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Sponsor: Sanofi	Study Identifiers: NCT00103649
Drug substance(s): SR57746 (xaliproden)	Study code: EFC2946
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): 117 centers in 2 countries (Canada and the United States)	
Study period: Date first patient enrolled: 11/Nov/2003 Date last patient completed: 22/Oct/2007	
Phase of development: Phase 3	
<p>Objectives:</p> <p>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).</p> <p>Secondary:</p> <ul style="list-style-type: none"> • To assess the effect of xaliproden on the annualized rate of progression of hippocampal atrophy and of 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 xaliproden and placebo groups; • To document plasma concentrations of xaliproden. <p>The efficacy objectives were evaluated during the 18-month core treatment period. The optional extension phase provided exploratory data on xaliproden long-term efficacy.</p> <p>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).</p>	
<p>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 extension phase planned for 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 18-month core treatment period to allow a comprehensive understanding of the benefits of treatment. The whole study period was defined as period covering the 18-month core treatment period and the optional extension phase.</p>	

<p>Number of patients:</p> <p>Planned: 1200</p> <p>Randomized: 1306</p> <p>Treated: 1299</p> <p>Evaluated:</p> <p>Efficacy: 1238</p> <p>Safety: 1299</p>	
<p>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.</p>	
<p>Study treatments</p> <p>Investigational medicinal product(s): Xaliproden (SR57746A) (in white hard gelatin size 3 capsules)</p> <p>Dose: titration phase during 3 months, then fixed dose of 0.25 mg or 0.5 mg of xaliproden/day</p> <p>Route(s) of administration: Oral route (capsules)</p>	
<p>Reference therapy: Placebo (in identical capsules as for the Investigational product)</p> <p>Route(s) of administration: Oral route (capsules)</p>	
<p>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.</p> <p>Duration of observation: About 21 months for patients who completed the 18-month core 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.</p>	
<p>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.</p> <p>Primary Efficacy variables:</p> <ul style="list-style-type: none"> • 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 the 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. <p>Secondary efficacy variables</p> <p>Secondary clinical efficacy endpoints were: MMSE, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS- ADL), NeuroPsychiatric Inventory (NPI), and Resource Utilization in Dementia (RUD).</p> <p>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.</p> <p>The pooled results of MRI substudies from EFC2946 and EFC2724 studies are presented in a separate report.</p> <p>Safety: The following criteria were evaluated: adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), vital signs, physical examination.</p> <p>The pooled results of echocardiography substudies from EFC2946 and EFC2724 studies are presented in a separate report.</p>	

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 1 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 an analysis of covariance (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 1 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 (57% mild, 43% moderate) with more than 75% 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 that is observed with the same intensity in both treatment groups. 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 that is observed with the same intensity in both treatment groups. Even if the global brain atrophy seemed to be slightly lower in the xaliproden group, analyses of the MRI variables on the disease-modifying effect of xaliproden showed no significant difference between the 2 treatment groups. 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 period was in the range of the protocol hypothesis. The percentages of patients with treatment-emergent adverse events (TEAEs) were higher in the xaliproden group (87%) than in the placebo group (84.9%). Incidence of serious TEAEs and incidence of TEAEs leading to death were comparable between treatment groups even if TEAEs with fatal outcome were reported with a higher number in the xaliproden group for cardiac disorders. On the whole, the TEAEs leading to withdrawal were more frequent in the xaliproden group (16.9%) compared to the placebo group (13.2%) and the difference were mainly observed within the psychiatric, nervous system and cardiac disorders.

Psychiatric disorders appeared to be the most frequently reported SOC with a higher incidence in the xaliproden group (37.6%) compared to the placebo group (25.6%). It was followed by gastrointestinal disorders (30.1% versus 27.6%), musculoskeletal and connective disorders (19.5% versus 18.0%), investigations (14.5% versus 12.7%), skin and subcutaneous tissue disorders (14.0% versus 9.0%), cardiac disorders (9.5% versus 7.8%), and vascular disorders (8.5% versus 7.5%).

Concerning the events leading to death, more cardiac disorders were observed in the xaliproden group (1.1%) than in the placebo group (0.2%) mainly due to acute myocardial infarction and cardio-respiratory arrest.

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: fall, diarrhea, agitation, urinary tract infection, nausea, insomnia, headache, confusional state, and hallucination.

The same incidence of serious TEAEs was reported between treatment groups, however with a few more cases in the xaliproden group for fall, agitation, syncope and dehydration.

No major imbalance between treatment groups was identified in the analysis of grouping AESIs possibly related to myocarditis, cardiomyopathy or cardiac failure as well as AESIs possibly related to cardiac failure, infarction or edema.

In either treatment groups, no clinically relevant changes in the clinical laboratory evaluations, vital signs and ECG were observed. The PCSAs were reported with a comparable frequency in both treatment groups except for the renal parameters (creatinine values ≥ 150 $\mu\text{mol/L}$), for decreased systolic and diastolic blood pressure (with comparable values in heart rate) and for increase from baseline [30 - 60] ms QTc interval (using Bazett and Fridericia formula) which were reported more frequently in the xaliproden group.

The number of patients with a weight decrease $\geq 7\%$ was higher in the placebo group (13.8%) than in the xaliproden group (10.2%). These results combined with the higher incidence of BMI ≥ 30 kg/m^2 in the xaliproden group (23.8%) than in the placebo group (19.6%) suggested that there may be a positive effect of xaliproden on weight.

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 the cardiac disorders in which subcategories still remained different between the treatment groups and except for the global incidence of serious TEAEs which is slightly higher in the xaliproden group (23.4%) than in the placebo group (21.9%).

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