750mg (N=38)	900mg (N=30)	1200mg (N=12)
Subjects with non-fatal SAEs, n (%)	0	0	0	2 (5%)	0	0
	N (%) [related]	N (%) [related]	N (%) [related]	N (%) [related]	N (%) [related]	N (%) [related]
Urinary Tract Infection	0	0	0	1(2.5%) [1]	0	0
Dermatitis allergic	0	0	0	1(2.5%) [1]	0	0
Subjects with fatal SAEs, n(%)	0	0	0	0	0	0

Conclusion:
Due to the early termination of this study (27/260 subjects completed the study) the primary objective could not be assessed as planned. There were no numerical differences observed between SB-683699 and placebo for the primary and secondary MRI efficacy variables. In the five SB-683699 dose groups a total of 89 subjects reported non-serious

adverse events with the most frequently reported being headache, nasopharyngitis and cough. In the placebo treated group 16 subjects reported non-serious adverse events with the most frequently reported being headache and abdominal pain. There were two serious adverse events, urinary tract infection and dermatitis allergic, in the SB-683699 groups. There were no fatalities reported in any treatment group.
Publications: None