Synopsis

Identifier: GM2007/00047/00 **Study Number:** AZ3100603

Title: A phase IIa/b double-blind, randomised, placebo-controlled, linear trend design, dose-ranging study to investigate the effects of 24 weeks of monotherapy with SB-742457 on cognition in subjects with mild-to-moderate Alzheimer's disease.

Investigator(s): This was a multicentre study conducted by 50 investigators.

Study center(s): A total of 50 centres screened and enrolled at least one subject in the following countries: Austria, Bulgaria, Chile, Croatia, Czech Republic, Greece, Korea, New Zealand, Poland, Russian Federation, Slovakia, South Africa and Spain.

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

Study Period: 21 September 2005 to 11 December 2006

Phase of Development: Phase IIa/b

Objectives: The primary objectives were: (1) To investigate the effects on cognitive function of once daily dosing for 24 weeks with SB-742457 or placebo; (2) To investigate the effects on global functioning of once daily dosing for 24 weeks with SB-742457 or placebo. The secondary objectives were: (1) To investigate the effects on cognitive function of SB-742457 or placebo after 8 and 12 weeks of treatment; (2) To investigate the effects on global functioning of SB-742457 or placebo after 8 and 12 weeks of treatment; (3) To investigate the effects on behaviour of SB-742457 or placebo after 8, 12 and 24 weeks of treatment; (4) To investigate the effects on activities of daily living of SB-742457 or placebo after 8, 12 and 24 weeks of treatment; (5) To seek post-hoc correlation of any effects of SB-742457 with apolipoprotein E (APOE) genotype, polymorphisms of the HTR6 gene and possibly other pharmacogenetic markers; (6) To investigate the safety and tolerability of SB-742457 or placebo in subjects with mild to moderate AD; (7) To evaluate the pharmacokinetics (PK) of SB-742457 in subjects with mild to moderate AD; (8) To evaluate the relationship, if any, between SB-742457 exposure and cognitive function and global functioning; (9) To evaluate subject and caregiver perception of benefit of treatment with SB-742457 for 24 weeks; (10) To investigate the effects on carers' quality of life of SB-742457 or placebo after 24 weeks of treatment (optional for caregiver).

Methodology: This was a phase IIa/b, multi-centre, double-blind, randomised, placebo-controlled, linear trend design dose-ranging trial in subjects with mild to moderate AD (MMSE 12-24) investigating 3 doses of SB-742457 and placebo. Approximately 380 subjects were randomised to ensure 318 evaluable subjects. Randomisation ratio was 2:1:1:2 for once daily dosing with placebo, 5mg, 15mg or 35mg SB-742457, respectively.

The study used a model based design to detect a linear trend across increasing dose levels (assessing the relationship between the primary endpoints and dose). In addition, the

study was powered to perform a pairwise comparison of the 35mg dose with placebo. The relationship between SB-742457 exposure and the primary endpoints were also evaluated. The study was designed in this manner to allow investigation of the dose range as well as establishing whether 35mg SB-742457 improves cognition and global functioning compared with placebo. Study participation involved a 2-week screening phase, a 4 week single-blind placebo run-in phase to establish cognitive baseline, followed by a 24-week double-blind treatment phase. Subjects attended a final follow-up visit 2 weeks after the end of treatment.

Number of subjects:

Number of Subjects:	Placebo n (%)	SB-742457 5 mg n (%)	SB-742457 15 mg n (%)	SB-742457 35 mg n (%)	Total n (%)
Randomised	124 (100)	62 (100)	62 (100)	123 (100)	371 (100)
Completed	102 (82)	54 (87)	51 (82)	97 (79)	304 (82)
Total Number Subjects Withdrawn	22 (18)	8 (13)	11 (18)	26 (21)	67 (18)
Withdrawn due to Adverse Events	3 (2)	3 (5)	4 (6)	7 (6)	17 (5)
Withdrawn due to Lack of Efficacy	0	0	0	0	0
Withdrawn for all other reasons n	19 (16)	5 (8)	7 (12)	19 (15)	50 (13)

Diagnosis and main criteria for inclusion: Male or female with a clinical diagnosis of probable Alzheimer's disease in accordance with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria; Subjects had mild to moderate Alzheimer's disease with MMSE score 12-24 inclusive at the screening visit and 12-26 inclusive at the end of the placebo run-in period; Age ≥ 50 to ≤ 85 years; Female subjects were post-menopausal (i.e. >24 weeks without menstrual period) or surgically sterile; Subjects had the ability to comply with procedures for cognitive and other testing; Subjects lived with (or had substantial periods of contact with) a permanent caregiver who was willing to attend all visits, oversee the subject's compliance with protocol-specified procedures and study medication, and report on subject's status.

Treatment administration: Three doses of SB-742457 (5mg, 15mg, or 35mg capsules once daily) and placebo were used in this study. Study medication was taken once daily in the morning, without regard to food. At visits 4, 5 and 8, subjects were instructed not to take their medication beforehand to allow trough PK sampling. At all other visits, subjects took their medication in the morning as usual.

Investigational Product	Batch numbers
Placebo	041032984
SB-742457 5mg	051071350
SB-742457 15mg	051072030
SB-742457 35mg	051072031

Criteria for evaluation: Primary Endpoints: (1) Change from baseline to Week 24 in Alzheimer's Disease Assessment Scale cognitive (ADAS-cog) score; (2) Week 24 Clinician's Interview-Based Impression of Change – plus (CIBIC+) score. Secondary Endpoints: (1) Change from baseline to Weeks 8 and 12 in ADAS-cog score; (2) Weeks 8 and 12 CIBIC+ score; (3) Change from baseline to Weeks 8, 12 and 24 in Neuropsychiatric Inventory (NPI) total score; (4) Change from baseline to Weeks 8, 12 and 24 in Disability Assessment for Dementia scale (DAD) total score; (5) Change from baseline to Week 24 in Mini Mental State Examination (MMSE) total score; (6) Change from baseline to Weeks 8, 12 and 24 in Paired Associate Learning (PAL), Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Pattern Recognition Memory (PRM) (Computerised Psychometric Test Battery); (7) Change from baseline to Weeks 8, 12 and 24 in domains of assessment scales; (8) Relationship between SB-742457 exposure and change from baseline in ADAS-cog and CIBIC+; (9) Subject and caregiver responses to questionnaire on benefit of treatment at Week 24; (10) Change from Week -4 to Week 24 in Alzheimer Carer's Quality of Life Instrument (ACQLI; optional for caregiver).

Safety: (1) Adverse events; (2) Change from baseline in vital signs; (3) Change from baseline in weight; (4) Change from baseline in routine laboratory tests (clinical chemistry, haematology, urinalysis); (5) Frequency of parameters of clinical concern.

Pharmacokinetics: Pharmacokinetic parameters.

Pharmacogenetics: Genes evaluated: ApoE, HTR6.

Statistical methods: Assuming a post-randomisation drop-out rate of approximately 15%, a total of 380 subjects were randomised into the study to ensure 318 evaluable subjects. The proposed sample size was statistically powered (90% power, alpha=0.05) to detect a linear trend in dose for the primary endpoints: change from baseline to Week 24 in ADAS-cog and Week 24 CIBIC+ score. The study design also provided power for a pairwise comparison of the highest dose (35mg) vs. placebo. This was based on a clinically relevant change of 3 units ADAS-cog (assumed SD=6) or 0.5 units CIBIC+ (assumed SD=1.12) at the 35mg dose. Sample size was driven by the most variable endpoint, CIBIC+, and assumed no adjustment for multiple comparisons.

The intent-to-treat (ITT) population consisted of all subjects randomised to treatment, who had taken at least one dose of study medication and who had at least one post baseline assessment of the primary endpoints. 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 one dose of study medication. The PK concentration population included subjects who took at least one dose and for whom a pharmacokinetic sample was obtained and analysed. The White PGx Intent-to-Treat population consisted of all subjects in the ITT population who were of White/Caucasian ethnic origin and who had evaluable PGx data, i.e. consented to genotyping, provided an identified blood sample for genotyping and were successfully genotyped for at least one of the genetic markers under study.

Efficacy Summary: The study was statistically powered to detect a linear trend in dose for the primary endpoints: change from baseline in ADAS-cog at Week 24 and Week 24

CIBIC+ score. The study design also provided power for a pairwise comparison of the highest dose (35mg) versus placebo.

The analysis of the primary endpoints for the ITT population at Week 24 LOCF showed evidence of a linear trend in response (p=0.016 and p=0.059 for CIBIC+ and ADAS-cog, respectively). The difference from placebo with SB-742457 35mg at Week 24 LOCF was statistically significant for CIBIC+ (p=0.047), but not for ADAS-cog (p=0.135).

The observed case CIBIC+ and ADAS-cog scores were analysed at Weeks 8, 12 and 24. The mean CIBIC+ score improved for all groups at Week 8. The placebo group showed a further small improvement in adjusted mean CIBIC+ score at Week 12 (3.69; 4 = no change, <4 = improvement), before declining slightly to Week 24 (3.87).

The mean CIBIC+ score did not demonstrate a decline in global function, with a peak mean improvement (score of 3.7; 4 = no change) noted at Week 12 and a score of 3.9 observed at Weeks 8 and 24. The profile was similar for the 5mg SB-742457 group. Mean CIBIC+ score was fairly consistent over the course of the study (3.5-3.6) in the 15mg and 35mg groups, with the exception of a peak of 3.3 for the 15mg group at Week 12. The treatment difference from placebo for 15mg and 35mg at Week 24 was 0.33 and 0.31 respectively (LOCF; ITT population).

The adjusted mean ADAS-cog score improved for most groups at Week 8, except the SB-742457 5mg group where the mean change was close to zero throughout the study. Both the placebo group and the SB-742457 15mg group demonstrated a mean improvement for the first 12 weeks (-1.22 and -1.48, respectively), before declining to Week 24 (-0.52 and -0.56, respectively). In contrast the SB-742457 35mg group showed the greatest mean improvement at Week 8 (-2.43), and this only declined slightly by Week 24 (-2.16).

Other endpoints were included in this study as supporting secondary measures. Treatment differences between SB-742457 groups and placebo were small for the NPI, DAD and ACQLI tests and none reached statistical significance. In general there was a low level of impairment in these domains at baseline, particularly for behaviour (NPI).

Cognition was also assessed using the MMSE and a computerised psychometric test battery. The results for the MMSE tests at Week 24 were consistent with the ADAS-cog results. Treatment differences between SB-742457 groups and placebo were small for SRT and CRT median reaction times, CRT accuracy, PAL global accuracy, the composite score for PAL and PRM accuracy. The data were highly variable and none of the treatment differences reached statistical significance.

The PAL global accuracy results were re-analysed excluding subjects who scored <0.8 on PRM. The PRM task is a control task for the PAL test. If patients have perceptual problems then they may not be able to differentiate between similar patterns. Failure to differentiate between patterns, as identified by a score of < 0.8 on PRM, would lead to poor performance on PAL, and this poor performance may not reflect a deficit in the cognitive paradigm that the PAL test seeks to assess. This planned re-analysis demonstrated a decline in the change from baseline in PAL global accuracy in the placebo group at all time points. In contrast, the SB-742457 treated groups showed little

change from baseline over the course of the study. The treatment difference for SB-742457 35mg group compared to placebo reached statistical significance at Week 12 (p= 0.025), but not at Week 24.

At the end of the study, subjects and caregivers were asked to record their opinion of how the subject had been during the study compared to before the study on a 7-point scale, similar to the CIBIC+ assessment. In general, there was a trend for subjects to record more favourable outcomes than caregivers. The trend of data followed a similar pattern to the clinician rating in CIBIC+, particularly for the caregiver response, but no statistically significant effects were observed.

Safety Summary:

SB-742457 was generally well tolerated in this study. The overall frequency of AEs was low and similar between placebo and each SB-742457 treatment group. The overall incidence of AEs was approximately 30%. Individual AEs were reported with low frequency, which given the age and diagnosis of the population, is perhaps surprising. The only AEs reported in ≥5% of subjects in any treatment group were headache (5% in the 5mg group) and urinary tract infection (UTI) (6% in the 15mg group). There were no dose-related trends for incidence of the individual AEs, nor where there marked differences between placebo and active treatment. The only AEs that were observed in more subjects treated with SB-742457 than placebo were headache (4% vs 2%), nausea and vomiting (2% vs 0 for both events).

The incidence of AEs leading to withdrawal was similar across the treatment groups. No non-fatal SAE was reported by more than one subject across the treatment groups. Four subjects experienced SAEs of fracture during the study: one subject in placebo group; two subjects in SB-742457 15mg treatment group; and one subject in the 35mg treatment group. None of the fractures were considered by the investigators to be related to treatment with investigational product.

Two subjects experienced a single non-fatal SAE that had a suspected or probable relationship to IP: a subject in the placebo group had mild general physical health deterioration; a subject in the SB-742457 35mg group had grade 2 or moderate ischaemic stroke.

Seven subjects died as a result of SAEs: 1 in the placebo run-in period, 2 in the placebo group and 4 in the SB-742457 treatment groups. The SAEs were intracerebral hemorrhagic stroke (placebo run-in period), accident involving a train (placebo group), colon cancer (placebo group), severe suspected cerebral stroke (15mg group; death occurred 2 months after withdrawal); severe acute myocardial infarction (35mg group); fatal road traffic accident (35mg group); malignant hepatobiliary neoplasm (35mg group; death occurred 4 months after withdrawal). None of the fatal SAEs were considered by investigators to be related to investigational product.

As preclinical testing had suggested that SB-742457 may have had a liability for phototoxicity, skin rash was designated as an AE of special interest. Three subjects on SB-742457 reported such AEs which could have represented photo-toxicity (rash or face erythema/face oedema). In two cases the AE was considered drug related and one of

these led to the subject's withdrawal from SB-742457. Of the two subjects not withdrawn: for one subject, the events resolved without withdrawing the investigational product; and for the other subject, the events occurred towards the end of the full course and resolved after the full course was completed.

No clinically significant trends were noted in the haematology, clinical chemistry, vital signs, weight, ECG examinations or urinalysis results.

Pharmacokinetics Summary:

For all subjects in the PK population, estimates of AUCτss and Cmin-ss could be obtained. The estimated exposures correspond well with what was predicted based on previous exposures and therefore no major differences in pharmacokinetics in the studied population were observed, compared to the phase I population. This is in concordance with observations in elderly subjects in previous studies and the fact that SB-742457 is mainly hepatically cleared.

The analysis assumed that the subjects took the treatment overall as prescribed. This is supported by the observation that all subjects had the majority of their observed SB-742457 plasma concentrations within the predicted range. It is unlikely that both the majority of subjects took only a percentage of the treatment and that this reduction in dose was off-set by an equal change in pharmacokinetics.

Pharmacogenetics Summary:

The available efficacy data was analysed by APOE status because subjects who carry one or two copies of the APOE4 variant (ie, APOE genotypes of 2/4, 3/4 or 4/4) have both an increased risk and decreased age of onset of late-onset AD, both sporadic and familial. No significant interactions between APOE4 carriage or APOE4 copies and SB-742457 treatment on either CIBIC+ or change from baseline in ADAS-cog were observed. APOE4 carriage and APOE4 copies had significant main effects on ADAS-cog at Week 24 (LOCF) (p values= 0.004 and 0.017, respectively) indicating that in all treatment groups, including placebo, mean change in ADAS-cog showed more improvement for APOE4 negative subjects than for APOE4 positive subjects. Similar to the full ITT population, CIBIC+ scores at Week 24 (LOCF) significantly improved in the APOE4 positive 15mg and 35mg dose groups (p= 0.022 and 0.025, respectively). In general accounting for APOE does not affect the overall interpretations of treatment effect in the full ITT population.

Conclusions:

- Linear trend analysis at Week 24 LOCF for the primary endpoints suggested a dose response (p=0.016 and p=0.059 for CIBIC+ and ADAS-cog, respectively).
- Pairwise comparisons for SB-742457 35mg versus placebo revealed statistically significant improvements in CIBIC+ score (p= 0.047), but not with ADAS-cog (p= 0.135).
- Statistically significant differences from placebo were not observed for any of the secondary endpoints at Week 24 LOCF.

- Daily doses of up to 35mg SB-742457 were generally well tolerated and overall incidence of AEs was approximately 30%.
- Seven fatal SAEs occurred during the study: 1 in the placebo run-in period, 2 in the placebo group and 4 in the SB-742457 treatment groups. None of the fatal SAEs were considered by investigators to be related to investigational product.
- A total of 16 subjects reported non-fatal SAEs. Two non-fatal SAEs were considered to be related to study medication: one placebo subject who experienced mild general physical health deterioration; one SB-742457 35mg subject who experienced moderate ischaemic stroke.
- The SB-742457 exposures were as expected from previous studies, suggesting good compliance.
- No significant interactions were observed between APOE4 carriage or APOE4 copies and SB-742457 dose on either ADAS-cog or CIBIC+, at Week 24(LOCF). However, there was a main effect of APOE4 status on ADAS-cog score, indicating that in all treatment groups, including placebo, mean change in ADAS-cog showed more improvement for APOE4 negative subjects than for APOE4 positive subjects.

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