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.: AZ3110865

Title Study AZ3110865, a study comparing SB742457 or donepezil versus placebo 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 randomized 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 randomized 198 subjects to placebo, SB742457, or donepezil in a 1:1:1 ratio). AZ3110865 further investigated the safety and efficacy of 15 mg and 35 mg SB742457 treatment in subjects with mild-to-moderate AD.

Phase: IIB

Study Period: 04 July 2008 – 09 March 2010

Study Design: A 24-week, randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group investigation of the efficacy and safety of SB742457 (15 mg, 35 mg) and donepezil (5-10 mg) compared to placebo in subjects with mild-to-moderate probable Alzheimer's disease. Study participation lasted approximately 32 weeks: 0-2 weeks for screening, a 4-week single-blind placebo run-in to evaluate baseline status, a 24-week double-blind treatment phase and a 2-week follow-up period after the end of treatment.

Centres: 68 centers from 11 countries (Bulgaria, Chile, Czech Republic, Estonia, Germany, Greece, Korea, Mexico, Poland, Russia, and South Africa)

Indication: Alzheimer's Disease

Treatment: All subjects were allocated single-blind placebo study treatment for the 4-week placebo run-in period. At Visit 3 (end of placebo run-in), eligible subjects were randomized to placebo, SB742457 15 mg, SB742457 35 mg, or donepezil 5-10 mg in a 1:1:1:1 ratio. Randomization was stratified by baseline Mini Mental State Exam (MMSE) score to ensure a balanced distribution of subjects across the severity range, i.e. baseline MMSE 10-15 (≤30% of study subjects), baseline MMSE 16-20 (≤60% of study subjects), and baseline MMSE 21-26 (≤30% of study subjects). 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. Consistent with approved labeling, dosing with donepezil required a one-step titration where subjects received 5 mg donepezil once daily (OD) for the first 4 weeks of double-blind treatment before up-titrating at Week 4 to 10 mg OD for the remaining 20 weeks of the treatment period. A one-step down-titration was permitted up until Week 8 should the 10 mg dose have been poorly tolerated. Subjects were instructed to take one tablet of SB742457 or matching placebo and one capsule of donepezil or matching placebo orally, each evening, just prior to going to bed.

Objectives: The primary objective was to assess the effects of OD dosing of SB742457 or donepezil versus placebo after 24 weeks of treatment on cognitive and global function.

Primary Outcome/Efficacy Variables:

- Change from baseline in Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) total score at Week 24
- Clinician's Interview-Based Impression of Change - plus (CIBIC+) score at Week 24

Secondary Outcome/Efficacy Variables:

- Change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score at Week 24
- Effect of baseline severity on the change from baseline in ADAS-Cog total score, the change from baseline in RBANS total score, and the CIBIC+ score at Week 24
- Change from baseline in ADAS-Cog total score at Week 12
- CIBIC+ score at Week 12
- Change from baseline in RBANS total score at Week 12
- Effect of baseline severity on the change from baseline in ADAS-Cog total score, the change from baseline in RBANS total score, and the CIBIC+ score at Week 12
- Change from baseline in Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL)

total score at Weeks 12 and 24

- Change from baseline in Cornell Scale for Depression in Dementia (CSDD) total score at Week 24
- Change from baseline in MMSE total score at Week 24
- Change from baseline in sections/domains of assessment scales at Weeks 12 and 24

Statistical Methods: Five hundred seventy-six subjects were expected to be randomized to ensure at least 488 evaluable subjects. A sample size of 122 subjects per treatment group (1:1:1:1 randomization ratio for placebo, SB74245715 mg, SB742457 35 mg, and donepezil [5-10 mg]) allowed a difference of 2.5 points between placebo and active treatment in the change from baseline in ADAS-Cog score to be detected with 90% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 6.0, as observed in previous trials with SB742457. The primary population for the efficacy analysis was the intent-to-treat (ITT) population, which consisted of all subjects randomized to treatment who took at least one dose of study medication and who had at least one post baseline efficacy or health outcomes assessment.

All endpoints were analyzed using a mixed model for repeated measures (MMRM), with the exception of MMSE and CSDD which were analyzed using analysis of covariance (ANCOVA). Primary inferences were based on the Week 24 treatment differences in the ITT Population.

Both co-primary endpoints needed to achieve a significance level of 0.05 at the same dose, to maintain an overall 5% significance level. To account for multiple dose groups a significant result at the 5% level was required for the SB742457 35 mg versus placebo comparison, otherwise the SB742457 15 mg versus placebo comparison could not be considered statistically significant. The nominal alpha level for all statistical tests was 0.05.

Results are presented as Least Squares Means (LSM), standard errors (SE), with treatment differences and 95% confidence intervals. p-values are presented for the co-primary endpoints.

The primary population for safety analyses consisted of all subjects who were randomized and took at least one dose of study medication. No formal statistical testing was performed on the safety data.

Study Population: The study population was male or females, aged ≥ 50 to ≤ 85 years with a clinical diagnosis of probable AD and no other likely causes of dementia; MMSE score of 12 – 24 inclusive at Screening and 10 – 26 inclusive at baseline and within ±3 points of the screening value; a documented history of AD symptoms for at least 6 months prior to entry into the study; the ability to comply with procedures for cognitive and other testing and living with (or has substantial periods of contact with) a regular caregiver; with no other treatment for AD and no other illnesses or medications that would preclude participation.

Number of Subjects:	**Placebo**	**SB742457 15mg**	**SB742457 35 mg**	**Donepezil 5-10mg**
Planned, N	144	144	144	144
Randomized, N	145	145	134	152
Safety Population, N	145	145	133	151
Completed, n (%)	118 (81)	127 (88)	118 (89)	130 (86)
Total Number Subjects Withdrawn, n (%)	27 (19)	18 (12)	15 (11)	21 (14)
Withdrawn due to Adverse Events n (%)	10 (7)	3 (2)	4 (3)	6 (4)
Withdrawn due to Lack of Efficacy n (%)	0	4 (3)	1 (<1)	0
Withdrawn for other reasons n (%)	17 (12)	11 (8)	10 (8)	15 (10)

Demographics	**Placebo**	**SB742457 15mg**	**SB742457 35 mg**	**Donepezil 5-10mg**
N (ITT)	135	142	130	147
Females (%): Males (%)	64:36	68:32	58:42	65:35
Mean Age, years (SD)	73.3 (6.80)	72.4 (8.12)	72.5 (7.38)	71.1 (7.49)
White, n (%)	128 (95)	126 (89)	118 (91)	130 (88)

Primary Efficacy Results:

Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score at Week 24

	Placebo (N=135)	SB742457 15mg (N=142)	SB742457 35 mg (N=130)	Donepezil 5-10mg (N=147)
Number of evaluable subjects (n)	116	124	115	123
Adjusted mean change from Baseline (SE)	-0.3 (0.56)	0.8 (0.58)	0.4 (0.62)	-0.5 (0.45)
Difference versus placebo		1.1	0.7	-0.2
95% CI		(-0.4, 2.7)	(-0.9, 2.3)	(-1.6, 1.2)
p-value for treatment difference		0.159	0.410	0.821

Repeated Measures Analysis of CIBIC+ Score at Week 24

	Placebo (N=135)	SB742457 15mg (N=142)	SB742457 35 mg (N=130)	Donepezil 5-10mg (N=147)
Number of evaluable subjects (n)	118	125	117	127
Adjusted Mean (SE)	4.0 (0.11)	4.2 (0.10)	3.9 (0.10)	3.7 (0.10)
Difference versus placebo		0.2	-0.1	-0.3
95% Confidence Interval (CI)		(-0.1, 0.5)	(-0.4, 0.2)	(-0.6, -0.0)
p-value for treatment difference		0.254	0.394	0.049

Secondary Efficacy Results:

		Placebo (N=135)	SB742457 15mg (N=142)	SB742457 35 mg (N=130)	Donepezil 5-10mg (N=147)
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score					
Week 12	Number of evaluable subjects (n)	124	133	126	137
	Adjusted mean change from baseline (SE)	-0.1 (0.45)	0.0 (0.46)	-0.2 (0.45)	-0.6 (0.40)
	Difference versus placebo		0.1	-0.1	-0.5
	95% CI		(-1.1, 1.4)	(-1.4, 1.1)	(-1.6, 0.7)
Repeated Measures Analysis of CIBIC+ Score at Week 12					
Week 12	Number of evaluable subjects (n)	126	133	126	139
	Adjusted mean (SE)	3.9 (0.08)	4.0 (0.08)	3.9 (0.09)	3.7 (0.08)
	Difference versus placebo		0.1	0.0	-0.2
	95% Confidence Interval (CI)		(-0.1, 0.3)	(-0.2, 0.2)	(-0.4, 0.0)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score					
Week 12	Number of evaluable subjects (n)	125	134	125	138
	Adjusted mean change from baseline (SE)	-6.7 (1.16)	-8.7 (1.24)	-5.9 (1.11)	-3.4 (1.06)
	Difference versus placebo		-1.9	0.9	3.4
	95% CI		(-5.2, 1.4)	(-2.2, 4.0)	(0.3, 6.4)
Week 24	Number of evaluable subjects (n)	116	125	115	127
	Adjusted mean change from baseline (SE)	-2.3 (1.44)	-4.0 (1.42)	-4.4 (1.49)	-0.3 (1.21)
	Difference versus placebo		-1.6	-2.1	2.0
	95% CI		(-5.6, 2.3)	(-6.1, 1.9)	(-1.7, 5.7)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Total Score					
Week 12	Number of evaluable subjects (n)	126	133	124	139
	Adjusted mean change from baseline (SE)	-0.4 (5.9)	-1.1 (0.64)	-0.1 (0.64)	0.2 (0.62)
	Difference versus placebo		-0.7	0.3	0.6
	95% CI		(-2.4, 1.0)	(-1.4, 2.0)	(-1.1, 2.2)
Week 24	Number of evaluable subjects (n)	118	123	114	128
	Adjusted mean change from baseline (SE)	-1.0 (0.71)	-1.4 (0.68)	-1.1 (0.81)	-1.2 (0.82)
	Difference versus placebo		-0.3	-0.1	-0.1
	95% CI		(-2.3, 1.6)	(-2.2, 2.0)	-2.3, 2.0
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Basic Score					
Week 12	Number of evaluable subjects (n)	126	133	124	139
	Adjusted mean change from baseline (SE)	-0.6 (0.17)	-0.5 (0.19)	-0.4 (0.24)	-0.2 (0.17)

	Difference versus placebo		0.0	0.2	0.3
	95% CI		(-0.5, 0.5)	(-0.4, 0.8)	(-0.1, 0.8)
Week 24	Number of evaluable subjects (n)	118	123	114	128
	Adjusted mean change from baseline (SE)	-0.7 (0.20)	-0.7 (0.19)	-0.6 (0.24)	-0.8 (0.23)
	Difference versus placebo		0.0	0.1	-0.1
	95% CI		(-0.6, 0.5)	(-0.5, 0.7)	(-0.7, 0.5)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Instrumental Score					
Week 12	Number of evaluable subjects (n)	126	133	124	139
	Adjusted mean change from baseline (SE)	0.2 (0.50)	-0.6 (0.55)	0.3 (0.52)	0.4 (0.55)
	Difference versus placebo		-0.8	0.0	0.2
	95% CI		(-2.2, 0.7)	(-1.3, 1.4)	(-1.3, 1.6)
Week 24	Number of evaluable subjects (n)	118	124	114	128
	Adjusted mean change from baseline (SE)	-0.3 (0.60)	-0.7 (0.61)	-0.5 (0.68)	-0.4 (0.70)
	Difference versus placebo		-0.4	-0.3	-0.1
	95% CI		(-2.1, 1.3)	(-2.0, 1.5)	(-1.9, 1.7)
Repeated Measures Analysis of Change from Baseline in ADCS-ADL Total Independence Score					
Week 12	Number of evaluable subjects (n)	126	133	124	139
	Adjusted mean change from baseline (SE)	-0.1 (0.23)	-0.1 (0.23)	0.2 (0.24)	0.2 (0.23)
	Difference versus placebo		0.0	0.3	0.3
	95% CI		(-0.7, 0.6)	(-0.4, 0.9)	(-0.3, 0.9)
Week 24	Number of evaluable subjects (n)	118	124	114	128
	Adjusted mean change from baseline (SE)	-0.3 (0.27)	-0.2 (0.26)	-0.1 (0.29)	-0.1 (0.30)
	Difference versus placebo		0.1	0.2	0.3
	95% CI		(-0.6, 0.9)	(-0.6, 1.0)	(-0.5, 1.1)
Repeated Measures Analysis of Change from Baseline in MMSE Total Score					
Week 24	Number of evaluable subjects (n)	118	124	117	128
	Adjusted mean change from baseline (SE)	-0.3 (0.29)	-0.3 (0.28)	-0.1 (0.29)	0.5 (0.27)
	Difference versus placebo		0.0	0.3	0.8
	95% CI		(-0.8, 0.8)	(-0.5, 1.1)	(0.0, 1.6)
Repeated Measures Analysis of Change from Baseline in CSDD Total Score					
Week 24	Number of evaluable subjects (n)	118	125	117	128
	Adjusted mean change from baseline (SE)	0.0 (0.26)	-0.1 (0.25)	0.3 (0.26)	0.3 (0.25)
	Difference versus placebo	NA	-0.2	0.2	0.3
	95% CI	NA	(-0.9, 0.5)	(-0.5, 0.9)	(-0.4, 1.0)
Subgroup Analyses by baseline severity (based on MMSE Scores) - Week 12 (ITT Population)					
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score					
Milder AD (MMSE 16-26)	N (ITT)	99	110	98	113
	Number of evaluable subjects (n)	93	104	94	106
	Adjusted mean change from baseline (SE)	-0.6 (0.48)	-0.4 (0.47)	-0.5 (0.52)	-0.5 (0.42)
	Difference versus placebo		0.2	0.1	0.1
	95% CI		(-1.1, 1.5)	(-1.3, 1.4)	(-1.2, 1.3)
More moderate (MMSE 10-20)	N (ITT)	92	94	89	95
	Number of evaluable subjects (n)	85	88	87	88
	Adjusted mean change from baseline (SE)	0.4 (0.51)	0.4 (0.61)	0.2 (0.60)	-0.9 (0.51)
	Difference versus placebo		0.1	-0.2	-1.2
	95% CI		(-1.5, 1.7)	(-1.7, 1.4)	(-2.7, 0.2)
Repeated Measures Analysis of CIBIC+ Score					
Milder AD (MMSE 16-26)	Number of evaluable subjects (n)	94	104	94	107
	Adjusted mean (SE)	3.8 (0.08)	3.8 (0.09)	3.7 (0.10)	3.6 (0.08)
	Difference versus placebo		0.1	-0.1	-0.1
	95% CI		(-0.2, 0.3)	(-0.4, 0.2)	(-0.4, 0.1)
More moderate (MMSE	Number of evaluable subjects (n)	86	88	87	90
	Adjusted mean (SE)	4.0 (0.10)	4.1 (0.10)	4.1 (0.11)	3.7 (0.11)
	Difference versus placebo		0.1	0.1	-0.3

10-20)	95% CI		(-0.2, 0.4)	(-0.2, 0.4)	(-0.5, 0.0)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score					
Milder AD (MMSE 16-26)	Number of evaluable subjects (n)	94	104	93	106
	Adjusted mean change from baseline (SE)	-7.5 (1.28)	-8.3 (1.51)	-4.4 (1.35)	-3.3 (1.31)
	Difference versus placebo		-0.8	3.1	4.2
	95% CI		(-4.7, 3.0)	(-0.4, 6.7)	(0.6, 7.7)
More moderate (MMSE 10-20)	Number of evaluable subjects (n)	85	89	87	89
	Adjusted mean change from baseline (SE)	-6.4 (1.36)	-10.0 (1.29)	-6.8 (1.26)	-1.7 (1.20)
	Difference versus placebo		-3.6	-0.4	4.7
	95% CI		(-7.3, 0.0)	(-4.0, 3.3)	(1.1, 8.2)

Subgroup Analyses by baseline severity (based on MMSE Scores) - Week 24 (ITT Population)					
Repeated Measures Analysis of Change from Baseline in ADAS-Cog Total Score					
Milder AD (MMSE 16-26)	N (ITT)	99	110	98	113
	Number of evaluable subjects (n)	88	99	86	94
	Adjusted mean change from baseline (SE)	-1.3 (0.55)	0.1 (0.66)	-0.4 (0.73)	-1.0 (0.53)
	Difference versus placebo		1.4	1.0	0.4
	95% CI		(-0.3, 3.1)	(-0.8, 2.8)	(-1.1, 1.9)
More moderate (MMSE 10-20)	N (ITT)	92	94	89	95
	Number of evaluable subjects (n)	77	80	78	81
	Adjusted mean change from baseline (SE)	0.0 (0.71)	1.6 (0.76)	1.3 (0.73)	-0.1 (0.58)
	Difference versus placebo		1.5	1.3	-0.1
	95% CI		(-0.5, 3.6)	(-0.7, 3.2)	(-1.9, 1.7)
Repeated Measures Analysis of CIBIC+ Score					
Milder AD (MMSE 16-26)	Number of evaluable subjects (n)	88	100	87	95
	Adjusted mean (SE)	3.8 (0.12)	4.0 (0.12)	3.7 (0.11)	3.5 (0.11)
	Difference versus placebo		0.2	-0.1	-0.2
	95% CI		(-0.1, 0.6)	(-0.4, 0.3)	(-0.5, 0.1)
More moderate (MMSE 10-20)	Number of evaluable subjects (n)	79	80	80	85
	Adjusted mean (SE)	4.2 (0.15)	4.4 (0.13)	4.1 (0.12)	3.9 (0.12)
	Difference versus placebo		0.2	-0.1	-0.3
	95% CI		(-0.2, 0.6)	(-0.5, 0.2)	(-0.6, 0.1)
Repeated Measures Analysis of Change from Baseline in RBANS Total Score					
Milder AD (MMSE 16-26)	Number of evaluable subjects (n)	87	100	85	95
	Adjusted mean change from baseline (SE)	-1.3 (1.61)	-2.4 (1.74)	-2.8 (1.82)	1.1 (1.52)
	Difference versus placebo		-1.1	-1.5	2.4
	95% CI		(-5.7, 3.6)	(-6.2, 3.3)	(-1.9, 6.8)
More moderate (MMSE 10-20)	Number of evaluable subjects (n)	78	80	79	85
	Adjusted mean change from baseline (SE)	-3.7 (1.79)	-5.8 (1.73)	-4.8 (1.68)	-1.0 (1.44)
	Difference versus placebo		-2.1	-1.1	2.7
	95% CI		(-7.0, 2.9)	(-5.9, 3.8)	(-1.9, 7.2)

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 randomized treatment and before or on the last day of randomized treatment plus 7 days, or an event with onset date missing and a stop date after the first day of double-blind randomized treatment.

	Placebo (N=145)	SB742457 15 mg (N=145)	SB742457 35 mg (N=133)	Donepezil 5-10 mg (N=151)
	n (%)	n (%)	n (%)	n (%)
Subjects with any on-treatment AE	45 (31)	42 (29)	39 (29)	65 (43)
Most frequent on-treatment AEs				
Headache	6 (4)	5 (3)	2 (2)	5 (3)
Nasopharyngitis	3 (2)	3 (2)	3 (2)	4 (3)
Dizziness	1 (<1)	3 (2)	2 (2)	5 (3)
Influenza	2 (1)	2 (1)	3 (2)	4 (3)
Diarrhoea	5 (3)	0	2 (2)	3 (2)
Nausea	2 (1)	2 (1)	1 (<1)	5 (3)
Urinary tract infection	0	4 (3)	3 (2)	3 (2)
Insomnia	0	2 (1)	1 (<1)	5 (3)
Back pain	3 (2)	1 (<1)	0	3 (2)
Bronchitis	2 (1)	3 (2)	1 (<1)	1 (<1)
Hyperglycaemia	1 (<1)	3 (2)	2 (2)	1 (<1)
Fall	3 (2)	0	2 (2)	1 (<1)
Hypertension	0	1 (<1)	1 (<1)	4 (3)
Agitation	0	1 (<1)	2 (2)	0
Nightmare	0	0	0	3 (2)
Hypercholesterolaemia	0	0	2 (2)	0

Serious Adverse Events - On-Treatment n (%) [n considered by the investigator to be related to study medication]				
	Placebo (N=145)	SB742457 15 mg (N=145)	SB742457 35 mg (N=133)	Donepezil 5-10 mg (N=151)
	n (%) [related]			
Subjects with on-treatment SAEs (includes both fatal and non-fatal events)	7 (5) [0]	7 (5) [1]	3 (2) [0]	10 (7) [0]
Anemia	0	0	0	1 (<1) [0]
Back pain	1 (<1) [0]	0	0	0
Bladder prolapsed	0	0	0	1 (<1) [0]
Breast cancer	1 (<1) [0]	0	0	0
Cardiac arrest	0	0	1 (<1)[0]	0
Cardiac failure acute	0	0	0	1 (<1)[0]
Cardiac pacemaker malfunction	0	1 (<1) [0]	0	0
Cerebrovascular accident	1 (<1)[0]	0	0	0
Cholelithiasis	1 (<1) [0]	0	0	0
Colitis	0	0	0	1 (<1) [0]
Concussion	0	0	0	1 (<1) [0]
Cough	1 (<1) [0]	0	0	0
Delirium	1 (<1) [0]	0	1 (<1) [0]	0
Dementia	0	1 (<1) [0]	0	0
Dementia Alzheimer's type	0	1 (<1) [1]	0	0
Diabetes mellitus inadequate control	0	0	1 (<1) [0]	0
Ear injury	1 (<1) [0]	0	0	0
Endocarditis	0	0	0	1 (<1) [0]
External ear inflammation	1 (<1) [0]	0	0	0
Femoral neck fracture	0	0	0	1 (<1) [0]
Gastritis	0	1 (<1) [0]	0	0
Gastritis erosive	0	0	0	1 (<1) [0]
Hip fracture	1 (<1) [0]	0	0	0
Joint dislocation	0	0	0	1 (<1) [0]
Metastasis to liver	1 (<1) [0]	0	0	0
Nephrolithiasis	0	1 (<1) [0]	0	0
Operative hemorrhage	0	0	1 (<1) [0]	0
Pancreatic carcinoma	1 (<1) [0]	0	0	0
Pelvic fracture	0	0	0	1 (<1) [0]
Pneumonia	0	1 (<1) [0]	0	0
Post procedural complication	0	0	1 (<1) [0]	0
Rectal prolapse	0	1 (<1) [0]	0	0
Systemic lupus erythematosus	0	0	0	1 (<1) [0]
Upper limb fracture	0	0	0	1 (<1) [0]
	Placebo (N=145)	SB742457 15 mg (N=145)	SB742457 35 mg (N=133)	Donepezil 5-10 mg (N=151)
	n (%) [related]			
Subjects with on-treatment fatal SAEs	1 (<1) [0]	0	1 (<1) [0]	1 (<1) [0]
Cardiac arrest	0	0	1 (<1) [0]	0
Cardiac failure acute	0	0	0	1 (<1) [0]
Cerebrovascular accident	1 (<1) [0]	0	0	0

Conclusions:

- There was no statistical difference between SB742457 (15 mg or 35 mg) and placebo for the co-primary endpoints (change from baseline in ADAS-Cog score and CIBIC+ score) for the ITT population at Week 24.

- There was a statistically significant difference between the active comparator, donepezil (5-10 mg), and placebo on CIBIC+ at Week 24; however, there was no statistically significant difference on ADAS-Cog at Week 24. Therefore, the assay sensitivity of the study was limited.

- On-treatment AEs were reported in 191 (33%) subjects (placebo: 45 [31%], SB742457 15 mg: 42 [29%], SB742457 35 mg: 39 [29%], and donezepil 5-10 mg: 65 [43%]). Overall, the most commonly reported (>2%) on-treatment AE across the 24-week study was headache (4%, 3%, 2%, 3% for the placebo, SB742457 15 mg, SB742457 35 mg, and donepezil 5-10 mg groups, respectively). The proportion of subjects reporting serious adverse events was 5%, 5%, 2%, and 7% for the placebo, SB742457 15 mg, SB742457 35 mg, and donepezil 5-10 mg groups, respectively; with no SAE reported by > 1 subject in any treatment group. One drug-related on-treatment SAE, Alzheimer's Type dementia in the SB742457 15 mg group was reported. Three subjects (<1%) experienced fatal on-treatment SAEs (placebo: 1 [<1%], SB742457 35 mg: 1 [<1%], and donepezil 5-10 mg: 1 [<1%]; none were considered drug-related by the investigator.