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Two randomized controlled trials of SB742457 in mild-to-moderate Alzheimer's disease

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Abstract

Background: Two previous studies of SB742457, a 5-hydroxytryptamine (5-HT_6) receptor antagonist, suggested the efficacy of improvements in cognition and global outcome in Alzheimer's disease (AD).

Methods: Two randomized, placebo-controlled trials investigated SB742457 15 and 35 mg daily in subjects with mild-to-moderate AD (Mini-Mental Health State Examination [MMSE] 10–26). Study 1 (n = 576) investigated SB742457 and donepezil (5–10 mg daily) as monotherapy for 6 months. Study 2 (n = 684) investigated SB742457 in subjects who were maintained on donepezil. Coprimary endpoints at 24 weeks assessed cognition (AD Assessment Scale-Cognitive Subscale [ADAS-Cog]) and global outcome (Study 1: Clinician Interview-Based Impression of Change Plus Caregiver Input [CIBIC+]; Study 2: Clinical Dementia Rating-Sum of Boxes [CDR-SB]). Safety was assessed throughout.

Results: Both studies failed to achieve formal statistical significance for their primary objectives. Study 1: SB742457 monotherapy was not statistically significantly different from placebo on any endpoint. Donepezil improved CIBIC+ but not ADAS-Cog. Study 2: SB742457 35 mg showed statistically significant differences relative to placebo for ADAS-cog (weeks 12, 24, and 48, but not week 36), ADCS-ADL (weeks 12–36, but not week 48), and CDR-SB (week 12 only).

Conclusion: Neither study met the overall criteria for success, but as an adjunct to donepezil, SB742457 was associated with sustained improvements for up to 48 weeks in cognition and ADL, compared with donepezil alone.

Clinical Trial Registration: Clinicaltrials.gov: Study 1 NCT00708552; Study 2 NCT00710684.

Keywords: 5-HT_6 antagonist; Alzheimer's disease; ADAS-Cog; CIBIC+; CDR-SB; Donepezil

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1. Background

Serotonin (5-hydroxytryptamine [5-HT]) plays a role in cognition and behavior, therefore, pharmacological agents that impact 5-HT pathways are of interest in Alzheimer's disease (AD). In particular, 5-HT_6 receptors are found almost exclusively within the central nervous system in regions associated with cognition and behavior, including the striatum, nucleus accumbens, and to a lesser extent the hippocampus and cerebral cortex [1].

SB742457 is a potent and selective 5-HT_6 receptor antagonist shown to reverse scopolamine-induced deficits in a rodent test of novel object recognition, and to enhance performance of a water maze task by aged rats [1]. Other 5-HT_6 receptor antagonists have also shown activity in these tests and in similar models [2–4]. Results from two previous Phase II studies of SB742457 as monotherapy, suggested some improvements in cognition and global function in patients with mild-to-moderate AD [5,6]. Post hoc analyses suggested that effects on cognition, measured using the AD Assessment Scale-cognitive subscale (ADAS-Cog), may be more evident in patients with moderate AD than in those with mild AD.

5-HT_6 antagonists have modulatory effects on cholinergic, glutamatergic, and monoaminergic systems [7–11]. Although the relative contributions of these neurotransmitter effects on cognition is unknown, this action is clearly distinct from that of acetylcholinesterase inhibitors (AChEIs) [3,4], which are approved for the symptomatic management of mild-to-moderate AD [12]. An adjunctive therapy that acts via a different neurotransmitter system to AChEIs could offer enhanced cognitive benefits. There are currently no treatments approved for adjunct therapy to AChEIs in mild-to-moderate AD, but preliminary data suggest that there are additive effects with AChEIs and 5-HT_6 antagonists in preclinical cognition models [13].

Here, the results of two Phase II studies in patients with probable mild-to-moderate AD are presented:

- Study 1 was performed to investigate the efficacy and safety of SB742457 15 and 35 mg when used as monotherapy for 24 weeks, compared with placebo. Donepezil was also included as an active control.
- Study 2 examined the same doses of SB742457 as an adjunct treatment to donepezil therapy over 48 weeks, compared with placebo.

2. Methods

2.1. Study details

The study design and methodology are summarized later. Additional details are provided in the Technical Appendix. Study 1 (GlaxoSmithKline study: AZ3110865; ClinicalTrials.gov identifier: NCT00708552) and Study 2 (GlaxoSmithKline study: AZ3110866; ClinicalTrials.gov identifier: NCT00710684) were multicenter, double-blind, randomized, placebo-controlled, parallel-group trials.

Study 1 was conducted from July 2008 to March 2010 in 68 centers across 11 countries (Bulgaria, Chile, Czech Republic, Estonia, Germany, Greece, Korea, Mexico, Poland, Russia, and South Africa). Study 2 was conducted from July 2008 to November 2010 in 97 centers across nine countries (Argentina, Australia, Canada, Chile, Czech Republic, Germany, Italy, Spain, and USA).

The studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed and approved by properly constituted ethics committees (national, regional, or investigational) or institutional review boards at each participating institution.

2.2. Research participants

Eligible participants were aged 50 to 85 years inclusive; met the criteria for probable AD in accordance with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria [14] and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria [15]; had a stable Mini-Mental Status Examination (MMSE) [16] score of 10 to 26 before randomization (with $\leq$3-point variation from screening to the end of the run-in period); had a Hachinski Ischemia score [17] of $\leq$4 at screening; and had a regular caregiver to assess cognitive function, activities of daily living (ADL), and behavior. In Study 2, participants were also required to have $\geq$6 months' history of donepezil therapy, with 2 months at a stable dose and no intent to change during the study.

Exclusion criteria included: significant psychiatric illness; history/evidence of another cause of dementia; history of seizures; known history of drug-related photosensitivity; abnormal findings precluding participation; or use of AChEIs (with the exception of donepezil in Study 2), memantine, selegiline, monoamine oxidase inhibitors, conventional antipsychotics, an investigational drug, or treatment with potential for interaction with SB742457. Antidepressants (other than monoamine oxidase inhibitors), thyroid hormones, atypical antipsychotics, benzodiazepines, and other sedatives/hypnotics were permitted conditionally if prescribed at a stable dose for $\geq$2 months before entry.

2.3. Study procedures

In both studies, research participants entered a 2-week screening period and a 4-week single-blind placebo run-in period.

- In Study 1, participants then entered a 24-week treatment phase, receiving SB742457 (15 or 35 mg), donepezil (5–10 mg [an active control to assess assay sensitivity]), or placebo.