SYNOPSIS

Issue Date: 17 December 2012

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	Reminyl®, Razadyne™
Name of Active Ingredient(s)	galantamine hydrobromide

Protocol No.: GALALZ3005

Title of Study: A Randomized, Double-blind, Placebo-controlled Trial of Long-term (2-year) Treatment of Galantamine in Mild to Moderately severe Alzheimer's Disease.

NCT No.: NCT00679627

Clinical Registry No.: CR012463

Coordinating Investigator: Klaus Hager, MD - Diakoniekrankenhaus Henriettenstiftung GmbH Schwemannstr 19, [redacted] Germany

Study Center(s): The study was conducted at 127 centers in 13 countries as follows: Czech Republic (7), Estonia (6), France (1), Germany (25), Greece (3), Italy (7), Latvia (1), Lithuania (2), Romania (12), Russia (29), Slovakia (9), Slovenia (3), and Ukraine (22).

Publication (Reference): Hager K, Baseman AS, Han JH, Sano M, and Richards HM. In a 2-Year Placebo-Controlled Randomized Trial, Galantamine-Treated Patients had Lower Mortality Rates and Slower Decline in Cognition and Activities of Daily Living. 2013. Neuropsychopharmacology (supplement). In Press.

Study Period: 19 May 2008 to 20 May 2012. Database lock date: 18 July 2012

Phase of Development: Phase 3b

Objectives: The overall objective of this study was to evaluate the benefits and risks of long-term (over the course of 2 years) treatment with galantamine as compared with placebo in subjects with mild to moderately severe Alzheimer's Disease (AD).

Hypotheses

The efficacy hypothesis was that galantamine 16 to 24 mg/day was superior to placebo in reducing cognitive decline from baseline as measured by the Mini-Mental State Examination (MMSE) over the course of 2 years. [NOTE: Throughout the clinical study report, the MMSE baseline score refers to the value assessed at the screening visit.]

The safety null hypothesis was that the mortality rate in the galantamine 16 to 24 mg/day treatment group was the same (relative risk [RR] =1) as that in the placebo group over the course of 2 years. The alternative hypothesis was that the mortality rate in the galantamine group was higher (RR>1) than that in the placebo group over the course of 2 years.

Efficacy Objectives

The primary efficacy objective was to compare galantamine with placebo in cognitive change from baseline to Month 24 as measured by the MMSE score.

The secondary efficacy objectives were to compare galantamine with placebo in the following: cognitive change from baseline at Month 6 as measured by the MMSE score; change from baseline over the course of 2 years in activities of daily living as measured by the Disability Assessment in Dementia (DAD); health care utilization over the course of 2 years as measured by the time to change in the level of

accommodation using the Assessment of Patient Accommodation Status and Caregiver Burden (APAS-CarB); and a caregiver time spent with the subject over the course of 2 years retrospectively estimated using the APAS-CarB.

Safety Objectives

The primary safety objective was to compare the rate of mortality between subjects randomly assigned to receive galantamine or matching placebo over the course of 2 years. The secondary safety objective was to compare the incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), between subjects randomly assigned to receive galantamine or matching placebo over the course of 2 years.

Methodology: This was a long-term (2-year), randomized, double-blind, placebo-controlled, parallel-group, multicenter study of galantamine versus placebo in subjects with mild to moderately severe AD. Approximately 2,000 subjects were planned to be enrolled in this study and randomly assigned in a 1:1 ratio to receive galantamine controlled release formulation or matching placebo based on a computer-generated randomization schedule.

The study consisted of 3 phases:

- Pretreatment phase included screening period (up to 4 weeks in duration) and baseline assessments (Day 0, Visit 2)
- Treatment phase consisted of 2 periods:
  - Titration period (Days 1 to 84): after the completion of Visit 2, visits occurred every 28 days up to 12 weeks with a visit window of ±7 days.
  - Maintenance period (Months 4 to 24): visits occurred every 3 months (every 90 days) for 21 months with a visit window of ±14 days with the exception of the Month 24 visit, which had a visit window of ±3 days.
- Posttreatment phase included a follow-up telephone contact (Month 25) occurring 1 month after the End-of-Study Visit with a visit window of ±7 days.

During titration period, galantamine 8 mg/day or matching placebo was to be started in the morning for the first 4 weeks, followed by 16 mg/day or matching placebo for the next 4 weeks. The dose of galantamine or placebo could be titrated upwards to 24 mg/day at the Day 56 visit for the next 4 weeks, based on the subject's tolerability. During the maintenance phase, the subject continued to receive the dose achieved at Day 84 until the completion of the Month 24 Visit. The dose of the study drug could be uptitrated from 16 mg/day to 24 mg/day if the subject demonstrated good tolerability, and the investigator believed that the improvement could be enhanced. Similarly, the dose of 24 mg/day at Day 84 could be downtitrated to 16 mg/day, 1 time, based on subject's tolerability. The dose of study drug could not be changed downward to 8 mg/day. The study drug was to be discontinued if the subject could not tolerate a dose of 16 mg/day.

A company-external Data Safety Monitoring Board (DSMB) was commissioned for this study to monitor the progress of the study and to ensure that the safety of subjects was not compromised.

Number of Patients (planned and analyzed): Planned: 2,000 subjects were planned to be enrolled in this study. Analyzed: A total of 2,051 subjects were randomized to study treatment of which 1028 subjects were randomly assigned to the galantamine treatment group and 1,023 subjects were randomly assigned to the placebo treatment group. A total of 2,045 subjects received study drug, of which 1,024 subjects received galantamine and 1,021 subjects received placebo. The numbers of subjects included in the various analysis sets by treatment group are summarized below.

Distribution of Patients by Analysis Set
All Randomized Patients (Study GALALZ3005)

	Placebo	Galantamine	Total
All Randomized Patients	1023	1028	2051
Intent-to-treat [a]	916 (89.5%)	918 (89.3%)	1834 (89.4%)
Per Protocol [b]	867 (84.8%)	877 (85.3%)	1744 (85.0%)
Safety [c]	1021 (99.8%)	1024 (99.6%)	2045 (99.7%)
Intent-to-treat exclude sites [d]	906 (88.6%)	906 (88.1%)	1812 (88.3%)
Per Protocol exclude sites [d]	860 (84.1%)	869 (84.5%)	1729 (84.3%)

[a] Intent-to-treat analysis set is defined as all randomized patients who have at least 1 post-baseline MMSE measure.

[b] Per Protocol analysis set is defined as a subset of ITT analysis set. It excludes patients with major protocol deviations (only those major protocol deviations that potentially affect the efficacy [prohibited conmed, inclusion/exclusion criteria not met, and treatment deviation]).

[c] Safety analysis set includes all randomized and treated patients.

[d] Two sites ([redacted] and [redacted] are excluded from the analysis due to GCP non-compliance.

Note: Percentages are calculated with the number of all randomized patients of each treatment group as the denominator.

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Diagnosis and Main Criteria for Inclusion: Outpatients, men or postmenopausal or surgically sterile women, 45 to 90 years of age, diagnosed with mild to moderately severe, probable or possible AD were included in the study. Subjects presenting with Alzheimer's disease and with or without cerebrovascular disease were also enrolled into the study.

Test Product, Dose and Mode of Administration, Batch No.: Galantamine, equivalent 8 mg, 16 mg, and 24 mg were supplied as controlled-release oral capsules. The details of the study drug lot number and expiration date are provided in the table below.

Packaged Lot Number	Study Drug Contained Bulk Lot Number	Bulk Lot Number	Expiry Date of Bulk Lot Number
353728	8 mg	07I25/F055	February 2010
	16 mg	07I26/F056	February 2010
	24 mg	07I27/F057	February 2010
353729	8 mg	07L04/F055	April 2010
	16 mg	07L04/F056	April 2010
		07I26/F056	February 2010
	24 mg	07L05/F057	May 2010
		07I27/F057	February 2010
354594	8 mg	07L04/F055	April 2010
	16 mg	07L04/F056	April 2010
	24 mg	07L05/F057	May 2010
360211	8 mg	08B13/F055	February 2010
	16 mg	08B15/F056	Feb-10
	24 mg	08B18/F057	February 2010
360863	8 mg	08J06/F055	June 2011
	16 mg	08J07/F056	October 2011
	24 mg	08J08/F057	June 2011
361448	8 mg	08K25/F055	June 2011
	16 mg	08K25/F056	June 2011
	24 mg	08K26/F057	June 2011
361393	8 mg	08K25/F055	June 2011
	16 mg	08J07/F056	October 2011
	24 mg	08K26/F057	June 2011
361936	8 mg	09G07/F055	March 2012
	16 mg	09G09/F056	July 2012
	24 mg	09G14/F057	July 2012

Packaged Lot Number	Study Drug Contained Bulk Lot Number	Bulk Lot Number	Expiry Date of Bulk Lot Number
	8 mg	09G07/F055	March 2012
	16 mg	09G10/F056	July 2012
361937	24 mg	09G14/F057	July 2012
	8 mg	09G07/F055	March 2012
	16 mg	09G08/F056	July 2012
361938	24 mg	09G13/F057	July 2012
	8 mg	09G07/F055	March 2012
	16 mg	09G08/F056	July 2012
363355	24 mg	09G14/F057	July 2012
	8 mg	09G07/F055	March 2012
	16 mg	09G09/F056	July 2012
363356	24 mg	09G13/F057	July 2012
	8 mg	10E26/F055	March 2013
	16 mg	5330.5	March 2013
363580	24 mg	5330.6	March 2013
	8 mg	10E26/F055	March 2013
	16 mg	5330.5	March 2013
363684	24 mg	5330.6	March 2013
	8 mg	10E26/F055	March 2013
	16 mg	5330.5	March 2013
363685	24 mg	5330.6	March 2013
	8 mg	10E26/F055	March 2013
	16 mg	5330.5	March 2013
364604	24 mg	5330 6 5330.6	March 2013
	8 mg	10E26/F055	March 2013
	16 mg	5330.5	March 2013
365182	24 mg	5330.6	March 2013

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, matching galantamine oral capsules in size and appearance were supplied. The details of the placebo lot number and expiration date are provided in the table below.

Packaged Lot Number	Study Drug Contained Bulk Lot Number	Bulk Lot Number	Expiry Date of Bulk Lot Number
353728	Placebo	07I24/F094	October 2010
353729	Placebo	07L03/F094	March 2010
		07I24/F094	October 2010
354594	Placebo	07L03/F094	March 2010
		08B19/F094	February 2011
360211	Placebo	08B19/F094	February 2011
360863	Placebo	08I08/F094	September 2011
361448	Placebo	08I08/F094	September 2011
361393	Placebo	08I08/F094	September 2011
361936	Placebo	09G06/F094	July 2012
361937	Placebo	09G06/F094	July 2012
361938	Placebo	09G06/F094	July 2012
363355	Placebo	09G06/F094	July 2012
363356	Placebo	09G06/F094	July 2012
363580	Placebo	5330.4	May 2015
363684	Placebo	5330.4	May 2015
363685	Placebo	5330.8	June 2015
364604	Placebo	5330.8	June 2015
365182	Placebo	5330.8	June 2015

Duration of Treatment: The total duration of the study, including the pretreatment phase, treatment phase, and posttreatment phase, was approximately 25.5 months for each subject.

Criteria for Evaluation:

Efficacy Evaluation: Efficacy was evaluated based on the following assessments:

Mini-Mental State Examination: This is a validated, brief examination that rated subjects on orientation (total score, 10), registration (total score, 3), attention (total score, 5), calculation (total score, 5), recall (total score, 3), and language (total score, 9). The maximum score is 30 (only the higher of the two scores for attention and calculation [each with a maximum score of 5] was used). A higher score for MMSE compared with baseline indicated less impairment.

Disability Assessment in Dementia: This is a well known, validated, disability assessment scale that collected information regarding the ability of a subject to initiate, plan, organize, and perform activities of daily living, as based on a structured interview with the caregiver. The following 10 categories of activity were assessed: hygiene, dressing, continence, eating, meal preparation, telephoning, going on an outing, finance and correspondence, medications, and leisure and housework. A maximum score of 13 for initiation, 10 for planning and organizing and 17 for effective performance that yield a total maximum score of 40. These scores were normalized to a scale of 100 for analysis. The items were scored as 'performed at least once' or 'not performed' during the prior 2 week period. When a subject had no opportunity to perform an item, the item was scored as not applicable. A higher score or percentage of items that were to be performed in DAD assessment represented fewer disabilities in carrying out activities of daily living, while a lower percentage indicated an increase in disabilities.

Assessment of Patient Accommodation Status and Caregiver Burden: The health-care utilization and caregiver burden endpoints were combined into one assessment instrument, the APAS-CarB, Part 1 and Part 2, to minimize the time required for completing the instrument and to focus on quantifiable measures of caregiver burden such as time and level of supportive care or accommodation. The items were scored for the recall period from the last 3 months for the subject type of accommodation and the last week for time spent by the caregiver assisting the subject. The time to change in residential status was considered clinically important, while a change to institutionalize was considered a significant decline.

Safety Evaluation: The safety assessment was based on reported adverse events (AEs), vital sign measurements (blood pressure, pulse rate, respiratory rate and temperature), body weight, physical and neurological examinations and vital status.

A 10 mL blood sample was collected at the baseline visit or in a later stage from subjects who had consented to participate in the pharmacogenomics component of the study to allow for pharmacogenomic research, as necessary.

Other Evaluations Done at Screening: Clinical laboratory tests (including hematology, chemistry, urinalysis, beta-human chorionic gonadotropin [β-hCG] and urine pregnancy) and electrocardiogram (ECG) were done.

Statistical Methods:

Sample Size Determination: A sample size of 1,000 subjects per group was chosen to achieve greater than 99% power to detect a 0.8 difference in MMSE between 2 treatment groups based on an MMSE standard deviation of 3.1. A mortality rate for AD subjects followed for 2 years while receiving placebo was not available. Based on 6-month studies, it was estimated that a 3% placebo mortality rate and a sample size of 1,000 subjects per group were to be used to ensure sufficiently high study power (greater than or equal to 80%) to detect an RR equal to 2.0.

For the planned sample size of 1,000 subjects per arm, to detect an RR equal to 2.0 with 80% power, EAST 4 (a statistical software for planning clinical studies with group sequential design) calculated that 5 analyses were to be performed when the total number of events (deaths) reached 16, 32, 48, 64, and 80, using the following settings: power equal to 80%; 2-year placebo mortality rate equal to 3%; and 5 analyses (4 interim and 1 final analysis) performed using an overall alpha level equal to 0.05. The Lan-DeMets boundary was used for rejecting the null hypothesis of no treatment-effect on the mortality rate, and for stopping for futility based on low conditional power.

Efficacy: The primary efficacy endpoint analysis was the change from baseline in the MMSE score at Month 24 for subjects treated with galantamine compared with those treated with matching placebo.

An intent-to-treat (ITT) with last observation carried forward (LOCF) approach was used for the primary analysis. The ITT analysis set included all randomized subjects who had at least 1 postbaseline MMSE measure. An analysis of covariance model was used to compare the treatment groups and included treatment and study site as factors, and the baseline MMSE value as a covariate. The same approach was used for analyzing the MMSE at Month 6.

A mixed-effect modeling analysis was carried out as a supportive analysis to address missing data and to explore the time course of the treatment effect. The covariance among measures was to be modeled using an unstructured covariance matrix. The model included treatment, study center, time, and time-by-treatment interaction along with a random subject effect and baseline value as a covariate. The mixed-effect modeling analysis was based on the observed case (OC) data, ie, with no imputation of missing values.

The DAD and APAS-CarB scores were analyzed using the same statistical approach as that used for the MMSE. Institutionalization status was summarized.

All statistical tests for efficacy data were performed at a 2-sided significance level of 0.05. No interim analysis of efficacy data was planned. However, if the DSMB considered it necessary, efficacy data were to be provided for the DSMB to make a benefit-risk assessment.

Safety: All safety analyses were based on the data from the safety analysis set that included all randomized and treated subjects. Mortality data were analyzed by the time-to-event (death) analysis method using the Cox Regression Model based on the randomized treatment group. Additional analyses of mortality data included: a survival analysis of death cases evaluated using Kaplan-Meier survival

curves that occurred within 30 days of the last dose of study drug; an analysis of fatal AEs (TEAEs leading to death) that occurred while subjects were exposed to study drug; and a Cox proportional hazards regression model, which provided a point estimate and 95% confidence interval (CI) for the hazard ratio (HR) comparing mortality between the treatment groups and explored any effect of covariates on mortality and the interaction between the treatment and covariates. Candidates for these covariates included age, sex, and baseline MMSE. In addition, the Cox proportional hazards regression model with time-dependent covariates was used to explore the effect of cardiovascular and pulmonary AEs on mortality.

Interim Analysis: An Interim Safety Analysis was to be performed based on the number of events, and results were provided to the DSMB at the time when the total number of deaths reached 16, 32, 48, 64, and 80 or at the end of the study.

Adverse Events: Adverse event data were summarized by treatment group, and 95% CIs were provided. A specific AE or AE category was analyzed using the time-to-event approach as planned for the mortality data.

Other Safety Data: Change from baseline in vital signs, weight, and the physical and neurological examination findings obtained over the course of the 2-year study were summarized.

RESULTS:

STUDY POPULATION:

Study and Treatment Information and Baseline Characteristics

Of the 2,051 subjects who were randomized, a total of 2,045 subjects received study drug and were included in the safety analysis set. A total of 661 subjects completed the 2-year study (339 [33.1%] subjects in the galantamine treatment group and 322 [31.5%] subjects in the placebo treatment group). Of the 1,384 subjects who withdrew from the study, 830 (60%) subjects withdrew due to early study closure when the DSMB recommended stopping the study early. A total of 340 subjects (galantamine treatment group: 172 subjects [16.8%]; placebo treatment group: 168 subjects [16.5%]) withdrew due to subject choice (withdrawal of consent). Ninety-six subjects were withdrawn from the study due to AEs (galantamine treatment group: 53 [5.2%] subjects; placebo treatment group: 43 [4.2%] subjects). A total of 70 subjects were withdrawn from the study due to death and the number of subjects who died during the study was greater in the placebo treatment group (41 [4.0%]) as compared with the galantamine treatment group (29 [2.8%]) (see below Table).

Study Completion/Withdrawal Information
Safety Analysis Set (Study GALALZ3005)

	Placebo	Galantamine
Number of subjects	1021	1024
Completed [a]	322 (31.5%)	339 (33.1%)
Withdrawn	699 (68.5%)	685 (66.9%)
Subject Choice (Subject Withdrew Consent)	168 (16.5%)	172 (16.8%)
Adverse Event	43 (4.2%)	53 (5.2%)
Death	41 (4.0%)	29 (2.8%)
Lost To Follow-Up	22 (2.2%)	26 (2.5%)
Other	425 (41.6%)	405 (39.6%)

[a] Subject completed the trial as per protocol.
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: The number of death represented in this table is different from the final numbers used in the mortality analysis as these numbers were calculated from total number of withdrawal subjects.
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A total of 408 (20%) subjects were reported with major protocol deviation (210 [20.5%] subjects in the galantamine treatment group; 198 [19.4%] subjects in the placebo treatment group). The most frequently reported protocol deviation (in 66 [3.2%] subjects), was "selection criteria not met."

During the study, a total of 722 subjects received study drug for more than 24 months (galantamine treatment group: 377 [36.8%] subjects; placebo treatment group: 345 [33.8%] subjects). The mean duration of exposure to the study drug among the subjects receiving galantamine and placebo was similar (16.08 months vs 15.88 months).

The demographic and baseline characteristics of all the subjects were consistent generally comparable between both the treatment groups. The majority of the subjects were female (64.8%) and white (99.9%). The median age of subjects was 74 years (range: 45-92 years) with a mean baseline body weight of 70.0(±12.89) kg. The mean baseline MMSE score was 19 (±4.08), and the mean baseline DAD scores was 61.4 (±21.35), representing a population with moderate AD.

There were no meaningful differences observed for Alzheimer Dementia history between the galantamine and the placebo treatment groups.

EFFICACY RESULTS:

Of a total of 2,045 subjects who were treated and included in the safety population, 1,834 (916 in the placebo group and 918 in the galantamine treatment group) were included in the ITT analysis set, and 1,744 (867 in the placebo treatment group and 877 in the galantamine treatment group) were included in the PP analysis set. After exclusion of the subjects from Sites [redacted] and [redacted] because of GCP issues, the ITT population included 1,812 subjects (906 subjects in each group), and the PP population included 1,729 subjects (860 in the placebo treatment group and 869 in the galantamine treatment group).

Primary Efficacy Analysis: The mean MMSE scores at baseline were 19 for both the placebo and galantamine treatment groups, and the mean score at Month 24 LOCF deteriorated to 16.9 and 17.5, respectively. There was a significantly greater cognitive impairment in the placebo treatment group compared with the galantamine treatment group based on the change from baseline in MMSE at Month 24 (-2.14 vs -1.41, respectively; $p<0.001$). The analysis of mean change in MMSE from baseline to Month 24 based on the PP population was consistent with the primary efficacy analysis. A sensitivity analysis was conducted using a mixed model repeated measures and OC approach, and the results were consistent with the primary LOCF analysis. Also consistent with the results of the primary LOCF analysis were the results of an analysis of mean change in MMSE from baseline to Month 24 for subjects who entered the maintenance period, based on both the ITT population.

Major Secondary Analyses: A statistically significant increase in mean change was observed from baseline in MMSE scores at Month 6 in the galantamine treatment group (0.15) compared with the placebo treatment group (-0.28), $p<0.001$ which showed greater improvement in cognitive impairment in the galantamine treatment group than placebo treatment group. The analysis of mean change in MMSE from baseline to Month 6 based on the PP population was consistent with the analysis based on the ITT population.

The mean DAD scores (±SD) at baseline were 61.04 (±21.118) for subjects treated with placebo and 61.22 (±21.230) for subjects treated with galantamine. The mean scores at Month 24 LOCF were 50.44 (±25.675) for subjects treated with placebo and 52.99 (±24.999) for subjects treated with galantamine. The change from baseline to Month 24 LOCF was significantly worse in the placebo treatment group compared to the galantamine treatment group (-10.8 vs -8.2, respectively; $p=0.002$). The analysis of mean change in DAD from baseline to Month 24 based on the PP population was consistent with the analysis based on the ITT population.

Changes in the various types of accommodation over the course of the 2-year study were generally small, with small differences between the placebo and galantamine treatment groups. The majority of subjects in

both the treatment groups resided at home with a relative or friend at all 3 timepoints (baseline, Month 12, and Month 24): 62.1%, 61.4%, and 55.3% in the placebo treatment group and 62.8%, 61.8%, and 60.1% in the galantamine treatment group. Relatively few subjects resided in nursing homes at the 3 timepoints: 5.8%, 6.8%, and 8.6% in the placebo treatment group and 4.7%, 7.3%, and 6.6% in the galantamine treatment group.

The percentage of subjects institutionalized during the course of the study was small in both the treatment groups (≤ 2.1% at any visit). There was no statistically significant difference between the 2 treatment groups in the percentage of subjects institutionalized at any visit. In both groups the number of subjects institutionalized increased from baseline to Month 6: from 1 (0.1%) to 14 (1.7%) in the placebo treatment group and from 0 to 9 (1.1%) in the galantamine treatment group. Between Month 6 and Month 24 there was no apparent pattern of increase or decrease in the percentage of subjects institutionalized in either treatment group.

The majority of caregivers (75%-80%) in both the treatment groups lived with the person cared for at each of the 3 reported visits (at baseline, Month 12, and Month 24). There was no apparent difference between the 2 treatment groups, nor was there any apparent pattern of change over the course of the 2-year study in either treatment group in the percentage of caregivers who lived with the person cared for.

Other Secondary Analyses: For each MMSE subscale item, the mean score decreased (ie, worsened) from baseline at most time points over the course of the 2-year study in both treatment groups. Most of the mean decreases from baseline over the course of the study were significantly greater with placebo than with galantamine.

For each DAD subscale item, the decreases (worsening) from baseline were greater at both timepoints with placebo than with galantamine. Nearly all of these differences between the 2 treatments were significant in favor of galantamine over placebo.

SAFETY RESULTS:

Mortality data: At the final interim mortality analysis (conducted when the study reached the prespecified milestone of 80 deaths), the DSMB recommended early termination of the study due to an imbalance of deaths between the treatment groups. In the final analysis of the primary safety endpoint, there were a total of 89 deaths; 56 (5.5%) deaths in the placebo treatment group and 33 (3.2%) deaths in the galantamine treatment group. This represents a significantly higher rate of death in placebo treatment group compared with the galantamine treatment group (HR and 95% CIs were 0.58 [0.37-0.89]; p=0.011). The subjects in the galantamine treatment group showed better survival (prognosis) than the subjects in the placebo treatment group. The beneficial effects of the galantamine over the placebo were greater.

Adverse events: The overall proportion of subjects with at least 1 TEAE was higher in the galantamine treatment group (54% of subjects) as compared with the placebo treatment group (48.6% of subjects). In comparing the subgroups by age, the incidences of TEAEs increased generally in proportion to the age of the subjects in both the treatment groups. When compared by gender, the incidence of TEAEs was greater in the female subjects as compared with the male subjects in both the treatment groups. The majority of the TEAEs reported in the study were mild or moderate in severity. The incidence of severe TEAEs was similar between the galantamine treatment group (101 severe TEAEs) and the placebo treatment groups (106 severe TEAEs). The majority of the TEAEs in the study were considered as not related or doubtfully related to the study drug. There were 46 very likely-related, 98 probably-related and 443 possibly-related TEAEs reported in the study. The number of subjects with TEAEs leading to study treatment discontinuation or study drug dose modification/interruption was higher in the galantamine treatment group as compared with the placebo treatment group.

The overall incidence of TESAEs was similar in both the treatment groups. Overall, there was no discernable pattern of SAEs observed in both the treatment groups.

The overall incidences of TEAEs leading to treatment discontinuation, TEAEs leading to death, TESAEs, and overall death in the study were low.

The Overall Summary of TEAEs is summarized in the Table below.

Overall Summary of Treatment Emergent Adverse Events; Safety Analysis Set (Study GALALZ3005)

	Placebo	Galantamine
Number of subjects	1021	1024
Subjects with treatment-emergent adverse event	496 (48.6%)	553 (54.0%)
Subjects with treatment-emergent drug-related adverse event	136 (13.3%)	250 (24.4%)
Treatment-emergent adverse events leading to treatment discontinuation	66 (6.5%)	87 (8.5%)
Treatment-emergent drug-related adverse events leading to treatment discontinuation	23 (2.3%)	45 (4.4%)
Treatment-emergent adverse events leading to death	47 (4.6%)	31 (3.0%)
Treatment-emergent serious adverse events	123 (12.0%)	129 (12.6%)
Treatment-emergent drug-related serious adverse events	10 (1.0%)	8 (0.8%)
Treatment-emergent serious adverse events leading to treatment discontinuation	34 (3.3%)	27 (2.6%)
Treatment-emergent serious adverse events leading to hospitalization	88 (8.6%)	113 (11.0%)
Deaths [a]	45 (4.4%)	30 (2.9%)

[a] Deaths occurred during study treatment or within 30 days after treatment discontinuation.
Note: Treatment-emergent adverse events (TEAEs) are defined as adverse events with onset date on or after randomization and on or before the end of the REACH. This REACH is defined as the following -- for AE's with onset date within therapeutic reach (ie 3 days) or SAE's/deaths with onset date within 30 days, inclusive, after end of treatment.
Note: Percentages are calculated with the number of subjects in safety analysis set of each treatment group as the denominators.

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Overall, there were no clinically relevant differences observed in the mean values of vital signs from baseline between the two treatment groups. The subjects in the galantamine treatment group had higher rate of TEAEs which were related to vital signs compared to placebo treatment group.

No clinically meaningful changes from baseline during the study were observed in physical and neurological findings across both the treatment groups.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): Efficacy and safety of galantamine in subjects with AD for long term use was well demonstrated. Mortality was statistically significantly lower in subjects treated with galantamine compared with subjects treated with placebo for 2 years.

The subjects in the galantamine treatment group showed better survival (prognosis) than the subjects in the placebo treatment group. The beneficial effects, ie slowing of cognitive decline, of galantamine over placebo persisted over the 2-year time course of this study.