NOTE: This is a sample placeholder document, to be replaced by summary specific to the CST SDTM and ADaM sample study.

STUDY SYNOPSIS

Name of Sponsor: CDISC Pilot Project

Name of Finished Product: Transdermal Xanomeline

Name of Active Ingredient: Xanomeline

Case Study Title:
Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's disease

Investigators and Study Centers:
This study was conducted at 17 centers. Due to the nature of this CDISC Pilot Project, a list of investigators is not provided.

Publications: Not applicable

Study Period: 06 July 2012 to 05 March 2015

Development Phase: Phase 2

Objectives:
The objectives of the study were to evaluate the efficacy and safety of transdermal xanomeline, 50 cm^2 and 75 cm^2, and placebo in subjects with mild to moderate Alzheimer's disease.

Methodology:
This was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. Subjects were randomized equally to placebo, xanomeline low dose, or xanomeline high dose. Subjects applied 2 patches daily and were followed for a total of 26 weeks.

Number of Subjects Planned:
300 subjects total (100 subjects in each of 3 groups)

Number of Subjects Enrolled:
254 subjects were randomized (86 placebo, 84 xanomeline low dose, 84 xanomeline high dose)

Sex: 111 (44%) Male; 143 (56%) Female

Mean (SD) Age: 75.1 (8.25) years

Ethnicity (Race): 218 (86%) Caucasian; 23 (9%) African Descent; 12 (5%) Hispanic; 1 (<1%) Other

Diagnosis and Main Criteria for Eligibility:
Subjects were males or females of non-childbearing potential, 50 years of age or older, had probable Alzheimer's disease according to the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and an Mini-Mental State Examination (MMSE) score of 10 to 23.

Investigational Product, Dose and Mode of Administration, Batch Number:
Xanomeline transdermal patches of 50 cm_2 or 25 cm_2 in area, with 54 mg and 27 mg of xanomeline, respectively. Two patches were applied daily. Xanomeline high dose group received an active patch of each size for a total dose of 81 mg and the xanomeline low dose received an active large patch and a placebo small patch for a total dose of 54 mg. Due to the nature of this CDISC Pilot Project, batch numbers are not provided in this study report.

Duration of Treatment: 26 weeks of treatment

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo transdermal patches of 50 cm_2 or 25 cm_2 in area. Placebo group received a placebo patch of each size. Due to the nature of this CDISC Pilot Project, batch numbers are not provided in this study report.

Criteria for Evaluation:

Primary Efficacy Endpoints:
- Alzheimer's Disease Assessment Scale - Cognitive Subscale, total of 11 items [ADAS-Cog (11)] at Week 24
- Video-referenced Clinician's Interview-based Impression of Change (CIBIC+) at Week 24

Secondary Efficacy Endpoints:
- ADAS-Cog (11) at Weeks 8 and 16
- CIBIC+ at Weeks 8 and 16
- Mean Revised Neuropsychiatric Inventory (NPI-X) from Week 4 to Week 24

Safety Endpoints:
- Adverse events
- Vital signs (weight, standing and supine blood pressure, heart rate)
- Laboratory evaluations

Statistical Methods:

Unless otherwise noted, hypothesis testing was evaluated at a significance level of 0.05. Summary statistics for continuous variables included the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Summary statistics for the categorical variables included frequency and percentage.

The number of subjects randomized, the number of subjects in each analysis dataset, and the disposition of subjects were tabulated by treatment group. Specific reasons for early study discontinuation (protocol completed, lack of efficacy, and adverse event) were compared using a Fisher's exact test.

The baseline characteristics were summarized by treatment group and across all treatment groups. The treatment groups were compared by analysis of variance (ANOVA) for continuous variables and by Pearson's chi-square test for categorical variables.

The primary analysis of the ADAS-Cog (11) or CIBIC+ at Week 24 used the efficacy population with LOCF imputation for any missing values at Week 24. For ADAS-Cog (11), an analysis of covariance (ANCOVA) model was used to test for dose response with the baseline score, site, and treatment included as independent variables. A supportive analysis for the ADAS-Cog (11) used a likelihood-based repeated measures (MMRM) analysis. For CIBIC+, an ANOVA model was used to test for dose response with site and treatment included as independent variables. Similar analyses were performed at Weeks 8 and 16 for ADAS-Cog (11) and CIBIC+. Summary statistics for ADAS-Cog (11) were also generated for each visit using the efficacy population with LOCF imputation.

The primary analysis of mean NPI-X total score from Week 4 to Week 24 used the efficacy population. For this endpoint, an ANCOVA model was used to test for dose response with the baseline score, site, and treatment included as independent variables.

Average daily dose and cumulative dose at end of study was computed for each subject based on the planned dose and the actual number of days in the study and was summarized for each treatment group.

Treatment emergent adverse events and serious adverse events were summarized by system organ class (SOC) and preferred term (PT). The incidence of treatment emergent events grouped under preferred terms for each active treatment were compared to placebo using Fisher's exact test. Additional analysis of dermatological adverse events was conducted. The time to the first dermatological event was compared across the treatment groups using Kaplan-Meier methods.

Hematology and clinical chemistry values were summarized at each visit week. The number of subjects with no abnormal measure during treatment and those with at least one abnormal measure during treatment were summarized for each lab analyte. Fisher's exact test was used to analyze the incidence of abnormal (high or low)

measures during the post-randomization phase. A display summarizing shifts from baseline by week in terms of abnormality based on threshold range was provided. The data were summarized comparing baseline and on drug categorization for each treatment group for each week for each laboratory analyte. Shift tables summarizing whether a subject's status changed from baseline during the treatment period were provided for changes based on threshold ranges and changes based on Hy's Law. Cochran-Mantel-Haenszel (CMH) tests, stratifying by status at baseline, were performed.

Vital sign data and weight were summarized by treatment group. The number and percent of subjects receiving each concomitant medication were summarized.

Summary of Results:

Disposition:
A total of 254 subjects were randomized and entered the double-blind treatment phase. The number of subjects randomized to each treatment arm was: 86 to placebo, 84 to the xanomeline low dose treatment group and 84 to the xanomeline high dose treatment group. Of the 254 subjects randomized to treatment, 118 completed the treatment phase (Week 24), and 110 completed the study through Week 26. A statistically significantly ($p < 0.0001$) higher number of subjects in the xanomeline low dose and high dose groups (67% and 64%, respectively) prematurely discontinued from the study prior to Week 24 as compared to the placebo group (30%). The most common reason for discontinuation was adverse event (9% placebo subjects, 52% xanomeline low dose subjects, 46% xanomeline high dose subjects), with a statistically significant association between discontinuation due to adverse event and treatment group ($p < 0.0001$).

Efficacy Results:
A statistically significant dose response was not seen for either of the primary efficacy endpoints, changes from baseline in ADAS-Cog (11) at Week 24 and CIBIC+ at week 24. Adjusted means for these 2 endpoints were similar for all 3 treatment groups. Additional analyses at earlier time points showed similar results. Subgroup analyses by gender, a sensitivity analysis for missing data, and a repeated measures analysis for ADAS-Cog (11) also indicated lack of treatment response. The secondary efficacy endpoint of the mean NPI-X values from Week 4 through Week 24 also did not demonstrate a statistically significant dose response.

Safety Results:
Over 90% of subjects receiving active therapy reported at least 1 adverse event compared to 75.6% of subjects receiving placebo. This difference is due largely to a disproportionate number of dermatologic type events that occurred in the xanomeline treatment groups. Approximately 73% of the subjects in either of the xanomeline groups experienced at least one dermatologic adverse event of interest compared to 33.6% of the placebo subjects. There was a statistically significant difference ($p < 0.001$) in the time to first dermatologic event between the treatment groups. There were 3 deaths (2 in placebo group, 1 in the xanomeline low dose group) observed during the study. None

of the deaths were judged related to treatment. Aside from the deaths, there were 3 serious adverse events reported in 3 subjects (2 in xanomeline high dose and 1 in the xanomeline low dose group) and all were related to the nervous system.

The association between treatment group and the number of abnormal values beyond the normal range was significant for three laboratory analytes: albumin ($p = 0.042$), urea nitrogen ($p = 0.023$), and eosinophils ($p = 0.001$). The association between clinically significant changes from the previous visit and treatment was statistically significant for aspartate aminotransferase ($p = 0.045$) and eosinophils ($p = 0.010$). The analysis of shifts from baseline to most abnormal value could not be calculated on 19 of the analytes. Of the remaining 11 analytes, only eosinophils showed a statistically significant association with treatment group ($p = 0.044$). There was no significant association with treatment group in the Hy's law analyses examining shifts in transaminase levels, and transaminase and total bilirubin levels between baseline values and values while on treatment.

Changes from baseline in vital signs (SBP, DBP, and pulse), at the Week 24 and end of treatment assessments, were generally small decreases. Changes from baseline in weight, at the Week 24 and end of treatment assessments, however, were generally small with no treatment-related pattern of increases or decreases.

Conclusions:
A statistically significantly higher proportion of subjects in the active treatment groups withdrew prematurely from the study as compared to the placebo group. This is largely due to the higher proportion of subjects in the active treatment groups experiencing a dermatologic event and subsequently resulting in premature withdrawal from the study. This further hindered the study's ability to demonstrate efficacy.

A statistically significant dose response was not seen for both of the primary efficacy endpoints, change from baseline in ADAS-Cog (11) at Week 24 and CIBIC+ at Week 24, and for the secondary efficacy endpoint, mean NPI-X values from Week 4 to Week 24. Adjusted means for all 3 endpoints were similar across all treatment groups.

There were an increased number of dermatologic adverse events reported in the active treatment groups as compared to the placebo group. There were 3 serious adverse events. In addition, there were 3 deaths that were deemed unrelated to treatment.

For the laboratory data, subjects in both the xanomeline low and high dose groups showed more observations above normal range than the placebo group. Albumin was more often lower than the normal range for subjects in the placebo and xanomeline low dose group. Subjects in the xanomeline treatment groups had statistically significantly more values above the normal range than subjects in the placebo group for both urea nitrogen and eosinophils. There was a statistically significant association between clinically significant changes from the previous visit and treatment group for aspartate aminotransferase and eosinophils. Shifts from baseline for eosinophils were statistically significant with both xanomeline treatment groups showing more changes from normal

to above normal than the placebo group. There was no significant association with treatment group in the Hy's law analysis examining shifts in liver function tests between baseline values and values while on treatment.

There were only minor changes from baseline in vital signs and weight at Week 24.

Report Date: 27 June 2006