SYNOPSIS

Title of the study:	A multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the effect on cognitive performance, safety, and tolerability of SAR110894D at the doses of 0.5 mg, 2 mg, and 5 mg/day for 24 weeks in patients with mild to moderate Alzheimer's Disease on stable donepezil therapy (DRI10734)
Coordinating Investigator:	[redacted]
Study centers:	82 centers in 9 countries (Australia, Canada, France, Germany, Italy, Poland, Portugal, Spain, and the USA)
Publications (reference):	Not applicable
Study period:	
Date first patient enrolled:	06 February 2011
Date last patient completed:	09 January 2013
Phase of development:	Dose ranging Phase 2
Objectives:	

Primary objective: To demonstrate the efficacy of at least one dose of SAR110894D in comparison to placebo on cognitive performance in patients with mild to moderate Alzheimer's Disease (AD) while on stable donepezil therapy.

Secondary objectives:

- To explore the effect of SAR110894D on functional impairment, global clinical status, and behavioral disturbances
- To assess the safety/tolerability of SAR110894D
- To assess pharmacokinetic (PK) of SAR110894 and concentrations of donepezil
- To explore caregiver time consumption and distress changes.

Methodology:	Randomized, double-blind, 4 parallel-groups, placebo-controlled; randomization was stratified on apathy status as assessed by the informant (caregiver) (Apathy Evaluation Scale - Informant [AES-I] ≤41, AES-I >41) and center.
Number of patients:	
Planned: 280 (per Amendment 3)	Randomized: 291 Treated: 290
Efficacy: 280	Safety: 290 Pharmacokinetics: 278 (donepezil population) and 215 (SAR110894D population)
Diagnosis and criteria for inclusion:	Outpatients with diagnosis of AD based on the dementia of Alzheimer type Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-4) criteria and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)/Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for probable AD, supported by a Modified Hachinski score ≤4 and magnetic resonance imaging (MRI) or computed tomography (CT) scan compatible with the diagnosis of AD, having Mini Mental State Examination (MMSE) score ≥15 and ≤25 and clinical dementia rating (CDR) score 0.5, 1, or 2 and being on stable and well-tolerated donepezil treatment at fixed dose of 5 or 10 mg daily for at least 3 months prior to screening.
Study treatments	
Investigational medicinal product:	SAR110894D
Formulation:	Capsules of 0.5 mg, 2 mg, and 5 mg
Route of administration:	Oral
Dose regimen:	One capsule of 0.5 mg, 2 mg, or 5 mg of SAR110894D once daily along with donepezil
Batch numbers:	[redacted]

Investigational medicinal product: Placebo

Formulation: Matching capsules for 0.5 mg, 2 mg, and 5 mg of SAR110894D

Route of administration: Oral

Dose regimen: 0 mg, once daily along with donepezil

Batch numbers: [redacted]

Noninvestigational medicinal product: Donepezil

Formulation: 5 mg or 10 mg tablet or orally disintegrated tablet (ODT)

Route of administration: Oral

Dose regimen: 5 mg or 10 mg tablet or ODT, once daily

Batch numbers: Not applicable as donepezil was used under the commercial labeling

Duration of treatment: 24 weeks

Duration of observation: 36 to 38 weeks (based on duration of screening period) and including a 10-week follow-up period

Criteria for evaluation: The current report is an abbreviated report, and as such, only the safety results are being presented in full.

Efficacy:

Primary endpoint: Change from baseline to Week 24 in the standard 11-item total score from the 13-item Alzheimer's Disease Cooperative Study - Cognitive subscale (ADAS-Cog) assessment scale

Secondary endpoints: Key secondary endpoints are:

- Change from baseline to Week 24 in the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) Inventory global score
- Change from baseline to Week 24 in five factors from the Cognitive Drug Research computerized assessment system (CDR-S): power of attention, continuity of attention, quality of working memory, cognitive reaction time, and speed of memory
- Change from baseline to Week 24 in the Neuropsychiatric Inventory (NPI) domain scores of irritability/lability, anxiety, agitation/aggression, sleep and nighttime behavior disorders

Other secondary endpoints are:

- Change from baseline to Week 24 in ADAS-Cog 13-item total score
- Change from baseline to Week 24 in the MMSE total score
- Change from baseline to Week 24 in the NPI total score summed over all domains from A to J
- The NPI aberrant motor behavior, apathy/indifference, appetite/eating change, delusions, depression/dysphoria, disinhibition, elation/euphoria, and hallucinations domain scores (frequency x severity)
- Change from baseline to Week 24 in the AES-I score
- Response to treatment by ADAS+ responders and ADAS+/AES-I+ responders
- The assessment at Week 12, Week 24 and at LOCF of the Clinical General Impression of Change (CGIC)
- Change from baseline to Week 24 in language and memory clusters based on ADAS-Cog
- Change from baseline to Week 24 in Hamilton depression rating scale (HAM-D) total score
- Change from baseline to Week 12 for the following circadian parameters based on actigraphy: inter-daily stability, intradaily variability, relative amplitude

Criteria for evaluation (cont'd):

Safety:

- Adverse events (AEs) reported by the patient or noted by the Investigator, including study specific Adverse Event with Prespecified Monitoring (AEPM)s with immediate notification (suspicion of cataract, suspicion of myocardial ischemia, suspicion of cardiac rhythm disorder, suspicion of gastro-duodenal lesion, suspicion of rhabdomyolysis)
- Clinical laboratory tests
- Vital signs and physical exam reported by the Investigator
- Standard central electrocardiogram (ECG) reading
- Ophthalmologic examinations including a slit lamp examination with Lens Opacities Classification System Version 3 (LOCS-III) grading by certified ophthalmologists

Pharmacokinetics:

Concentrations of SAR110894 and donepezil in plasma samples were measured using a validated liquid chromatography method coupled with tandem mass spectrometry (LC-MS/MS).

Statistical methods: The primary efficacy analysis aimed at quantifying and testing the statistical significance (at a nominal 2-sided 5% level, without adjustment for multiplicity of testing) of the treatment effect, for each dose of SAR110894D, on the change from baseline to Week 24 in the ADAS-Cog total score as derived on 11 of the 13 items of this scale. In practice, a mixed model for repeated measurements (MMRM) was fitted, in the modified intent-to-treat (mITT) population (patients treated at least once with at least a baseline and a post-baseline assessment of the ADAS-Cog total score), on changes from baseline to Weeks 4, 12, and 24 data with an unstructured correlation matrix: data were adjusted for time of assessment, and for treatment, centered ADAS-Cog total score, apathy status (non apathic: AES-I≤41; apathic: AES-I>41) and severity at baseline (mild: MMSE ≥20; moderate: MMSE <20), and for their interactions with time of assessment.

Key secondary efficacy endpoints were analyzed through the same statistical methodology.

Safety analyses were only descriptive, except treatment-emergent adverse events (TEAEs) for which statistical significance information is provided in terms of false discovery rate (FDR) and non-discovery rate (NDR).

Summary:

Population characteristics: A total of 291 elderly male and female patients with mild to moderate AD, treated with stable dose of donepezil >3 months prior to randomization were equally randomized into 4 groups, stratified by center and patient baseline status related to apathy (AES-I ≤41, AES-I >41).

The demographic characteristics at baseline were similar across all treatment groups. The mean age of population was 72.6 years old; 51.9% were male and 99.0% of the patients were Caucasians.

Disease characteristics at baseline were similar across treatment groups except for severity status and ADAS-Cog standard 11-item total score. There were 40.2% of the patients who had CDR global score of 0.5, 50.2% of 1, and 9.6% of 2. Based on MMSE total score, there were 69.4% of mild AD patients (MMSE≥20) and 30.6% of moderate AD patients (MMSE<20) overall.

The distribution of mild AD patients was of 62.8% in the placebo group versus 61.1%, 72.2%, and 82.6% in the SAR110894D 0.5 mg, 2 mg, and 5 mg treatment groups, respectively. The mean ADAS-Cog standard 11-item total score was 21.6 overall, with 24.1 in the placebo group versus 19.9, 21.5, and 20.6 in the SAR110894D 0.5 mg, 2 mg, and 5 mg treatment groups, respectively. There were 47.8% of randomized patients who were apathic (AES-I >41).

The median duration from onset of symptoms to randomization was 3.7 years and from diagnosis of AD to randomization 1.6 years. Donepezil 5 mg was taken by 13.7% of the patients whereas donepezil 10 mg was taken by 86.3% of the patients. There were 53.6% of the patients who were taking donepezil in the evening, 43.6% in the morning, and 2.7% at noon. The median duration of donepezil treatment before randomization was around 17 months.

Forty-two (42) patients did not complete the study treatment period: 10.3% in the placebo group, 16.7% in the SAR110894D 0.5 mg, 8.3% in 2 mg, and 23.2% in 5 mg groups, mainly due to adverse events. The median duration of study treatment was 167 to 168 days according to treatment groups.

Summary (Cont'd)

Efficacy results: The observed mean change from baseline to Week 24 in the ADAS-Cog standard 11-item total score was of 1.01 in the placebo group versus 1.32, 1.32, and 1.41 in the 0.5 mg, 2 mg, and 5 mg treatment groups, respectively, where positive values stand for worsening. The corresponding estimates obtained from the main model are slightly different from the observed mean changes from baseline due to imbalance in adjustment factors (severity and mean ADAS-Cog total score) at baseline. These estimated mean changes are of 0.87 for placebo and 1.13, 1.49, and 1.59 for the SAR110894D 0.5 mg, 2 mg, and 5 mg treatment groups, respectively, resulting in estimated difference from placebo of 0.26, 0.62, and 0.72, all statistically non-significant (nominal 2-sided p-value of respectively 0.77, 0.47, and 0.42). With regards to secondary endpoints, the comparison of SAR110894D 5mg to placebo in the change from baseline to Week 24 in ADCS-ADL total score results in a nominal 2-sided p-value (0.02) lower than 5% threshold, in favor of SAR110894D 5mg (tested without adjustment for multiplicity). All secondary endpoints observations and analyses were consistent with primary efficacy findings.

Safety results: None of the active treatment groups shows higher percentage of patients having experienced at least one treatment-emergent serious adverse event (SAE) than placebo: 13.9% (0.5 mg), 14.1% (2 mg), and 11.6% (5 mg) versus 15.4% in the placebo group. Two deaths occurred during the study treatment emergent period (one in a patient treated with placebo and one in a patient treated with SAR110894D 2 mg).None of these cases were considered as drug-related. Twenty six (26) patients prematurely withdrew from the study treatment period due to TEAE. Patients who withdrew accounted for 3.8% in the placebo group and for 9.7%, 7.0%, and 15.9% in the SAR110894D 0.5 mg, 2 mg, and 5 mg groups, respectively. Among the 11 patients in the SAR110894D 5 mg group who prematurely discontinued the study treatment, psychiatric disorders (2 confusions and 3 insomnias) were the most prominent events.

Signal detection methodology identify the High Level Term (HLT) "Disturbances in initiating and maintaining sleep" and the Preferred term (PT) "Muscle spasm" as safety signals. The TEAEs with possible cholinergic origin, which include insomnia and muscle spasms, were the most common TEAEs in all treatment groups with a trend to higher incidence in the 2 mg and 5 mg.

Based on their apparent dose relationship, TEAEs in the HLGT "Depressed mood disorders and disturbances" were also considered as a new safety finding.

According to ophthalmologic LOCS-III data evaluating lens opacity, 3 patients of the 5 mg group exhibited a confirmed bilateral class II event (of nuclear localization; for 2 of them, they were even class III events) while no patients of the placebo group did. In a population where age related lens opacities are expected, given the size of the groups, the variability of the LOCS-III grading, and the low number of Class 2-3 LOCS-III events, the clinical significance of the findings cannot be determined at this stage.

Pharmacokinetic results: Within each treatment group and for all doses of SAR110894, donepezil concentrations remained stable during treatment versus baseline. This confirms that there is no PK interaction of SAR110894 on donepezil.

Conclusions: [redacted]

Date of report: 18-Jul-2013