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.: AZ3110866

Title: Study AZ3110866, a fixed dose study of SB742457 versus placebo when added to existing donepezil treatment in subjects with mild-to-moderate Alzheimer's disease

Rationale: SB742457 is a potent and selective 5 hydroxytryptamine (serotonin) receptor-6 (5-HT_6) antagonist, which is being developed as an oral treatment for subjects with mild-to-moderate Alzheimer's disease (AD). Preclinically, SB742457 has been shown to have activity in the novel object recognition and Morris water maze models of cognitive enhancement in rats. In addition, cognitive and global effects of SB742457 as monotherapy have been investigated in subjects with mild-to-moderate AD in two multinational Phase IIa studies, AZ3100603 (a 24-week, dose-ranging study that randomised 371 subjects in a 2:1:1:2 ratio to placebo, 5 mg, 15 mg or 35 mg SB742457, respectively) and AZ3106242 (an exploratory 24-week study that randomised 198 subjects to placebo, SB742457 or donepezil in a 1:1:1 ratio). Preclinical evidence also suggests there is a potential for synergistic effects of donepezil and 5-HT_6 antagonists on cognition and acetylcholine release. This study was the first to investigate the safety and efficacy of SB742457 when added to stable donepezil treatment in subjects with mild-to-moderate AD.

Phase: IIb

Study Period: 01July 2008 to 16 November 2010

Study Design: A 48-week international, multi-centre, double-blind, randomised, placebo-controlled, parallel group trial to investigate the efficacy and safety of SB742457 (15 mg, 35 mg) compared with placebo when added to existing donepezil treatment. Study participation lasted approximately 32 or 56 weeks depending on continuation status: 0-2 weeks for screening, a 4-week placebo run-in to evaluate baseline status, a 48-week randomised treatment phase, and a 2-week follow up period after the end of treatment. At the end of 24 weeks of double-blind treatment, eligible subjects were asked to consent to continue their randomised treatment for a further 24 weeks. Once all subjects completed Week 24, data were unblinded and analysed by GSK. Details of unblinding were not provided to investigators or subjects and subject level unblinding was only available to members of the GSK biostatistics and programming team and an Independent Data Monitoring Committee (IDMC) who monitored safety throughout the study.

Centres: 100 centres from 9 countries (Argentina, Australia, Canada, Chile, Czech Republic, Germany, Italy, Spain, and USA)

Indication: Alzheimer's Disease

Treatment: All subjects were allocated single-blind placebo study treatment for the 4-week placebo run-in period. Eligible subjects were then randomised to placebo, SB742457 15 mg, or SB742457 35 mg in a 1:1:1 ratio in addition to their stable donepezil regimen. Randomisation was stratified by baseline Mini Mental State Examination (MMSE) score with thresholds to ensure recruitment of $\leq$30% of subjects with a baseline score of 10-15, $\leq$60% with 16-20, and $\leq$30% with 21-26. The purpose of this ratio was to ensure a minimum of 70% of the recruited population would contribute to a pre-defined subgroup analysis of either milder (MMSE 16-26) or more moderate (MMSE 10-20) subjects. GSK provided 15 mg and 35 mg tablets of SB742457 and matched placebo tablets. Subjects were instructed to take one tablet of their assigned medication each morning, without regard to food. Donepezil was administered/supplied as per the subject's normal regimen/provider.

Objectives:

- To assess the effects of once daily dosing of SB 742457 versus placebo as an adjunct therapy to stable donepezil treatment after 24 weeks of treatment on cognitive function.
- To assess the effects of once daily dosing of SB 742457 versus placebo as an adjunct therapy to stable donepezil treatment after 24 weeks of treatment on global function.

Primary Outcome/Efficacy Variable

Change from baseline in Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) total score and Clinical Dementia Rating – Sum of Boxes (CDR-SB) score at Week 24.

Secondary Outcome/Efficacy Variable(s):

1. Change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score at Week 24
2. Effect of baseline severity (including subgroup analyses based on baseline MMSE scores) on change from baseline in ADAS-Cog total score, CDR-SB and RBANS at Week 24
3. Change from baseline in ADAS-Cog total score at Week 12, 36 and 48

4. Change from baseline in CDR-SB score at Week 12, 36 and 48
5. Change from baseline in RBANS score at Week 12, 36 and 48
6. Effect of baseline severity (including subgroup analyses based on baseline MMSE scores) on change from baseline in ADAS-Cog total score, CDR-SB and RBANS at Weeks 12, 36 and 48
7. Change from baseline in Alzheimer's Disease Cooperative Society – Activities of daily Living (ADCS- ADL) total score at Weeks 12, 24, 36 and 48
8. Change from baseline in MMSE total score at Week 24 and 48
9. Change from baseline in sections/domains of assessment scales at Weeks 12, 24, 36 and 48.

Statistical Methods: A total of 684 subjects were randomised to ensure at least 570 evaluable subjects. A sample size of 190 subjects per treatment group was required to provide 90% power to detect a difference of 2.0 points and 0.6 points between placebo and active treatment in the change from baseline in ADAS-Cog score, and CDR-SB, respectively. This assumed a standard deviation (SD) of 6.0 and 1.8, respectively and two-sided tests at the 5% significance level. It was estimated that this sample size would also provide approximately 80% power to detect a difference from placebo of 2.0 points in ADAS-Cog in a subgroup (based on baseline MMSE) that included approximately 70-75% of subjects. To control for multiplicity, both ADAS-Cog and CDR-SB needed to achieve a significance level of 0.05 at the same dose to maintain an overall 5% significance level. A hierarchical approach was adopted with SB742457 35 mg versus placebo tested first.

Three populations were defined for efficacy and safety analyses: Safety (subjects randomised who took at least one dose of study medication), Intent-to treat (ITT) (subjects in the Safety population who also had at least one post-baseline efficacy or health outcomes assessment), and Per Protocol (PP) (subjects in the ITT population who were not major protocol violators).

Two reporting efforts were produced:

- Week 24 Analysis - including all data up to Week 24 (produced during the conduct of the study at a time when all subjects had completed their Week 24 or Early Withdrawal assessment).
- Week 48 Analysis - including all study data (conducted at the end of the study when all subjects had completed their Week 48 or Early Withdrawal assessment). The Week 48 analysis is a cumulative presentation of all data reported throughout the study including that of the Week 24 Analysis.

Change from baseline in the primary endpoints (ADAS-Cog and CDR-SB) and secondary endpoints (RBANS, ADCS-ADL, and MMSE) were analysed using a mixed model for repeated measures (MMRM). All analyses were adjusted for the following covariates: baseline MMSE, baseline of endpoint, baseline body mass index (BMI), time since diagnosis, and country group. Primary inference was based on the Week 24 treatment differences for the full ITT population using the observed cases (no missing data estimated or data carried forward) dataset.

Subgroup analyses of subjects with milder AD and more moderate AD (based on baseline MMSE scores) were conducted for change from baseline endpoints including ADAS-Cog, CDR-SB, and RBANS.

The safety population was used for the analysis of the safety data. No formal hypothesis testing was performed on these data.

Study Population: Eligible subjects were 50-85 years of age with a clinical diagnosis of probable AD and a documented history of at least 6 months of ongoing donepezil therapy for AD with stable dosing of 5-10 mg/day for at least the last 2 months. A screening MMSE score of 12-24 inclusive, a baseline score of 10-26 inclusive (and within +/-3 points of screening value), cohabitation (or regular contact) with a caregiver, and no other likely causes of dementia were also required criteria. Medical conditions, concomitant medications, and abnormal test/laboratory findings that would preclude participation were specified.

	Placebo	**SB742457 15 mg**	**SB742457 35 mg**
Number of Subjects:			
Planned, N	224	224	224
Randomised, N	226	221	237
Safety Population, N	225	221	236
Completed Week 24, n (%)	198 (88)	191 (86)	210 (89)
Completed Week 48, n (%)	151 (67)	147 (67)	172 (73)
Total Number Subjects Withdrawn before Week 24, n (%)	27 (12)	30 (14)	26 (11)
Withdrawn due to Adverse Events n (%)	6 (3)	11 (5)	10 (4)

Withdrawn due to Lack of Efficacy n (%)	3 (1)	0	2 (<1)
Withdrawn for other reasons n (%)	18 (8)	19 (9)	14 (6)
Total Number Subjects Withdrawn before Week 48, n (%)	49 (22)	53 (24)	48 (20)
Withdrawn due to Adverse Events n (%)	11 (5)	19 (9)	16 (7)
Withdrawn due to Lack of Efficacy n (%)	4 (2)	3 (1)	5 (2)
Withdrawn for other reasons n (%)	34 (15)	31 (14)	27 (11)
Note: All completed and withdrawn percentages are based on the Safety Population.			
Demographics	**Placebo**	**SB742457 15 mg**	**SB742457 35 mg**
N (ITT)	223	218	236
Females (%): Males (%)	58:42	54:46	63:37
Mean Age, years (SD)	73.1 (7.49)	74.2 (6.82)	73.8 (6.92)
White, n (%)	223 (100)	215 (99)	233 (>99)

Primary Efficacy Results:

Week 24 Analysis (ITT Population)			
	Placebo (N=223)	**SB742457 15 mg (N=218)**	**SB742457 35 mg (N=236)**
Summary of Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score at Week 24			
n	193	184	200
Adjusted Mean Change from baseline (SE)	1.2 (0.45)	0.5 (0.44)	-0.4 (0.41)
Difference between treatments (SB742457 minus placebo)		-0.7	-1.5
95% Confidence Interval (CI)		(-1.9, 0.5)	(-2.7, -0.3)
p-value		0.279	0.012
Summary of Repeated Measures Analysis of Change from Baseline in CDR-SB Score at Week 24			
n	191	184	200
Adjusted Mean Change from baseline (SE)	0.9 (0.13)	0.8 (0.13)	0.7 (0.11)
Difference between treatments (SB742457 minus placebo)		-0.1	-0.1
95% CI		(-0.4, 0.3)	(-0.5, 0.2)
p-value		0.711	0.462

Note: ADAS-Cog and CDR-SB: A negative difference represents benefit over placebo.

Secondary Outcome Variables:

Week 48 Analysis (ITT Population)				
		Placebo (N=223)	**SB742457 15 mg (N=218)**	**SB742457 35 mg (N=236)**
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score				
Week 12	n	206	202	219
	Adjusted Mean Change from baseline (SE)	0.4 (0.33)	0.1 (0.37)	-0.9 (0.34)
	Difference between treatments (SB742457 - placebo)		-0.2	-1.3
	95% CI		(-1.2. 0.7)	(-2.2, -0.4)
Week 24	n	194	185	207
	Adjusted Mean Change from baseline (SE)	1.2 (0.45)	0.5 (0.44)	-0.3 (0.41)
	Difference between treatments (SB742457 - placebo)		-0.7	-1.5
	95% CI		(-1.9, 0.6)	(-2.7, -0.3)
Week 36	n	164	156	181
	Adjusted Mean Change from baseline (SE)	2.1 (0.45)	2.1 (0.48)	0.9 (0.45)
	Difference between treatments (SB742457 - placebo)		0.0	-1.2

	95% CI		(-1.3, 1.2)	(-2.5, 0.0)
Week 48	n	145	142	170
	Adjusted Mean Change from baseline (SE)	3.4 (0.52)	3.4 (0.60)	1.8 (0.50)
	Difference between treatments (SB742457 - placebo)		-0.1	-1.6
	95% CI		(-1.6, 1.5)	(-3.1, -0.2)
Repeated Measures Analysis of Change from Baseline in CDR-SB Score				
Week 12	n	203	199	221
	Adjusted Mean Change from baseline (SE)	0.5 (0.10)	0.4 (0.09)	0.2 (0.08)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.3
	95% CI		(-0.4, 0.1)	(-0.5, -0.1)
Week 24	n	192	185	207
	Adjusted Mean Change from baseline (SE)	0.9 (0.14)	0.8 (0.13)	0.7 (0.11)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.1
	95% CI		(-0.5, 0.3)	(-0.5, 0.2)
Week 36	n	163	154	179
	Adjusted Mean Change from baseline (SE)	1.2 (0.15)	1.4 (0.18)	1.0 (0.13)
	Difference between treatments (SB742457 - placebo)		0.2	-0.2
	95% CI		(-0.3, 0.6)	(-0.6, 0.2)
Week 48	n	146	142	170
	Adjusted Mean Change from baseline (SE)	1.6 (0.16)	1.9 (0.20)	1.5 (0.16)
	Difference between treatments (SB742457 - placebo)		0.3	-0.1
	95% CI		(-0.2, 0.8)	(-0.5, 0.4)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score				
Week 12	n	200	194	214
	Adjusted Mean Change from baseline (SE)	-7.2 (0.94)	-8.5 (1.02)	-6.5 (0.79)
	Difference between treatments (SB742457 - placebo)		-1.3	0.6
	95% CI		(-4.0, 1.4)	(-1.7, 3.0)
Week 24	n	191	177	200
	Adjusted Mean Change from baseline (SE)	-3.5 (1.17)	-5.8 (1.27)	-4.1 (1.09)
	Difference between treatments (SB742457 - placebo)		-2.3	-0.6
	95% CI		(-5.7, 1.1)	(-3.7, 2.5)
Week 36	n	161	153	174
	Adjusted Mean Change from baseline (SE)	-3.9 (1.32)	-4.8 (1.21)	-1.8 (1.19)
	Difference between treatments (SB742457 - placebo)		-0.9	2.1
	95% CI		(-4.4, 2.7)	(-1.4, 5.6)
Week 48	n	143	136	164
	Adjusted Mean Change from baseline (SE)	-7.3 (1.36)	-9.4 (1.45)	-4.7 (1.25)
	Difference between treatments (SB742457 - placebo)		-2.1	2.6
	95% CI		(-6.0, 1.8)	(-1.0, 6.2)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Total Score				
Week 12	n	202	200	222
	Adjusted Mean Change from baseline (SE)	-1.4 (0.57)	-0.8 (0.49)	0.3 (0.47)
	Difference between treatments (SB742457 - placebo)		0.6	1.7
	95% CI		(-0.8, 2.1)	(0.3, 3.2)
Week 24	n	192	185	209

	Adjusted Mean Change from baseline (SE)	-3.4 (0.66)	-1.9 (0.61)	-1.4 (0.60)
	Difference between treatments (SB742457 - placebo)		1.4	2.0
	95% CI		(-0.3, 3.2)	(0.3, 3.7)
Week 36	n	164	159	183
	Adjusted Mean Change from baseline (SE)	-3.7 (0.67)	-3.8 (0.80)	-1.8 (0.65)
	Difference between treatments (SB742457 - placebo)		-0.1	1.9
	95% CI		(-2.1, 2.0)	(0.1, 3.8)
Week 48	n	147	144	171
	Adjusted Mean Change from baseline (SE)	-5.5 (0.85)	-5.0 (0.87)	-3.5 (0.76)
	Difference between treatments (SB742457 - placebo)		0.5	1.9
	95% CI		(-1.9, 2.9)	(-0.3, 4.2)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Basic Score				
Week 12	n	204	202	222
	Adjusted Mean Change from baseline (SE)	-0.4 (0.18)	-0.4 (0.15)	-0.3 (0.14)
	Difference between treatments (SB742457 - placebo)		0.0	0.1
	95% CI		(-0.5, 0.4)	(-0.4, 0.5)
Week 24	n	193	186	209
	Adjusted Mean Change from baseline (SE)	-0.8 (0.20)	-0.7 (0.17)	-0.6 (0.18)
	Difference between treatments (SB742457 - placebo)		0.1	0.2
	95% CI		(-0.4, 0.7)	(-0.4, 0.7)
Week 36	n	164	159	183
	Adjusted Mean Change from baseline (SE)	-1.1 (0.23)	-1.0 (0.22)	-0.7 (0.21)
	Difference between treatments (SB742457 - placebo)		0.1	0.4
	95% CI		(-0.6, 0.7)	(-0.2, 1.0)
Week 48	n	147	145	171
	Adjusted Mean Change from baseline (SE)	-1.5 (0.27)	-1.3 (0.22)	-1.1 (0.24)
	Difference between treatments (SB742457 - placebo)		0.2	0.4
	95% CI		(-0.5, 0.9)	(-0.3, 1.1)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Instrumental Score				
Week 12	n	203	200	223
	Adjusted Mean Change from baseline (SE)	-1.1 (0.47)	-0.5 (0.42)	0.5 (0.40)
	Difference between treatments (SB742457 - placebo)		0.7	1.6
	95% CI		(-0.6, 1.9)	(0.4, 2.8)
Week 24	n	193	186	210
	Adjusted Mean Change from baseline (SE)	-2.5 (0.53)	-1.3 (0.52)	-0.8 (0.49)
	Difference between treatments (SB742457 - placebo)		1.2	1.7
	95% CI		(-0.3, 2.6)	(0.3, 3.1)
Week 36	n	165	159	184
	Adjusted Mean Change from baseline (SE)	-2.7 (0.54)	-2.8 (0.65)	-1.2 (0.55)
	Difference between treatments (SB742457 - placebo)		-0.1	1.6
	95% CI		(-1.8, 1.6)	(0.1, 3.1)
Week 48	n	149	144	173
	Adjusted Mean Change from baseline (SE)	-4.0 (0.66)	-3.7 (0.71)	-2.5 (0.61)
	Difference between treatments (SB742457 - placebo)		0.3	1.5
	95% CI		(-1.6, 2.2)	(-0.3, 3.2)

Repeated Measures Analysis of Change from Baseline in ADCS-ADL Total Independence Score				
Week 12	n	205	202	223
	Adjusted Mean Change from baseline (SE)	-0.5 (0.19)	-0.3 (0.20)	-0.0 (0.17)
	Difference between treatments (SB742457 - placebo)		0.2	0.5
	95% CI		(-0.3, 0.8)	(-0.0, 1.0)
Week 24	n	194	187	210
	Adjusted Mean Change from baseline (SE)	-1.1 (0.22)	-0.7 (0.23)	-0.1 (0.21)
	Difference between treatments (SB742457 - placebo)		0.4	1.0
	95% CI		(-0.3, 1.0)	(0.4, 1.6)
Week 36	n	165	159	184
	Adjusted Mean Change from baseline (SE)	-1.2 (0.25)	-1.3 (0.27)	-0.4 (0.24)
	Difference between treatments (SB742457 - placebo)		-0.1	0.7
	95% CI		(-0.8, 0.6)	(0.1, 1.4)
Week 48	n	149	145	173
	Adjusted Mean Change from baseline (SE)	-1.6 (0.30)	-1.6 (0.29)	-0.9 (0.25)
	Difference between treatments (SB742457 - placebo)		0.0	0.7
	95% CI		(-0.9, 0.8)	(-0.1, 1.4)
Repeated Measures Analysis of Change from Baseline in MMSE Total Score				
Week 24	n	196	188	209
	Adjusted Mean Change from baseline (SE)	-0.4 (0.21)	-0.3 (0.23)	0.1 (0.21)
	Difference between treatments (SB742457 - placebo)		0.0	0.4
	95% CI		(-0.6, 0.6)	(-0.1, 1.0)
Week 48	n	149	145	172
	Adjusted Mean Change from baseline (SE)	-1.1 (0.28)	-1.3 (0.33)	-0.7 (0.27)
	Difference between treatments (SB742457 - placebo)		-0.1	0.4
	95% CI		(-1.0, 0.7)	(-0.3, 1.2)
Subgroup Analyses by Baseline Severity (based on MMSE scores) - Week 12 (Week 48 Analysis, ITT Population)				
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score				
Milder AD (MMSE 16-26)	n	153	162	172
	Adjusted Mean Change from baseline (SE)	0.1 (0.36)	0.0 (0.43)	-1.1 (0.36)
	Difference between treatments (SB742457 - placebo)		-0.1	-1.2
	95% CI		(-1.1, 1.0)	(-2.1, -0.2)
More moderate (MMSE 10-20)	n	144	133	140
	Adjusted Mean Change from baseline (SE)	0.7 (0.42)	0.6 (0.45)	-0.6 (0.45)
	Difference between treatments (SB742457 - placebo)		-0.2	-1.3
	95% CI		(-1.4, 1.0)	(-2.5, -0.1)
Repeated Measures Analysis of Change from Baseline in CDR-SB Total Score				
Milder AD (MMSE 16-26)	n	152	159	173
	Adjusted Mean Change from baseline (SE)	0.5 (0.12)	0.4 (0.10)	0.2 (0.08)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.3
	95% CI		(-0.4, 0.2)	(-0.6, -0.0)
More moderate (MMSE 10-20)	n	141	131	141
	Adjusted Mean Change from baseline (SE)	0.6 (0.12)	0.5 (0.12)	0.3 (0.10)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.3

	95% CI		(-0.4, 0.3)	(-0.6, 0.0)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score				
Milder AD (MMSE 16-26)	n	152	158	168
	Adjusted Mean Change from baseline (SE)	-7.1 (1.09)	-7.7 (1.19)	-6.3 (0.87)
	Difference between treatments (SB742457 - placebo)		-0.7	0.7
	95% CI		(-3.8, 2.5)	(-2.0, 3.5)
More moderate (MMSE 10-20)	n	138	127	135
	Adjusted Mean Change from baseline (SE)	-6.8 (1.13)	-9.1 (1.20)	-7.0 (0.94)
	Difference between treatments (SB742457 - placebo)		-2.3	-0.2
	95% CI		(-5.5, 0.9)	(-3.0, 2.7)
Subgroup Analyses by Baseline Severity (based on MMSE scores) - Week 24 (Week 48 Analysis, ITT Population)				
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score				
Milder AD (MMSE 16-26)	n	146	148	167
	Adjusted Mean Change from baseline (SE)	0.9 (0.51)	0.1 (0.48)	-0.7 (0.43)
	Difference between treatments (SB742457 - placebo)		-0.8	-1.5
	95% CI		(-2.1, 0.6)	(-2.8, -0.2)
More moderate (MMSE 10-20)	n	133	123	130
	Adjusted Mean Change from baseline (SE)	1.2 (0.55)	1.0 (0.57)	0.4 (0.56)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.8
	95% CI		(-1.7, 1.4)	(-2.3, 0.8)
Repeated Measures Analysis of Change from Baseline in CDR-SB Total Score				
Milder AD (MMSE 16-26)	n	144	147	165
	Adjusted Mean Change from baseline (SE)	0.7 (0.15)	0.7 (0.13)	0.5 (0.11)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.2
	95% CI		(-0.5, 0.3)	(-0.6, 0.2)
More moderate (MMSE 10-20)	n	132	125	132
	Adjusted Mean Change from baseline (SE)	1.1 (0.18)	1.0 (0.18)	1.0 (0.15)
	Difference between treatments (SB742457 - placebo)		-0.1	-0.1
	95% CI		(-0.6, 0.4)	(-0.6, 0.3)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score				
Milder AD (MMSE 16-26)	n	144	146	162
	Adjusted Mean Change from baseline (SE)	-2.3 (1.41)	-4.7 (1.49)	-2.9 (1.15)
	Difference between treatments (SB742457 - placebo)		-2.4	-0.6
	95% CI		(-6.4, 1.6)	(-4.2, 3.0)
More moderate (MMSE 10-20)	n	130	115	124
	Adjusted Mean Change from baseline (SE)	-4.0 (1.46)	-6.7 (1.39)	-6.3 (1.49)
	Difference between treatments (SB742457 - placebo)		-2.6	-2.2
	95% CI		(-6.6, 1.3)	(-6.4, 1.9)
Subgroup Analyses by Baseline Severity (based on MMSE scores) - Week 36 (Week 48 Analysis, ITT Population)				
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score				
Milder AD (MMSE 16-26)	n	125	125	149
	Adjusted Mean Change from baseline (SE)	1.7 (0.51)	2.2 (0.54)	0.2 (0.47)
	Difference between treatments (SB742457 - placebo)		0.5	-1.5
	95% CI		(-1.0, 1.9)	(-2.9, -0.2)
More	n	111	102	111

moderate (MMSE 10-20)	Adjusted Mean Change from baseline (SE)	2.6 (0.59)	2.6 (0.62)	1.7 (0.63)
	Difference between treatments (SB742457 - placebo)		0.0	-0.9
	95% CI		(-1.7, 1.6)	(-2.6, 0.7)
Repeated Measures Analysis of Change from Baseline in CDR-SB Total Score				
Milder AD (MMSE 16-26)	n	123	121	144
	Adjusted Mean Change from baseline (SE)	1.0 (0.17)	1.2 (0.17)	0.7 (0.14)
	Difference between treatments (SB742457 - placebo)		0.2	-0.2
	95% CI		(-0.3, 0.7)	(-0.7, 0.2)
More moderate (MMSE 10-20)	n	112	102	110
	Adjusted Mean Change from baseline (SE)	1.4 (0.20)	1.7 (0.24)	1.2 (0.17)
	Difference between treatments (SB742457 - placebo)		0.3	-0.3
	95% CI		(-0.3, 0.9)	(-0.8, 0.3)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score				
Milder AD (MMSE 16-26)	n	123	123	143
	Adjusted Mean Change from baseline (SE)	-2.0 (1.58)	-3.5 (1.36)	-0.0 (1.32)
	Difference between treatments (SB742457 - placebo)		-1.4	2.0
	95% CI		(-5.5, 2.7)	(-2.0, 6.0)
More moderate (MMSE 10-20)	n	108	100	105
	Adjusted Mean Change from baseline (SE)	-4.5 (1.64)	-6.7 (1.41)	-3.6 (1.56)
	Difference between treatments (SB742457 - placebo)		-2.2	0.9
	95% CI		(-6.5, 2.0)	(-3.6, 5.3)
Subgroup Analyses by Baseline Severity (based on MMSE scores) - Week 48 (Week 48 Analysis, ITT Population)				
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score				
Milder AD (MMSE 16-26)	n	113	115	138
	Adjusted Mean Change from baseline (SE)	2.4 (0.59)	3.1 (0.66)	0.9 (0.51)
	Difference between treatments (SB742457 - placebo)		0.7	-1.5
	95% CI		(-1.0, 2.4)	(-3.0, 0.1)
More moderate (MMSE 10-20)	n	99	90	104
	Adjusted Mean Change from baseline (SE)	4.2 (0.66)	4.4 (0.77)	2.3 (0.67)
	Difference between treatments (SB742457 - placebo)		0.2	-1.9
	95% CI		(-1.8, 2.2)	(-3.7, -0.0)
Repeated Measures Analysis of Change from Baseline in CDR-SB Total Score				
Milder AD (MMSE 16-26)	n	111	117	137
	Adjusted Mean Change from baseline (SE)	1.2 (0.18)	1.7 (0.21)	1.2 (0.17)
	Difference between treatments (SB742457 - placebo)		0.4	0.0
	95% CI		(-0.1, 1.0)	(-0.5, 0.4)
More moderate (MMSE 10-20)	n	101	90	106
	Adjusted Mean Change from baseline (SE)	1.9 (0.21)	2.3 (0.27)	1.8 (0.21)
	Difference between treatments (SB742457 - placebo)		0.4	-0.1
	95% CI		(-0.3, 1.1)	(-0.7, 0.4)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score				
Milder AD (MMSE 16-26)	n	112	109	135
	Adjusted Mean Change from baseline (SE)	-5.5 (1.62)	-8.9 (1.60)	-3.2 (1.32)
	Difference between treatments (SB742457 - placebo)		-3.4	2.3
	95% CI		(-7.9, 1.0)	(-1.8, 6.4)

More moderate (MMSE 10-20)	N	97	85	101
	Adjusted Mean Change from baseline (SE)	-9.1 (1.79)	-10.5 (1.75)	-7.4 (1.76)
	Difference between treatments (SB742457 - placebo)		-1.3	1.8
	95% CI		(-6.3, 3.6)	(-3.1, 6.7)

Note: ADAS-Cog and CDR-SB: A negative difference represents benefit over placebo. RBANS, ADCS-ADL and MMSE: A positive difference represents benefit over placebo.

Safety Results: An on-treatment adverse event (AE) or serious adverse event (SAE) was defined as an event with onset on or after the first day of double-blind randomised treatment but not later than 7 days after the last day of randomised treatment, or an event with onset date missing and a stop date after the first day of double-blind randomised treatment.

	Placebo (N=225) n (%)	**SB742457 15 mg (N=221) n (%)**	**SB742457 35 mg (N=236) n (%)**
Week 24 Analysis (Safety Population)			
Subjects with any on-treatment AE	**97 (43)**	**105 (48)**	**115 (49)**
Most frequent on-treatment AEs			
Nasopharyngitis	9 (4)	13 (6)	8 (3)
Urinary tract infection	12 (5)	7 (3)	11 (5)
Diarrhoea	5 (2)	9 (4)	5 (2)
Fall	9 (4)	4 (2)	4 (2)
Headache	3 (1)	6 (3)	4 (2)
Nausea	6 (3)	2 (<1)	4 (2)
Cough	2 (<1)	3 (1)	5 (2)
Hypertension	3 (1)	2 (<1)	5 (2)
Insomnia	2 (<1)	1 (<1)	6 (3)
Upper respiratory tract infection	5 (2)	3 (1)	0
Week 48 Analysis (Safety Population)			
Subjects with any on-treatment AE	**125 (56)**	**137 (62)**	**146 (62)**
Most frequent on-treatment AEs			
Nasopharyngitis	17 (8)	19 (9)	18 (8)
Urinary tract infection	16 (7)	11 (5)	13 (6)
Diarrhoea	9 (4)	12 (5)	11 (5)
Fall	13 (6)	4 (2)	5 (2)
Headache	6 (3)	8 (4)	7 (3)
Hypertension	7 (3)	5 (2)	7 (3)
Bronchitis	3 (1)	4 (2)	9 (4)
Nausea	8 (4)	4 (2)	4 (2)
Dizziness	7 (3)	5 (2)	3 (1)
Cough	2 (<1)	4 (2)	8 (3)

Note: Week 24 Analysis includes all data from the primary analysis, up to and including the Week 24 visit.
Week 48 Analysis includes all data from the complete and final dataset up to Week 48, and including that of the Week 24 Analysis.

Serious Adverse Events - On-Treatment n (%) [n considered by the investigator to be related to study medication]			
	Placebo (N=225)	SB742457 15 mg (N=221)	SB742457 35 mg (N=236)
	n (%) [related]	n (%) [related]	n (%) [related]
Week 24 Analysis (Safety Population)			
Subjects with on-treatment SAEs (includes both fatal and non-fatal events)	9 (4) [1]	14 (6) [0]	17 (7) [0]
Abdominal abscess	0	0	1 (<1) [0]
Adams-Stokes syndrome	0	0	1 (<1) [0]
Aphasia	1 (<1) [1]	0	0
Arteriosclerosis coronary artery	0	0	1 (<1) [0]
Bradycardia	0	1 (<1) [0]	0
Cardio-respiratory arrest	0	1 (<1) [0]	0
Cerebral haemorrhage	0	1 (<1) [0]	0
Cerebrovascular accident	0	2 (<1) [0]	0
Chronic obstructive pulmonary disease	0	0	1 (<1) [0]
Circulatory collapse	0	0	1 (<1) [0]
Confusional state	0	1 (<1) [0]	0
Decreased appetite	0	0	1 (<1) [0]
Deep vein thrombosis	0	0	1 (<1) [0]
Dehydration	1 (<1) [0]	1 (<1) [0]	0
Dementia Alzheimer's type	0	0	1 (<1) [0]
Diarrhoea	0	1 (<1) [0]	0
Disorientation	0	0	1 (<1) [0]
Diverticulitis	1 (<1) [0]	0	0
Dizziness	0	0	1 (<1) [0]
Epilepsy	0	1 (<1) [0]	0
Epistaxis	0	0	1 (<1) [0]
Fall	1 (<1) [0]	0	0
Glioblastoma	1 (<1) [0]	0	0
Haematoma	0	0	1 (<1) [0]
Humerus fracture	1 (<1) [0]	0	0
Influenza	0	1 (<1) [0]	0
Lower limb fracture	0	0	1 (<1) [0]
Metrorrhagia	0	0	1 (<1) [0]
Oesophageal carcinoma	0	0	1 (<1) [0]
Penile neoplasm	0	1 (<1) [0]	0
Pneumonia	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Psychomotor hyperactivity	0	0	1 (<1) [0]
Pyrexia	0	1 (<1) [0]	0
Radius fracture	1 (<1) [0]	0	0
Sciatica	0	1 (<1) [0]	0
Sick sinus syndrome	1 (<1) [0]	0	0
Skin infection	0	1 (<1) [0]	0
Skull fracture	0	0	1 (<1) [0]
Splenic injury	0	1 (<1) [0]	0
Subdural haematoma	0	1 (<1) [0]	0
Syncope	1 (<1) [0]	0	1 (<1) [0]
Transient ischaemic attack	0	0	1 (<1) [0]

Urinary tract infection	1 (<1) [0]	0	0
Vertigo	0	0	1 (<1) [0]
Vomiting	0	1 (<1) [0]	0
Week 48 Analysis (Safety Population)			
Subjects with on-treatment SAEs (includes both fatal and non-fatal events)	17 (8) [1]	26 (12) [0]	27 (11) [0]
Abdominal abscess	0	0	1 (<1) [0]
Abdominal pain upper[1]	0	1 (<1) [0]	0
Adams-Stokes syndrome	0	0	1 (<1) [0]
Angina pectoris[1]	1 (<1) [0]	0	0
Aphasia	1 (<1) [1]	0	0
Arteriosclerosis coronary artery	0	0	1 (<1) [0]
Biliary colic[1]	0	1 (<1) [0]	0
Bradycardia[1]	0	1 (<1) [0]	1 (<1) [0]
Bronchopneumonia[1]	0	0	1 (<1) [0]
Cardiac failure[1]	0	1 (<1) [0]	0
Cardio-respiratory arrest	0	1 (<1) [0]	0
Cerebral haemorrhage[1]	0	2 (<1) [0]	0
Cerebrovascular accident[1]	1 (<1) [0]	3 (1) [0]	1 (<1) [0]
Chronic obstructive pulmonary disease	0	0	1 (<1) [0]
Circulatory collapse	0	0	1 (<1) [0]
Colonic polyp[1]	0	1 (<1) [0]	0
Confusional state	0	1 (<1) [0]	0
Death[1]	0	0	1 (<1) [0]
Decreased appetite	0	0	1 (<1) [0]
Deep vein thrombosis	0	0	1 (<1) [0]
Dehydration	1 (<1) [0]	1 (<1) [0]	0
Dementia Alzheimer's type	0	0	1 (<1) [0]
Diarrhoea	0	1 (<1) [0]	0
Disorientation	0	0	1 (<1) [0]
Diverticulitis	1 (<1) [0]	0	0
Diverticulum[1]	0	0	1 (<1) [0]
Dizziness	0	0	1 (<1) [0]
Dyspepsia[1]	0	1 (<1) [0]	0
Dyspnoea[1]	1 (<1) [0]	0	0
Epilepsy	0	1 (<1) [0]	0
Epistaxis	0	0	1 (<1) [0]
Erysipelas[1]	0	1 (<1) [0]	0
Fall[1]	2 (<1) [0]	0	0
Fatigue[1]	1 (<1) [0]	0	0
Femur fracture[1]	0	1 (<1) [0]	0
Glioblastoma	1 (<1) [0]	0	0
Gastric cancer[1]	0	1 (<1) [0]	0
Haematoma	0	0	1 (<1) [0]
Hand fracture[1]	1 (<1) [0]	0	0
Hip fracture[1]	0	0	1 (<1) [0]
Humerus fracture[1]	1 (<1) [0]	0	1 (<1) [0]
Influenza	0	1 (<1) [0]	0
Joint dislocation[1]	1 (<1) [0]	0	0
Loss of consciousness[1]	1 (<1) [0]	0	0
Lower limb fracture	0	0	1 (<1) [0]
Malignant melanoma[1]	1 (<1) [0]	0	0
Metrorrhagia	0	0	1 (<1) [0]
Neck pain[1]	1 (<1) [0]	0	0
Oesophageal carcinoma	0	0	1 (<1) [0]

Oesophageal obstruction[1]	0	0	1 (<1) [0]
Penile neoplasm	0	1 (<1) [0]	0
Pneumonia[1]	3 (1) [0]	1 (<1) [0]	3 (1) [0]
Post procedural haemorrhage[1]	0	1 (<1) [0]	0
Psychomotor hyperactivity	0	0	1 (<1) [0]
Pyrexia	0	1 (<1) [0]	0
Radius fracture	1 (<1) [0]	0	0
Respiratory tract infection[1]	0	1 (<1) [0]	0
Sciatica	0	1 (<1 [0]	0
Sick sinus syndrome	1 (<1) [0]	0	0
Skin infection	0	1 (<1 [0]	0
Skin laceration[1]	1 (<1) [0]	0	0
Skull fracture	0	0	1 (<1) [0]
Splenic injury	0	1 (<1) [0]	0
Squamous cell carcinoma[1]	0	0	1 (<1) [0]
Subdural haematoma	0	1 (<1) [0]	0
Syncope[1]	1 (<1) [0]	1 (<1) [0]	2 (<1) [0]
Transient ischaemic attack	0	0	1 (<1) [0]
Urethral stenosis[1]	0	1 (<1) [0]	0
Urinary tract infection[1]	1 (<1) [0]	1 (<1) [0]	0
Vertigo[1]	0	0	2 (<1) [0]
Vomiting	0	1 (<1) [0]	0
1. Contain new events since the Week 24 Analysis			
Note: Week 24 Analysis includes all data from the primary analysis, up to and including the Week 24 visit. Week 48 Analysis includes all data from the complete and final dataset up to Week 48, and including that of the Week 24 Analysis.			

	Placebo (N=225)	**SB742457 15 mg (N=221)**	**SB742457 35 mg (N=236)**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Week 24 Analysis (Safety Population)			
Subjects with on-treatment fatal SAEs	0	1 (<1) [0]	1 (<1) [0]
Skin Infection	0	1 (<1) [0]	0
Cardio-respiratory arrest	0	1 (<1) [0]	0
Pyrexia	0	1 (<1) [0]	0
Oesophageal carcinoma	0	0	1 (<1) [0]
Week 48 Analysis (Safety Population)			
Subjects with on-treatment fatal SAEs	1 (<1) [0]	5 (2) [0]	4 (2) [0]

Pneumonia	1 (<1) [0]	0	1 (<1) [0]
Bronchopneumonia	0	0	1 (<1) [0]
Skin Infection	0	1 (<1) [0]	0
Cerebrovascular accident	0	2 (<1) [0]	0
Cerebral haemorrhage	0	1 (<1) [0]	0
Cardiac failure	0	1 (<1) [0]	0
Cardio-respiratory arrest	0	1 (<1) [0]	0
Death	0	0	1 (<1) [0]
Pyrexia	0	1 (<1) [0]	0
Oesophageal carcinoma	0	0	1 (<1) [0]

Note: Week 24 Analysis includes all data from the primary analysis, up to and including the Week 24 visit. Week 48 Analysis includes all data from the complete and final dataset up to Week 48, and including that of the Week 24 Analysis.

Conclusions:

- The primary objective of the study was met for one of the co-primary endpoints (ADAS-Cog) for subjects randomised to the SB742457 35 mg dose group, as demonstrated by a clinically relevant and statistically significant difference from placebo in the change from baseline at Week 24.
- Statistical significance was not achieved at the SB742457 35 mg dose for the second co-primary endpoint (change from baseline in CDR-SB) at Week 24.
- There was no evidence of efficacy for subjects receiving SB742457 15 mg.
- Treatment effects were observed for ADAS-Cog at all timepoints.
- On-treatment AEs were reported in 408 (60%) subjects (placebo: 125 [56%], SB742457 15 mg: 137 [62%], SB-742447 35 mg 146 [62%]). Overall, the most commonly reported (>2%) on-treatment AEs across the 48-week study were nasopharyngitis (8%, 9%, 8%), urinary tract infection (7%, 5%, 6%), diarrhoea (4%, 5%, 5%), fall (6%, 2%, 2%), headache (3%, 4%, 3%), and hypertension (3%, 2%, 3%) for the treatment groups placebo, SB742457 15 mg, and SB742457 35 mg, respectively. The proportion of subjects reporting SAEs was 8%, 12%, and 11% for placebo, SB742457 15 mg, and SB742457 35 mg, respectively; there were none considered by the investigator as related to study medication for subjects receiving either dose of SB742457. Ten subjects (1%) experienced fatal on-treatment SAEs (placebo: 1 [<1%], SB742457 15 mg: 5 [2%], SB742457 35 mg: 4 [2%]). One subject receiving SB742457 35 mg experienced raised laboratory values that met pre-defined stopping criteria for liver events, which resolved approximately one month after removal of study medication.