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Sponsor: Sanofi **Drug substance(s):** SR57746 (xaliproden)	**Study Identifiers:** NCT00104013 **Study code:** EFC2724
Title of the study: A randomized, multicenter, double-blind, placebo-controlled, 18-month study of the efficacy of xaliproden in patients with mild-to-moderate dementia of the Alzheimer's type	
Study center(s): 129 centers in 11 countries (Australia, France, Hong Kong, Italy, The Netherlands, New Zealand, Singapore, South Africa, Spain, Taiwan, and the United States).	
Study period: Date first patient enrolled: 24/Nov/2003 Date last patient completed: 23/Nov/2007	
Phase of development: Phase 3	

Objectives:

Primary: The main objective of the study was to assess the efficacy of xaliproden in comparison to placebo on cognitive function and global decline in patients with mild-to-moderate dementia of the Alzheimer's type (AD).

Secondary:

- To assess the effect of xaliproden on the annualized rate of progression of hippocampal atrophy and global brain atrophy (assessed with volumetric whole brain atrophy and ventricular expansion) as measured by magnetic resonance imaging (MRI);
- To evaluate the effect of xaliproden on functional decline, behavioral symptoms and healthcare resource utilization;
- To evaluate the long-term safety and tolerability of xaliproden, notably to compare the change over time of the left ventricular ejection fraction (LVEF) between the xaliproden and the placebo groups;
- To document plasma concentrations of xaliproden.

The efficacy objectives were evaluated during the 18-month core treatment period. The optional extension phase provided exploratory data on xaliproden long-term efficacy.

All safety data are provided in this report including the safety data obtained during the whole study period (18-month core treatment period + optional extension phase).

Methodology: International, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 3, 18-month study treatment period. The core study period (18 months) was followed by an optional, double-blind, extension period of at least one year per patient. Following a recommendation from the Data Monitoring Committee (DMC) that was monitoring the safety of Studies EFC2946 and EFC2724, the treatment in extension phase was temporarily discontinued late January 2007, until the analysis of the main 18-month treatment period to allow a comprehensive understanding of the benefits of treatment. The whole study period was defined as period including the 18-month core treatment period and the optional extension phase.

Number of patients**:**	Planned: 1200
	Randomized: 1455
	Treated: 1455
Evaluated:	
	Efficacy - Intent-to-Treat (ITT) population: 1390
	Safety: 1445

Diagnosis and criteria for inclusion: Male and female outpatients of at least 50 years at screening with probable Alzheimer's disease according to the national institute of neurological and commutative stroke/Alzheimer's disease and related disorders association (NINCDS/ADRDA) and diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV) criteria, and mini-mental state examination (MMSE) between 16 and 26.

Study treatments

Investigational medicinal product(s): Xaliproden (SR57746A) (in white hard gelatin size 3 capsules)

Dose: titration phase during 3 months, then fixed dose of 0.25 mg or 0.5 mg of xaliproden/day

Route(s) of administration: Oral route (capsules)

Reference therapy: Placebo (in identical capsules as for the Investigational product)

Route(s) of administration: Oral route (capsules)

Duration of treatment: 18 months core treatment period. This duration was extended to 30 months total treatment for patients participating in the optional extension period.

Duration of observation: About 21 months for patients who completed the core 18-month treatment period (including a 1-month screening period, the treatment period and 1-2 months after the last study drug intake), extended to 32 to 50 months for patients entering in the optional extension period.

Criteria for evaluation: The current report is an abbreviated report, and as such, only the primary and key secondary efficacy variables over the 18-month core treatment period are presented. All the safety variables during the 18-month core treatment period and during the whole study period are presented.

Primary Efficacy variables:

- The rate of change over time of Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) total score calculated as the sum of the 11 items: orientation, word recall, word recognition task, remembering test instructions on word recognition, naming objects and fingers, spoken language ability, comprehension of spoken language, word finding difficulty, commands, ideational praxis, and constructional praxis;
- The rate of change over time of Clinical Dementia Rating scale (CDR) sum of boxes score calculated as the sum of the 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Secondary efficacy variables

Secondary clinical efficacy endpoints were: mini-mental state examination, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Neuro Psychiatric Inventory (NPI), and Resource Utilization in Dementia (RUD).

Only the key secondary efficacy endpoints evaluating the disease-modifying effect of xaliproden assessed using volumetric MRI on the annualized rate of hippocampal and whole brain atrophy, and on annualized rate of ventricular expansion are presented in the current report.

The pooled results of MRI substudies from EFC2946 and EFC2724 studies are presented in a separate report.

Safety: The following criteria were evaluated: adverse events (AEs), clinical laboratory tests, electocardiogram (ECG), vital signs, physical examination.

The pooled results of echocardiography substudies from EFC2946 and EFC2724 studies are presented in a separate report.

Statistical methods:

Efficacy analysis:

The primary efficacy variables were the rate of change over time in ADAS-Cog total score and the rate of change over time in CDR sum of boxes. The treatment effect had to be demonstrated on both primary endpoints simultaneously to conclude on a positive study. The key secondary efficacy variables described in this report were MRI variables.

Analysis of primary variables:

The primary analysis of the primary variables was based on the intent-to-treat (ITT) population defined as all patients who were randomized, took at least one dose of double-blind study medication, and provided a baseline and at least one post-baseline assessment for ADAS-Cog total score or CDR sum of boxes or both, during the 18-month treatment period. The rate of change over time in ADAS-Cog total score and CDR sum of boxes was compared between treatment groups by estimating the slope (and intercept) in a random coefficient regression model, using all available assessments from baseline to month 18. Baseline was defined as the last available value prior to randomization. Statistical tests were two-sided at 4.9% (to account for performing an interim analysis to assess futility).

The following sensitivity analyses were performed on the ITT population:

- An analysis of covariance (ANCOVA) on the change from baseline to last visit (LOCF approach) with treatment group as the main factor and the baseline ADAS-Cog score or CDR sum of boxes as a continuous covariate;
- A two-way analysis of covariance (ANCOVA) on the change from baseline to last visit (LOCF approach), including baseline as the covariate and with the following 2 factors: treatment and a categorical variable accounting for the time of the patient's last efficacy assessment: (0-6), (6-12) or (12-18) months (alternate statistical model assuming non-linearity);
- Adding to the primary model (random coefficient regression model) the time of the patient's last efficacy assessment as defined above (to assess the impact of potentially non-ignorable missing data due to dropouts).

Descriptive statistics and graphs were used to summarize the data. Exploratory analyses were performed on all data collected during the study (including the optional extension period).

Analysis of secondary variables:

Each MRI parameter was analyzed using ANCOVA with treatment and baseline volume in the model (baseline hippocampal volume for hippocampal atrophy, baseline brain volume for whole brain atrophy and ventricular expansion), on the MRI-ITT population (defined as a subgroup of ITT patients evaluable for the MRI analysis). If the data could not be considered as normally distributed, non-parametric analyses based on ranks methods were used.

Correlations between MRI parameters and the primary efficacy variables were evaluated through linear regression models.

Safety analysis:

Adverse events were coded with preferred term (PT) and associated system-organ class (SOC) according to medical dictionary for regulatory activities (MedDRA) version 10.1 or higher. Descriptive statistics were provided for all safety criteria, on the safety population defined as all patients who were randomized and took at least one dose of double-blind study medication. Abnormalities in laboratory data, vital signs and ECG parameters were assessed using mean changes from baseline and potentially clinically significant abnormalities (PCSA) criteria.

Summary:

Study population: The study population consisted of patients with AD (50% mild, 50% moderate) with more than 80% patients treated with AD therapy (acetylcholinesterase inhibitors or memantine) at baseline. The treatment groups appeared to be comparable at baseline for demographic data, disease severity and concomitant therapy for AD at baseline.

Efficacy results: Analyses of ADAS-Cog total score and of the change from baseline of this score showed a cognitive deterioration over the 18-month core treatment period. The difference between the 2 groups is in favor of placebo even if the difference is not statistically significant. Analyses of CDR sum of boxes score and of the change from baseline of this score showed a global clinical worsening over the 18-month core treatment period.

The difference between the 2 groups is in favor of placebo even if the difference is not statistically significant. Analyses of the MRI variables on the disease-modifying effect of xaliproden showed no difference in the global brain atrophy rate whereas the hippocampal atrophy rate was slower in patients receiving xaliproden. This study did not show significant efficacy of xaliproden after 18 months at the dose of 0.25 or 0.5 mg/day in the treatment of patients with mild-to-moderate AD.

Safety results: Overall, the proportion of patients completing the 18-month core treatment was in the range of the protocol hypothesis. The initial dose of xaliproden was 0.25 mg daily and was increased to 0.50 mg daily for most patients (80%) based on the Investigator's decision prior to completion of 3 months of treatment. The percentages of patients with treatment emergent adverse events (TEAEs) were higher in the xaliproden group (84.6%) than in the placebo group (80.9%). Incidence of serious TEAEs and incidence of TEAEs that led to a fatal outcome during the 18-month core study were comparable between treatment groups. The number of patients with TEAEs leading to discontinuation was higher in the xaliproden group (14.9%) than in the placebo group (11.1%) and the difference was observed within the psychiatric, gastrointestinal (mainly due to diarrhea) and cardiovascular disorders.

Psychiatric disorders (anxiety symptoms, hallucination, and sleep disturbances) appeared to be the most frequently reported TEAE with a higher incidence in the xaliproden group (36.2%) compared to the placebo group (24.9%). It was followed by gastrointestinal disorders (26.6% versus 24.2%), cardiac disorders (8.4% versus 6.5%), and metabolism and nutrition disorders (9.5% versus 8.8%).

There were more cardiac disorders and psychiatric disorders in serious TEAEs observed in the xaliproden group (3.6% and 2.8%, respectively) than in the placebo group (2.8% and 1.1%, respectively) and there were more cardiovascular events leading to withdrawal in the xaliproden group (2.2%) than in the placebo group (1.0%).

Concerning the events leading to death, more cardiac disorders were observed in the xaliproden group (0.6%) than in the placebo group (0.3%) mainly due to acute myocardial infarction.

TEAEs reported with an incidence >5% and with a higher frequency in the xaliproden group than in the placebo group were by decreasing order of frequency: diarrhea, agitation, insomnia, urinary tract infection, and depression.

No major imbalance between treatment groups was identified in the analysis of AEs of special interest (AESIs) possibly related to myocarditis, cardiomyopathy or cardiac failure, possibly related to cardiac failure, infarction or edema, and possibly related to edema. No clear trend suggesting a probable causal relationship was identified in the analysis of grouping of TEAEs which might possibly be related to the proposed physiopathological edema origin.

In either treatment group, no clinically relevant changes in the clinical laboratory evaluations were observed. The post-baseline PCSAs were reported with a comparable frequency in both treatment groups except for metabolism evaluation, hyperglycemia with same observed trend for glycated hemoglobin was more frequent in the xaliproden group (16.7%) than in the placebo group (12.5%) over the 18-month treatment period. The number of patients with a weight decrease ≥7% was slightly higher in the placebo group (13.1%) than in the xaliproden group (12.6%) and the number of patients with a weight increase ≥7% was slightly higher in the xaliproden group (15.1%) than in the placebo group (14.2%). These results combined with the higher incidence of BMI ≥30 kg/m² in the xaliproden group (18.3%) than in the placebo group (16.0%) suggested that there may be a positive effect of xaliproden on weight.

No clinically relevant changes were observed in either group for vital signs and ECG parameters. For ECG, the post-baseline PCSAs were reported with a comparable frequency in both treatment groups except for increase from baseline (30-60) ms QTc interval (using Bazett and Fridericia formula) which were reported more frequently in the xaliproden group (18.0% for Fridericia formula and 24.3% for Bazett formula) than in the placebo group (14.0% for Fridericia formula and 20.9% for Bazett formula).

All the safety data observed during the whole study period were consistent with the safety data observed during the 18-month core treatment period except for cardiac disorders in serious TEAEs and except for syncope in TEAEs possibly related to myocarditis, cardiomyopathy or cardiac failure for which no imbalance was observed between the treatment groups.

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