Synopsis

Identifier: GM2007/00433/00 **Study Number:** AZ3106242

Title: A double-blind, randomised, placebo-controlled, parallel group study to investigate the effects of SB-742457, donepezil and placebo on cognition in subjects with mild to moderate AD

Investigator(s): Multicentre study.

Study centre(s): Twenty-four centres in 8 countries.

Publication(s): None at the time of this report.

Study Period: 10 May 2006 to 12 June 2007.

Phase of Development: II

Objectives: The primary objective was to investigate the effects in subjects with mild-to-moderate probable AD on cognitive and global functioning of once daily dosing of SB-742457 and donepezil versus placebo after 24 weeks of treatment.

Secondary objectives were to investigate the effects of SB-742457 and donepezil versus placebo on cognitive function, global functioning, activities of daily living, behaviour, caregiver quality of life and safety and tolerability; to evaluate the subject and caregiver perception of benefit of treatment and the pharmacokinetics (PK) of SB-742457 and donepezil; to explore the PK/pharmacodynamic (PD) relationship of SB-742457 and donepezil in subjects with mild to moderate AD; and to seek post-hoc correlation of any effects of SB-742457 and donepezil with apolipoprotein E (APOE) status, 5-hydroxytryptamine (serotonin) receptor 6 (5-HT6) polymorphisms and 5-hydroxytryptamine (serotonin) receptor 2A (5-HT2a) polymorphisms.

Methodology: A multi-centre, double-blind, randomised, placebo-controlled trial in subjects with mild to moderate probable AD (MMSE 12-24) comparing SB-742457 and donepezil with placebo. Study participation lasted for approximately 32 weeks: 0 to 2 weeks for Screening, a 4-week placebo run-in to evaluate cognitive Baseline, a 24-week blinded treatment phase and a 2-week follow-up period after the end of treatment.

Number of subjects:

Number of Subjects	Placebo (N=62) n (%)	SB-742457 (N=68) n (%)	Donepezil (N=67) n (%)	Total (N=197) n (%)
Completed	46 (74)	58 (85)	57 (85)	161 (82)
Prematurely Withdrawn	16 (26)	10 (15)	10 (15)	36 (18)
Adverse Event	2 (3)	1 (1)	4 (6)	7 (4)
Withdrawal of consent	8 (13)	5 (7)	3 (4)	16 (8)
Other	6 (10)	4 (6)	3 (4)	13 (7)

Diagnosis and main criteria for inclusion: Male or female subjects aged ≥50 to ≤85 years with a clinical diagnosis of mild to moderate probable AD (Mini Mental State Examination [MMSE] score of 12 to 24). Subjects must have had the ability to comply with procedures for cognitive and other testing and have lived with (or had substantial periods of contact with) a permanent caregiver. Subjects with probable or definite vascular dementia, with a history and/or evidence of any other central nervous system disorder that could be interpreted as a cause of dementia or with a significant psychiatric illness or depression that could interfere with participation in the study were excluded.

Treatment and administration: All subjects received treatment at dose level 1 (15 mg SB-742457 [batch number: 051114370], placebo to 15 mg SB-742457 [batch number: 051103407], 5 mg donepezil [batch numbers: 061116407, 051114316] or placebo to 5 mg donepezil [batch number: 051103407]) for the first 4 weeks of the study and were then titrated up to the higher dose level 2 (35 mg SB-742457 [batch number: 051114371], placebo to 35 mg SB-742457 [batch number: 0511034047] or 10 mg donepezil [batch numbers: 061116407, 051114316]). Subjects were permitted to down-titrate up to Week 8, with the dose remaining stable thereafter. On titration, the dose of 10 mg donepezil was administered by way of 2 capsules of the 5 mg dose. Therefore, all subjects took 2 capsules at all times during the study. Additional capsules containing placebo were dispensed where necessary to maintain the study blind. All medication was taken in the evening just prior to retiring.

Criteria for evaluation: The following efficacy assessments were conducted:

- Primary Efficacy Endpoints: ADAS-cog, Clinician's Interview-Based Impression of Change - plus (CIBIC+)
- Secondary Efficacy Endpoints: Neuro Psychiatric Inventory (NPI), MMSE, Disability Assessment for Dementia (DAD), Computerised Psychometric Test Battery, Digit Vigilance Test (DVT), Color Trails Test (CTT), Subject/Caregiver Questionnaire, Alzheimer Carer's Quality of Life Instrument (ACQLI)

Safety assessments included the incidence of adverse events (AEs); changes from Baseline in routine laboratory tests, vital signs and electrocardiograms (ECGs); physical examinations; and frequency of parameters of clinical concern.

PK assessments included plasma concentrations of SB-742457 and donepezil, area under the curve during the dosing interval at steady state ($AUC_{\tau ss}$) and maximum plasma concentration at steady state ($C_{max\text{-}ss}$) for SB-742457 and average plasma concentration at steady state (C_{avgss}) for donepezil.

Pharmacogenetic (PGx) samples were assessed for the genetic markers in three genes: apolipoprotein E (APOE), 5- hydroxytryptamine (serotonin) receptor 6 (HTR6) and 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A).

Statistical methods: Approximately 200 subjects were to be randomised to ensure 150 evaluable subjects. The randomisation ratio was 1:1:1 for placebo, SB-742457 and donepezil. Based on a standard deviation (SD) of 6 units for Alzheimer's Disease Assessment Scale – cognitive (ADAS-cog) and 1.12 units for Clinician's Interview-

Based Impression of Change – plus (CIBIC+), the proposed sample size (n=50 per group) would be sufficient to estimate a treatment difference in ADAS-cog between active treatment groups and placebo to a 90% confidence interval (CI) of ±1.972 units, and a difference in CIBIC+ to a CI of ±0.371 units.

Five study populations were identified:

The intent-to-treat (ITT) population consisted of all subjects randomised to treatment, who received at least 1 dose of study medication and who had at least 1 post Baseline assessment of the endpoint;

The per-protocol (PP) population consisted of those members of the ITT population who had no major protocol violations.

The safety analysis population consisted of all subjects who were randomised and took at least 1 dose of study medication;

The PK concentration population included subjects for whom a PK sample was obtained and analysed.

The White PGx ITT population comprised all subjects in the ITT population who were of White/Caucasian ethnic origin and who had evaluable PGx data.

Two datasets were of interest, the last observation carried forward (LOCF) dataset and the observed cases (OC) dataset. In the LOCF dataset, missing values were imputed from the OC dataset, allowing estimates of treatment effect to be made with the complete study population. The OC dataset makes no assumptions about the missing values, excluding them from the analyses.

The primary comparisons of interest were to estimate the Week 24 change from Baseline LOCF ADAS-cog and Week 24 CIBIC+ score using analysis of covariance (ANCOVA), including covariate for Baseline, and fixed effect term for treatment. Estimates of treatment differences from placebo for SB-742457 and donepezil were generated from the model with 90% CI. The assumptions of normality and homogeneity of variance were assessed using diagnostic plots.

For each primary endpoint a forward selection approach was used to select which of the following covariates were to be included in the adjusted analysis of change model: Baseline efficacy measure of the endpoint being analysed; MMSE at Baseline; age; gender; country; body mass index; education (number of years full time); duration of disease (symptoms and diagnosis).

If the assumptions of normality and homogeneity of variance were not met a non-parametric ANCOVA was used to compare the treatment groups, allowing adjustment for covariates.

For PK analyses, concentrations of SB-742457 and donepezil were summarised and plotted. For SB-742457, the exposures were estimated for each subject via nonlinear

mixed effect analysis and subsequently summarised. For donepezil, the exposure was calculated for each subject directly from the observations and subsequently summarised.

Pharmacogenetic analyses performed included: assessing genotype distribution deviations using Hardy Weinberg Equilibrium analysis; linkage disequilibrium was assessed using Pearson correlation coefficient to determine whether significant linkage disequlibrium existed between genetic markers within the same genes. Summary statistics by genotype, APOE genotype, APOE4 copies and APOE4 carriage were produced for the primary efficacy variables. ANCOVA was conducted for change in ADAS-cog at Week 24 (LOCF) and CIBIC+ score at Week 24 (LOCF) to evaluate the main effect of genotype, APOE genotype, APOE4 copies and APOE4 carriage and to evaluate the possible effect of genotype-by-treatment interactions on the efficacy endpoints. APOE haplotype analyses were conducted to evaluate the haplotype and haplotype-by-treatment effect on the primary efficacy variables.

Study population: No major differences were seen in demographic characteristics between the groups. Approximately two-thirds of subjects were female and the majority were Caucasian. The mean age was approximately 71 years. On average, subjects had symptoms of AD for approximately 3.5 years and were diagnosed just under 1 year prior to the study, with just over half reporting a worsening in their condition in the 6 months prior to study entry. The majority of subjects had no family history of AD.

Primary efficacy endpoints: A summary of the ANOVA analysis for the primary efficacy endpoints at Week 24 (LOCF) are given in the table below for both the ITT and PP populations.

Treatment	N	n[a]	Mean / Adjusted mean[b]	Adjusted mean change from Baseline	SE of adjusted mean	Difference versus placebo[c]	90% CI for treatment difference
ITT Population							
ADAS-cog							
Placebo	61	56	27.7	-0.3	0.80		
SB-742457	68	66	25.3	-0.7	0.74	-0.4	[-2.2, 1.4]
Donepezil	67	65	25.6	-1.5	0.73	-1.2	[-3.0, 0.6]
CIBIC+							
Placebo	61	55	3.90	N/A	0.148		
SB-742457	68	66	3.73	N/A	0.136	-0.17	[-0.50, 0.16]
Donepezil	67	65	3.62	N/A	0.135	-0.28	[-0.61, 0.05]
PP Population[d]							
ADAS-cog							
Placebo	51	46	26.3	-0.9	0.86		
SB-742457	41	39	25.1	-1.9	0.92	-1.1	[-3.1, 1.0]
Donepezil	48	46	26.6	-2.0	0.85	-1.1	[-3.1, 0.9]
CIBIC+							
Placebo	51	45	3.85	N/A	0.167		
SB-742457	41	39	3.58	N/A	0.179	-0.27	[-0.67, 0.13]
Donepezil	48	46	3.48	N/A	0.164	-0.37	[-0.76, 0.02]

Adjusted for Baseline ADAS-cog (ADAS-cog results only), Baseline MMSE, centre group and BMI.

a. Number of subjects contributing to the analysis.
b. Mean Baseline scores for ADAS-cog and adjusted mean at Week 24 for CIBIC+.
c. Difference in adjusted least square means are active treatment – placebo.
d. The PP population presented was redefined after the original statistical analysis was released, since PK analysis revealed additional 9 subjects with poor compliance.

The number of subjects with a 7-point or better or 4-point or better improvement in ADAS-cog scores from Baseline at Week 24 (LOCF) was 11% and 20%, respectively, in the placebo group, 14% and 29%, respectively, in the SB-742457 group and 11% and 26%, respectively, in the donepezil group.

A significant interaction (p=0.019) was seen between change in ADAS-cog at Week 24 (LOCF) and Baseline MMSE severity (>18 vs ≤18). The treatment difference (90% CI) from placebo was -2.9 (-5.5, -0.2) in the SB-742457 group and -4.5 (-7.1, -1.9) in the donepezil group for subjects with an MMSE ≤18 at Baseline and 1.6 (-0.8, 4.0) in the SB-742457 group and 1.4 (-1.0, 3.8) in the donepezil group for subjects with an MMSE >18 at Baseline.

Secondary efficacy endpoints: Secondary endpoints investigating activities of daily living (DAD) and behaviour (NPI) showed only small differences from placebo for both treatments, which might partly be attributed to the low level of baseline impairment in these domains. Similarly, the assessment of the caregiver quality of life (ACQLI) showed very little change. MMSE was repeated at Week 24 and showed consistency with the ADAS-cog results. Other cognitive assessments were inconsistent and difficult to interpret. In particular, those measures that involved assessment of time were highly variable.

Safety Results The theoretical duration of exposure was 168 days. The majority of subjects had a total duration of treatment of either 113 to 168 days or >168 days.

All treatments were generally well tolerated. The majority of AEs were mild or moderate intensity. No severe AE was reported by more than 1 subject in any treatment group. On-treatment AEs reported in ≥2% of subjects in any treatment group are presented in the table below.

Preferred Term	Placebo (N=62)	SB-742457 (N=68)	Donepezil (N=67)
Any adverse event, n (%)	18 (29)	25 (37)	26 (39)
Nasopharyngitis	2 (3)	7 (10)	2 (3)
Urinary tract infection	2 (3)	3 (4)	4 (6)
Abdominal pain upper	1 (2)	3 (4)	2 (3)
Headache	2 (3)	2 (3)	1 (1)
Nausea	1 (2)	1 (1)	2 (3)
Dry mouth	2 (3)	1 (1)	0
Abdominal pain	2 (3)	0	0
Blood creatine phosphokinase increased	2 (3)	0	0
Dermatitis	2 (3)	0	0
Gamma-glutamyl transferase increased	0	2 (3)	0

There were 2 deaths in the study, both in subjects who received donepezil. One subject died from pneumonia and the other from bronchopneumonia and cardiopulmonary failure. Neither event was considered to be related to treatment. A total of 8 subjects experienced non-fatal serious adverse events (SAEs) during the study. No non-fatal SAE was reported by more than 1 subject across the treatment groups and no subject reported

more than 1 SAE. Seven subjects had AEs leading to permanent discontinuation from the study. Four subjects were in the donepezil group (cardiopulmonary failure and bronchopneumonia; aggression and tension; normal pressure hydrocephalus; nausea), 2 in the placebo group (upper abdominal pain; hip fracture) and 1 subject in the SB-742457 group (cholecystitis).

Liver function test values for ALT, aspartate transaminase, alkaline phosphatase and total bilirubin were all below 3xULN. No clinically significant trends were noted in the haematology, clinical chemistry, vital signs, weight, ECG examinations or urinalysis results.

Pharmacokinetic Results Summary statistics for SB-742457 Cmin-ss and AUCτss and donepezil Cmin-ss are presented in the table below.

Final Dose Level	n	Mean	Standard deviation	Median	Range	Geometric mean	%CVb
SB-742457 Cmin-ss (ng/mL)							
15 mg	2	57.04			(39.70 to 74.40)		
35 mg	58	143.38	61.46	132.49	(57.20 to 445.70)	133.02	40.0
SB-742457 AUCτss (ng•hr/mL)							
15 mg	2	1659			(1243 to 2215)		
35 mg	58	4573	2058	4195	(1821 to 13,434)	4214	42
Donepezil Cavg-ss[a] (ng/mL)							
5 mg	1	10.08	-	-	-	-	-
10 mg	59	37.13	16.77	35.14	(0.00 to 84.90)	34.50	60.9

a. Cavg-ss: Average Concentration over visits 7,8 and 9 (wks 12,16, and 24)
%CVb – between-subject Coefficient of Variation (%)

Pharmacogenetic Results There were no significant genetic main effects or genotype-by-treatment interactions for APOE4 carriage, APOE4 copies, APOE genotype, or the four APOE single nucleotide polymorphisms (SNPs) in either the ADAS-cog or CIBIC+ analyses at Week 24 (LOCF). A significant genotype-by-treatment interaction (p=0.022) was observed for HTR2A SNP RS7997012 in the CIBIC+ analysis at Week 24 LOCF. Within SB-742457 treatment, response differed significantly by genotype with AA subjects showing most clinical improvement and GG subjects showing clinical decline.

Conclusions:

- There was no decline in ADAS-cog in the placebo group over 24 weeks and although SB-742457 and donepezil showed a trend for improvement compared with placebo, this was less than that which has previously been observed in studies with donepezil
- A significant interaction (p=0.014) was seen between change in ADAS-cog at Week 24 (LOCF) and Baseline MMSE.
    - In subjects with baseline MMSE ≤18, placebo subjects showed decline from Baseline on ADAS-cog and SB-742457 and donepezil showed improvement compared with placebo that were greater than observed in the overall population

and consistent with those seen historically for donepezil in mild to moderate subjects.

- No differences from placebo were observed in subjects with Baseline MMSE >18, where placebo showed an improvement from Baseline.

- Improvements in CIBIC+ were similar for SB-742457 and donepezil and consistent with those observed previously for both treatments. There was no interaction between Baseline MMSE and Week 24 CIBIC+ score
- Secondary endpoints did not reveal any consistent differences from placebo for either treatment. Cognitive endpoints showed high variability, whilst baseline incidence of deficits in activities of daily living and behaviour was low.
- A total of 29% of subjects were excluded from the PP population. Although, there were some changes to the mean differences from placebo in the PP population compared to the ITT population, inspection of the 90% confidence intervals did not change overall interpretation between the two populations.
- Both donepezil and SB-742457 were well tolerated with an overall incidence of AEs of under 40% in all 3 treatment groups.
- No clinically significant trends were noted in the haematology, clinical chemistry, vital signs, weight, ECG examinations or urinalysis results.
- The estimated SB-752457 exposures were on average about 30% higher than expected from previous studies, but within the 95% prediction interval.
- The donepezil exposures were similar to those expected from the literature.
- No APOE4 genotype-by-treatment interactions or genetic main effects were observed in either the ADAS-cog or CIBIC+ analyses.
- Two HTR6 markers (RS10917509 and RS9659997) demonstrated significant genotype-by-treatment interactions (p=0.063 and p=0.069, respectively) in analyses of change from Baseline in ADAS-cog at Week 24 LOCF. However, the patterns of response observed within this study are complex and may not suggest clinical relevance.
- HTR2A marker RS7997012 showed a significant genotype-by-treatment interaction at week 24 LOCF (p=0.022) in analysis of CIBIC+. Within the SB-742457 group, carriage of the A allele was associated with clinical improvement.

Date of Report: Dec 2007.