Janssen Research & Development

Clinical Study Report Synopsis
[GAL ITA 2; Phase III]

JNJ-17335630-AAD (Galantamine)

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2. SYNOPSIS

Name of Sponsor:
Janssen Cilag S.p.A.
Name of Finished Product:
Reminyl
Name of active ingredient:
Galantamine HBr (R113675)
Title of study
Long term treatment with galantamine in dementia.
Evaluation of long term treatment with galantamine or placebo in AD patients in delaying cognitive deterioration
Coordinating Investigator: [redacted],

No. of study centres: 29

Publication (reference): not yet available

Study period (years)
Date of first enrolment: 13 July 2001
Date of last completed**:** 28 November 2005

Phase of development:
III

Objectives
Primary: To assess whether a long term treatment with galantamine will result in delaying the cognitive deterioration associated with the Alzheimer's Disease (AD). To investigate the long term efficacy and safety of the treatment with galantamine in a population of patients with dementia.
Secondary: To assess the possible benefit of the treatment with galantamine on disability of patients with dementia.
Methodology
Two phases study:
Open Label Phase (OL): 12-month treatment period in which consecutive patients were given galantamine 16 mg/day. At the end of OL phase, eligible patients were randomized to the Double Blind Phase.
Double Blind Phase (DB): Up to 24-month treatment period in which " responders" patients (i.e. patients with a deterioration of < 4 points on the 11-item Alzheimer's Disease Assessment scale cognitive subscale -ADAS-COG/11), were randomly allocated to one of the following treatment groups: galantamine 16 mg/day or placebo (no treatment)
Number of patients (planned and analysed):
255 planned / 254 analysed for safety and 176 for efficacy in OL Phase; 139 entered the DB Phase and were analysed for safety and 126 for efficacy in DB phase.
Diagnosis and main criteria for inclusion:
Alzheimer's Disease
Inclusion criteria: Male and female out-patients, aged ≥ 50 years; diagnosis of probable Alzheimer's Disease according to NINCDS-ADRDA; mild to moderate cognitive impairment: MMSE score from 11 to 24
Exclusion criteria: evidence of any other neurodegenerative disease; previous cerebral trauma, subdural haematoma or head injury; previous cerebral infection; cerebral neoplasia; mental retardation; epilepsia; psychiatric diseases; treatment with

cholinesterase inhibitors within 3 months prior to inclusion; use of disallowed concomitant therapy; history or suspicion of alchool or drug abuse; pregnancy or breast-feeding female; participation in an investigational drug trial in the 30 days prior to selection; known sensitivity to galantamine; history of severe drug allergy or hypersensitivity; any serious illness thought likely to prevent completion of the study
Withdrawal criteria: patients' and/or caregivers' consent withdrawal; cognitive deterioration ≥ 4-point at the 11 Item AD Assessment Scale-cognitive subscale (ADAS-COG/11) during DB phase (primary endpoint); unblinding of randomization code.

Test product, dose and mode of administration:
Galantamine HBr 4 and 8 mg tablets.
OL phase: galantamine 16 mg/day divided in two administrations 12 hours apart (after a titration period of 4 weeks with 8 mg/day);
DB phase: galantamine 16 mg/day (8 mg tablet twice daily) or corresponding placebo

Duration of treatment:
36 months globally

Criteria for evaluation:

Efficacy
The primary efficacy parameter was the time to deterioration, defined as the time from the start of DB treatment to a change ≥4-point at the cognitive subscale of the ADAS-COG/11 in comparison with the baseline value (the score registered at visit 6, end of OL phase).
Secondary efficacy measures were: changes over time of scores at ADAS-COG/11, Clinician's Interview-Based Impression of Change – Plus Caregiver Input (CIBIC-plus) and Disability Assessment of Dementia (DAD).

Safety
Safety was based on the incidence of treatment-emergent adverse events and on changes from baseline in physical examination, vital sign and ECG measurements, and laboratory evaluations.

Statistical methods
In OL, changes in the ADAS-COG/11and DAD scales were analysed using analysis of variance (ANOVA) with repeated measures. Multiple comparisons versus basal values were performed according to Bonferroni's correction and 95% Confidence Interval of difference versus baseline mean was calculated. Analysis of CIBIC-plus scale was only descriptive; scores were clustered from 1 to 3 = improved, 4 = unchanged and from 5 to 7 = worsened.
The risk to show a ≥4-point change in ADAS-COG/11 versus baseline after one year of treatment with galantamine was analysed according to a logistic regression model where ADAS-COG/11 score at basal visit, sex, age and MMSE were used as independent variables and the dependent variable was the efficacy parameter: a ≥4-point change in ADAS-COG/11 versus baseline. Percentage of "responders" (patients with a change vs baseline in ADAS-COG/11 score at end of OL Phase < 4 points) was analysed using the same logistic regression model.
In DB, endpoint was change in ADAS-COG/11 ≥4-point versus value at visit 6 (end of OL score); primary efficace measure was time to deterioration, defined as time to meet the the predefined endpoint. It was analysed with using a stepwise regression analysis according to the Cox proportional hazard model. Treatment, sex, age at randomization, ADAS-COG/11 and DAD scores at visit 6 were tested as covariates.
Secondary endpoints were changes over time in ADAS-COG/11, DAD and CIBIC-plus scores. ADAS-COG/11 and DAD changes were analysed using an analysis of covariance

(ANCOVA) using scores at visit 6 as a covariate. The dependent variable was the last score available other than the one at visit 6. Changes in CIBIC-plus were analysed at each visit according to the Fischer χ^2 test with Yates correction if applicable.
Safety: adverse events (AE) were coded using the MEDRA dictionary (V. 9.0).
In OL, vital signs were evaluated using analysis of variance with repeated measures without any grouping factor; changes versus baseline of physical examination, laboratory parameters and ECG were analysed using the McNemar test.
In DB, the relative risk (galantamine/placebo) of AE and the two-sided 95% confidence interval was calculated. Comparison between groups was performed by the chi-square test for fourfold tables or the Fisher's exact test. Vital signs were evaluated according to an analysis of variance (ANOVA) with repeated measures with treatment as grouping factor and value at baseline, visit 6 and the last visit available as dependent variable. Changes in physical examination, laboratory parameters and ECG were analysed.

Efficacy results

A total of 254 patients affected by AD were enrolled in this study. 176 patients (69.3%) completed the Open Label Phase of the study. 139 (79%) out of 176 patients that completed the Open Label Phase of the study were included in the Double Blind Phase and randomized in the two study arms (76 in the galantamine group and 63 in the placebo group). Mean age of the enrolled patients was 74.2 years (range: 52 – 90), and almost two third of them were females (61.4%). About 80% of patients were resident at home with partner or familial caregivers, and 187 patients (73.6%) were retired from work at the moment of inclusion. An important medical history was present in 74% of the patients; 164 patients (64.6%) had a concomitant disease at the moment of enrolment, especially cardiovascular diseases (49.2%), metabolism and nutrition (19.7%) and gastrointestinal diseases (6.7%). 29 patients (11.4%) had received a previous anti-dementia therapy. During the Open Label Phase, 179 patients (70,5%) were treated with at least a concomitant drug. During the Bouble Blind Phase, 52 patients (69.1%) in the active group and 43 patients (68.3%) in the placebo group were treated with at least a concomitant drug. At baseline, the mean score of Mini Mental State Examination (MMSE) test was 18.9 ± 3.6 (min 11.4 – max 24.4). Throughout the Open Label Phase, the ADAS-cog score decrease significantly after 6 months ($p<0.01$) and it got back to baseline value at the 12-month evaluation. DAD score remained stable at 6 months and then decreased of 5 points after 12 months ($p<0.01$). At 6 months global functions (CIBIC – plus score) were improved, unchanged or worsened in 40.1%, 36.5% and 23.4% of patients respectively. At the 12-month evaluation, 34.3% of the patients improved, 30.9% remained stable and 34.9% worsened. According to the primary analysis, based on decrease of ADAS-COG/11 score > 4, 80.1% of the patients who finished the Open Label Phase (141 out of 176) were judged as responders to the study treatment. The regression analysis, performed according to a logistic model, showed a significant ($p < 0.01$) influence of MMSE on the probability to show a difference of ADAS-COG/11 score < 4. In Double Blind Phase, 69 patients treated with galantamine and 57 patients treated with placebo were evaluable for primary efficacy. The efficacy results showed that the treatment with galantamine delayed time to cognitive deterioration. In fact, the mean time to deterioration was 607.08 ± 29.70 days and 504.9 ± 33.38 days in galantamine and placebo group, respectively The median time was 726.1 ± 15.9 days and 552.0 days ± 83.0 respectively ($p<0.05$). At the end of study period, 35 patients (50.7%) of galantamine group and 35 patients (61.4%) of placebo group showed a change of ADAS-COG/11 ≥ 4 from visit 6 value. The difference between study groups concerning the probability to show a change in ADAS-COG/11 < 4 is statistically significant ($p < 0.05$).

Safety results

254 patients received at least one dose of study drug, and were evaluable for safety.

During the Open Label Phase of the study, 128 patients (50.4%) experienced at least one adverse event. In 51 patients (20.1%), the adverse event was judged as related to the study drug by the Investigator. The most frequently reported adverse events were: gastrointestinal disorders (21.3%), psychiatric disorders (19.7%) and nervous system disorders (9.8%).
38 patients prematurely stopped the treatment with galantamine due to an adverse event; in 22 out of 38 cases, the adverse event was judged as related to the study treatment. 31 patients (12.2%) experienced a serious adverse event (SAE); in 4 patients (1.6%) , the SAE was considered as related to the study drug. 5 patients with a SAE died during the Open Label Phase of the study, but in no cases the event was judged as related to the treatment by the Investigator.
During the Double Blind Phase of the study, 26 patients (34.1%) in the galantamine group and 17 patients (27%) experienced at least one adverse event. The adverse event was judged as related to the study drug by the Investigator in only 2 patients (2.6%) treated with galantamine, respect to 4 cases (6.3%) in the placebo group. 8 patients treated with galantamine and 4 patients treated with the placebo prematurely stopped the treatment due to an adverse event; only in one case (placebo group), the adverse event was judged as related to the study treatment. A serious adverse event (SAE) occurred more frequently in the galantamine group (11 patients, 14.5%) than in placebo group (4 cases, 6.3%), but only 2 SAE, were considered as related to the study drug. Globally, 7 patients died during the Double Blind Phase of the study (5 patients in the galantamine group and 2 patients in the placebo group), none of the precipitative AE was attributed to study medication or considered unespected in elderly patients with AD and comorbidities. Survival analyisis did not show any statistically significant difference between groups

Conclusions

The results of this study demonstrates that 12-month galantamine treatment (16 mg/day) was able to guarantee a high rate of responders patients and confirmed the data already published concerning changes over time of cognitive function, daily functioning and global functions. Over the 24-month DB phase, galantamine significantly delayed the time to cognitive deterioration of about 6 months compared to placebo group. Galantamine treatment was also safe, and only a minority of patients discontinued the treatment due to an adverse event.
In conclusion, Safety and efficacy data of this study supports the long term use of galantamine as it is well tolerated and effective in delaying time to cognitive deterioration in pts with mild to moderate AD, .

Date of report

May 2007