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: BA1106006

Title: A randomised, single-blind, placebo-controlled study to investigate the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of intravenous infusion of GSK933776 in patients with Alzheimer's disease

Rationale: Beta-amyloid (Aβ) peptides are a major therapeutic target for the treatment of Alzheimer's disease (AD). Immunotherapeutic approaches based on active or passive immunisations against Aβ have demonstrated efficacy in experimental models of brain amyloid accumulation. GSK933776 is a humanised immunoglobulin G1 monoclonal antibody directed against the N-terminal of Aβ. When administered to transgenic mice over-expressing mutant amyloid precursor protein and presenilin, the parent molecule of GSK933776, GSK719556A, decreased the amyloid brain content. It was therefore hypothesised that treatment of subjects with AD with GSK933776 would result in the clearance of soluble amyloid from the brain, reducing its neurotoxic effect, and ultimately result in improved cognition and prevention or substantial slowing of AD pathology in these subjects.
The Fc part of GSK933776 is inactivated by introduction of two mutations. This modification was done with the aim of improving the safety profile, in particular with regard to the risk of vasogenic oedema reported in association with other anti-Aβ antibodies.

Phase: I/IIa

Study Period: 06 March 2007–30 May 2011.

Study Design: Randomised, single-blind, placebo-controlled.

Centres: Three centres in Sweden, one centre in Norway and three centres in Australia.

Indication: Alzheimer's disease.

Treatment: Subjects were randomised to a single intravenous (iv) administration (Part A) or three iv administrations (Part B) of either GSK933776 or placebo in a ratio of 3:2 (first two cohorts in Part A) or 6:2 (remaining cohorts in Part A and all of Part B). Three single dose (SD) cohorts were dosed during Part A of the study (GSK933776 0.001, 0.01 and 0.1 mg/kg), as criteria for transition to the repeat dose (RD) cohorts were achieved at 0.1 mg/kg. In Part B, four cohorts were dosed: GSK933776 0.1, 1, 3 and 6 mg/kg. Dosing in Part A in a new cohort only began once 3 weeks' data were available for all subjects in the previous cohort. The overall duration of each subject's participation in Part A of the study, from screening to follow-up, was approximately 4–7 months. The overall duration of each subject's participation in Part B of the study, from screening to follow-up, was approximately 9–12 months.

Objectives: To assess the safety and tolerability of GSK933776 after single and multiple dose iv administration in subjects with AD.

Statistical Methods: Safety Analysis: safety data were graphically presented, summarised and listed.
For the digital vigilance test (DVT) and category fluency test (CFT), the change from baseline weighted mean in DVT total time and CFT total score was statistically analysed using a mixed model, with dose fitted as a fixed effect and baseline as a covariate. The primary comparisons of interest compared each dose of GSK933776 (RD) to Placebo (RD), with the secondary comparison of interest comparing each dose of GSK933776 (RD) to Placebo (SD+RD Pooled). The adjusted mean and estimated treatment differences (95% confidence interval) were presented.
Pharmacokinetic Analysis: drug concentrations of GSK933776 in plasma and cerebrospinal fluid (CSF) were graphically presented, summarised and listed. Non-compartmental and population analysis pharmacokinetic parameters were derived from plasma GSK933776 concentration data and were summarised and listed using the 'Pharmacokinetic Parameter Population'. Dose proportionality for each dosing administration using the power model (primary) was assessed by fitting log-transformed parameter AUC(0–∞) from the population analysis using a mixed effects model, fitting log-transformed dose (continuous variable) as fixed effects. The estimated slope of log dose and associated 90% confidence intervals, on the $\log_e$ scale, was calculated for AUC(0–∞) for each dosing administration. Additionally, dose proportionality for each dosing administration using the analysis of variance (ANOVA) model (secondary) was assessed by fitting log-transformed dose-normalised (using 0.1 mg/kg RD dose as reference) AUC(0–672 h) and maximum observed concentration (Cmax) from non-compartmental analysis and AUC(0–∞) from population analysis. The ANOVA model was fitted using a mixed effects model, fitting dose (categorical variable) as fixed effects. The dose ratios and associated 90% confidence intervals were calculated for each parameter and dose administration and presented as back-transformed estimates.
Pharmacodynamics and Biomarkers: pharmacodynamic and biomarker data were graphically presented, summarised and listed. No formal statistical analysis of pharmacodynamic or biomarker data was conducted.
Pharmacodynamic parameters were determined from plasma concentration-time data for free and total Aβ as defined in the Reporting and Analysis Plan (RAP) and were summarised and listed.

Pharmacogenetics: pharmacogenetic data were summarised and listed. No formal statistical analysis to correlate pharmacogenetic data and study endpoints was conducted. The All Subjects Population comprised all subjects who received GSK933776 or placebo. This population was used in all safety and pharmacodynamics analyses, with the exception of positron emission tomography (PET)-related endpoints, which used the PET Population. The Pharmacokinetic Concentration Population comprised all subjects for whom a pharmacokinetic sample was obtained and analysed. The Pharmacokinetic Parameter Population comprised all subjects in the Pharmacokinetic Concentration Population who provided pharmacokinetic parameters. The PET Population comprised all Subjects who underwent PET screening. The Pharmacogenetics Population comprised all subjects randomised to either study drug or placebo who consented to genotyping, provided a blood sample for genotyping and were successfully genotyped for the two apolipoprotein E (*APOE*) genetic markers under study.
Study Population: Male and female subjects aged 55–80 years, inclusive, with a diagnosis of mild-to-moderate AD and a Mini Mental State Examination score of 18–26 were eligible for this study. Subjects had to be capable of giving consent and were supported by a caregiver who consented to support them throughout the study. Subjects had to be fluent in the local language and capable of following instructions. Female subjects had to be of non-childbearing potential and male subjects had to use appropriate forms of contraception if their partner was of childbearing potential. Subjects were excluded if they had other central nervous system or psychiatric disorders, including signs or risk factors for vascular dementia, or were taking prohibited medication.
Number of Subjects: Six subjects participated in both Part A and Part B. Accordingly, a total of 44 individuals participated in the study and 33 individuals were exposed to GSK933776.

	Placebo	GSK933776							Total
		0.001 mg/kg SD	0.01 mg/kg SD	0.1 mg/kg SD	0.1 mg/kg RD	1 mg/kg RD	3 mg/kg RD	6 mg/kg RD	
Planned N									74
Randomised N	14	3	3	6	6	6	6	6	50
Completed n (%)	14 (100)	3 (100)	3 (100)	6 (100)	6 (100)	5 (83)	6 (100)	5 (83)	48 (96)
Total Number Subjects Withdrawn N (%)	0	0	0	0	0	1 (17)	0	1 (17)	2 (4)
Withdrawn due to Adverse Events n (%)	0	0	0	0	0	0	0	1 (17)	1 (2)
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0	0	0	0	0	0
Withdrawn for Protocol Violation n (%)	0	0	0	0	0	1 (17)	0	0	1 (2)
Demographics									
N	14	3	3	6	6	6	6	6	50
Females: Males	9 : 6	2 : 1	3 : 0	2 : 4	4 : 2	3 : 3	4 : 2	4 : 2	31 : 19
Mean Age in years (SD)	69.9 (7.98)	72.7 (0.58)	69.7 (8.39)	68.2 (7.25)	66.2 (6.77)	71.3 (4.50)	68.2 (9.11)	69.8 (5.56)	69.3 (6.81)
Mean Weight in kg (SD)	69.3 (16.04)	69.17 (16.86)	59.67 (6.43)	71.80 (13.40)	72.77 (13.59)	76.93 (14.31)	66.90 (10.26)	66.70 (8.96)	69.77 (13.23)
Mean Height in cm (SD)	170.1 (9.41)	165.0 (11.27)	161.3 (7.51)	168.2 (11.96)	167.5 (9.03)	173.0 (11.26)	167.8 (11.21)	165.7 (8.87)	168.3 (9.79)
Mean Body Mass Index in kg/m^2 (SD)	23.8 (3.87)	25.1 (2.50)	22.9 (0.78)	25.4 (4.08)	25.8 (2.33)	25.6 (3.40)	23.7 (2.62)	24.2 (1.83)	24.5 (3.09)
Not Hispanic or Latino n (%)	14 (100)	3 (100)	3 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	50 (100)
White n (%)	14 (100)	3 (100)	3 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	50 (100)

Safety Results: Adverse event (AE) and serious adverse event (SAE) data were collected and recorded in the case report form from Day 1 until the follow-up visit. A summary of AES occurring in more than one subject in any group is presented below.

Adverse Events:	Placebo	GSK933776						
		0.001 mg/kg SD	0.01 mg/kg SD	0.1 mg/kg SD	0.1 mg/kg RD	1 mg/kg RD	3 mg/kg RD	6 mg/kg RD
No. subjects with AEs n (%)	10 (71)	2 (67)	2 (67)	6 (100)	5 (83)	6 (100)	5 (83)	5 (83)
Fatigue	2 (14)	0	0	0	2 (33)	1 (17)	2 (33)	1 (17)
Nasopharyngitis	2 (14)	0	1 (33)	2 (33)	0	0	1 (17)	0
Nausea	2 (14)	0	0	1 (17)	1 (17)	1 (17)	0	1 (17)
Vomiting	1 (7)	0	0	0	1 (17)	1 (17)	0	2 (33)
Dizziness	1 (7)	0	0	0	1 (17)	0	0	2 (33)
Confusional state	2 (14)	0	0	0	0	1 (17)	0	0
Diarrhoea	0	1 (33)	0	0	2 (33)	0	0	0
Haematoma	2 (14)	0	0	0	0	0	1 (17)	0
Blood creatine phosphokinase increased	0	0	0	2 (33)	0	0	0	0

Serious Adverse Events: Two SAEs occurred after administration of GSK933776, gout and transient ischaemic attack, neither of which was judged to be drug-related by an Investigator. No clinically significant electrocardiogram, vital signs or clinical laboratory results were recorded during the study in subjects who received GSK933776. No magnetic resonance imaging findings associated with drug administration were noted, in particular no cases of vasogenic oedema. One novel microbleed was recorded in a subject receiving placebo. No adverse effects on cognitive function or structural changes of the brain were recorded.
Novel anti-GSK933776 antibodies were detected in two subjects. One of these was reported as neutralising with antibody titre up to 80. For the other subject the reactivity was around the assay cut point (titre 1). In addition, serum components interfered with the immunogenicity assay, i.e., anti-reactivity was detected for two subjects pre-treatment. The titres did not increase markedly during treatment.
Neuropsychological testing was part of the safety assessment. None of the primary or secondary comparisons of interest on the neuropsychological tests attained statistical significance as the 95% confidence intervals included zero. Detection of signals of efficacy was unlikely due to the small sample size based on feasibility and short duration of treatment.

Pharmacokinetic Endpoints: Plasma: The terminal phase half-life (t½) ranged from 10–15 days (non-compartmental analysis), clearance estimated with the population analysis was 0.132 mL/h/kg for doses equal to or higher than 1 mg/kg, but was approximately 0.272 mL/h/kg at 0.1 mg/kg. This higher value appeared to be due to a higher estimated volume of distribution of the central compartment: 72.8 mL/kg at 0.1 mg/kg (versus 40.7 mL/kg for doses equal or higher than 1 mg/kg). Volume of distribution at steady-state (Vdss) in Part B was on average 103.63 mL/kg at 0.1 mg/kg while it was 59.96, 60.92 and 45.72 mL/kg at 1, 3 and 6 mg/kg, respectively.
NONMEM summary statistics for GSK933776 compartmental pharmacokinetic parameters are presented below.

Parameter	Name	Estimate	95% Confidence Interval		Standard Error	%RSE	%CV
			Lower	Upper			
THETA (1)	CL (mL/kg/h)	0.132	0.116	0.148	8.39	6.36	
THETA (2)	V2 (mL/kg)	13.7	9.25	18.1	2.27	16.6	
THETA (3)	V1 (mL/kg)	40.7	36.6	44.8	2.07	5.09	
THETA (4)	Q1 (mL/kg/h)	0.455	0.194	0.716	0.133	29.2	
THETA (5)	CL (mL/kg/h) at 0.1 mg/kg	0.272	0.232	0.312	0.0204	7.50	
THETA (6)	V2 (mL/kg) at 0.1 mg/kg	36.5	22.5	50.5	7.12	19.5	
THETA (7)	V1 (mL/kg) at 0.1 mg/kg	72.8	61.5	84.1	5.78	7.94	
THETA (8)	Q1 (mL/kg/h) at 0.1 mg/kg	0.582	0.286	0.878	0.151	25.9	
ETA (1,1)	IIV_CL	0.0676	0.0330	0.102	0.0178	26.3	26.0
ETA (2,2)	IIV_V2	0.225	0.0380	0.412	0.0953	42.4	47.4
ETA (3,3)	IIV_V1	0.0555	0.0270	0.0840	0.0144	25.9	23.6
EPS (1,1)	SIGMA11	0.0325	0.0250	0.0400	3.60	11.1	18.0

RSE=relative standard error.
THETA denotes typical values of the pharmacokinetic parameters.
ETA denotes variance of the log of the pharmacokinetic parameters.
EPS/SIGMA denotes variance of the proportional residual error.

Summary statistics for $\log_e$-transformed GSK933776 compartmental pharmacokinetic parameters from the population analysis are presented below.

Parameter	Treatment	N	n	Geometric Mean	95% Confidence Interval		SD (Logs)	%CVb
					Lower	Upper		
AUC(0–∞) (h.mg/mL)	0.1 mg/kg SD	6	6	0.32	0.25	0.42	0.254	25.8
	0.1 mg/kg RD	6	6	0.42	0.35	0.50	0.167	16.8
	1 mg/kg RD	6	6	8.16	5.84	11.42	0.320	32.8
	3 mg/kg RD	6	6	18.31	15.68	21.39	0.148	14.9
	6 mg/kg RD	6	6	51.68	41.32	64.64	0.213	21.6
AUC(0–28 days) (h.mg/mL)	0.1 mg/kg SD	6	6	0.26	0.20	0.35	0.258	26.2
	0.1 mg/kg RD	6	6	0.33	0.27	0.40	0.193	19.5
	1 mg/kg RD	6	6	5.99	4.83	7.43	0.205	20.8

	3 mg/kg RD	6	6	15.21	13.15	17.60	0.139	13.9
	6 mg/kg RD	6	6	42.11	33.87	52.35	0.207	21.0
AUC(28–56 days) (h.mg/mL)	0.1 mg/kg SD	6	6	0.31	0.24	0.40	0.254	25.8
	0.1 mg/kg RD	6	6	0.39	0.33	0.47	0.176	17.7
	1 mg/kg RD	6	6	7.51	5.65	10.00	0.272	27.7
	3 mg/kg RD	6	6	17.75	15.24	20.68	0.145	14.6
	6 mg/kg RD	6	6	49.83	39.97	62.11	0.210	21.2
AUC(56–84 days) (h.mg/mL)	0.1 mg/kg SD	6	6	0.32	0.24	0.41	0.253	25.8
	0.1 mg/kg RD	6	6	0.41	0.34	0.49	0.170	17.1
	1 mg/kg RD	6	6	7.96	5.80	10.92	0.302	30.9
	3 mg/kg RD	6	6	18.21	15.60	21.26	0.147	14.8
	6 mg/kg RD	6	6	51.31	41.07	64.10	0.212	21.4
Vd_{SS} (mL/kg)	0.1 mg/kg SD	6	6	116.46	84.90	159.75	0.301	30.8
	0.1 mg/kg RD	6	6	103.63	78.50	136.81	0.265	26.9
	1 mg/kg RD	6	6	59.96	51.54	69.76	0.144	14.5
	3 mg/kg RD	6	6	60.92	52.63	70.53	0.139	14.0
	6 mg/kg RD	6	6	45.72	36.45	57.33	0.216	21.8
t½ (day)	0.1 mg/kg SD	6	6	11.33	9.46	13.57	0.172	17.3
	0.1 mg/kg RD	6	6	13.37	10.63	16.80	0.218	22.1
	1 mg/kg RD	6	6	14.41	10.30	20.17	0.320	32.9
	3 mg/kg RD	6	6	11.09	9.83	12.51	0.115	11.6
	6 mg/kg RD	6	6	11.59	10.28	13.05	0.114	11.4

Results from the assessment of dose proportionality (slope and 90% confidence interval) for AUC and Cmax (power model) are presented below.

Analysis	**Parameter**	**Dose**	**Adjusted Mean Slope (Standard Error)**	**90% Confidence Interval**
Non-Compartmental	AUC(0–672 h) (h.mg/mL)	1	1.16 (0.030)	(1.11, 1.21)
		2	1.15 (0.031)	(1.09, 1.20)
		3	1.18 (0.036)	(1.11, 1.24)
	Cmax (μg/mL)	1	1.14 (0.025)	(1.09, 1.18)
		2	1.16 (0.035)	(1.10, 1.22)
		3	1.15 (0.038)	(1.08, 1.21)
Population	AUC(0–∞) (h.mg/mL)	1	1.15 (0.036)	(1.09, 1.21)

The parameters Ro and Rs were calculated to assess possible accumulation of the study drug. In Period 3, Ro ranged from 1.28 to 1.68, excluding the 1 mg/kg dose. For Rs the highest value (1.4) was observed in Period 3 at 6 mg/kg. All other values were around 1.

The adjusted mean slope for the non-compartmental analyses across the dose periods for AUC(0–672 h) and Cmax are all over 1. This suggests more than proportional increases in AUC(0–672 h) and Cmax for each dosing period with increasing doses. Further, the 90% confidence intervals are not inclusive of 1 and therefore further evidence to suggest some degree of non-proportionality. The results and inferences are similar for AUC(0–∞) from the population analysis for Period 1.

Pharmacokinetic Endpoints: Cerebrospinal fluid: GSK933776 CSF pharmacokinetics was measured at Day 78 for doses of 1 mg/kg and higher. Two subjects out of four at 1 mg/kg, five out of six subjects at 3 mg/kg and five out of five subjects at 6 mg/kg had detectable concentrations. The mean of the CSF versus plasma concentration ratios at Day 78 for the quantifiable concentrations (both in CSF and plasma) was 0.217% at 6 mg/kg (n=4) and 0.272% at 3 mg/kg (n=5).

Pharmacodynamic Endpoints: Plasma: There was a dose-dependent increase in total Aβ levels and a dose-dependent decrease in free Aβ levels, which began immediately after the first administration of GSK933776. This effect was most pronounced after the 1, 3 and 6 mg/kg doses. Placebo had no effect on free or total plasma Aβ levels. The dose-dependent increases in total plasma Aβ levels and decreases in free plasma Aβ levels were still apparent when baseline plasma Aβ levels were taken into account.

Peak : trough ratios for Aβ decreased with increasing dose of GSK933776. For total Aβ1–42, the peak : trough ratio was ≤2 at a dose of 3 mg/kg; for total Aβ1–34, the ratio was ≤2 at a dose of 6 mg/kg.

Pharmacodynamic Endpoints: Cerebrospinal fluid: There were increases from baseline in Aβ1–38 MSD at the

6 mg/kg dose. In addition, there were increases when comparing the pooled values from patients receiving GSK933776 with placebo. There were no apparent changes from baseline on APOE, tau or P-tau for placebo or any repeat doses of GSK933776.
Pharmacogenetic Results: All subjects consented to the pharmacogenetics analyses. Six subjects from the single dose part re-entered in the repeat dose part. The *APOE* ε4 carrier frequency in the overall study population (64%, n=44) was similar to the expected frequency in the general AD population (64.8%). Nine subjects (20%) carried two copies of the *APOE* ε4 allele.