1.   TITLE PAGE

Project:	CDISCPILOT01 – Initial Case Study of the CDISC SDTM/ADaM Pilot Project
Case Study Title:	Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease
Investigational Product:	Xanomeline Transdermal
Indication:	Alzheimer's Disease
Brief Description of Case Study:	This study was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. 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.
Study Sponsor:	CDISC Pilot Project
Protocol No.:	CDISCPILOT01
Study Phase:	2
Study Initiation Date:	06 July 2012 (Date of first subject visit)
Study Completion Date:	05 March 2015 (Date of last subject completion)
Principal Investigators	Due to the nature of this CDISC Pilot Project, a list of principal investigators is not provided in this study report.
Good Clinical Practice	This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	27 June 2006

2.   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

3.   TABLE OF CONTENTS

3.1.   List of Tables

3.2.   List of Figures

4.   LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADaM	Analysis Dataset Model
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
AE	adverse event
ALT	alanine aminotransferase (also known as SGPT [serum glutamic pyruvic transaminase])
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase (also known as SGOT [serum glutamic oxalacetic transaminase])
BMI	body mass index
BPM	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CIBIC+	Video-referenced Clinician's Interview-based Impression of Change
cm^2	centimeters squared – measure of area
CMH	Cochran-Mantel-Haentzel
CNS	central nervous system
DBP	diastolic blood pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase (also known as GGPT [gamma glutamyl transpeptidase]; SGGT [serum gamma gutamyl transferase]; YGGT)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
kg	kilograms
LLN	lower limit of normal
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligrams
mmHg	millimeters of mercury
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (developed criteria for the diagnosis of Alzheimer's disease)
NPI-X	Revised Neuropsychiatric Inventory
PT	preferred term

SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	system organ class
TTS	Transdermal Therapeutic System
ULN	upper limit of normal
XAN	xanomeline

5.   ETHICS

5.1.   Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

5.2.   Ethical Conduct of the Study

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

5.3.   Subject Information and Consent

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

6.   INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

7.   INTRODUCTION

The objective of the CDISC SDTM/ADaM Pilot Project is to demonstrate the effective transformation of legacy data into CDISC SDTM domains and ADaM datasets and their associated metadata. The Project team will produce a "pilot submission" that will be delivered to FDA reviewers for their evaluation in a mock review, assessing whether data submitted to the FDA using the CDISC Standard will meet the needs and expectations of both medical and statistical FDA reviewers. This abbreviated study report documents the analysis results of the legacy data for this first pilot submission.

The legacy data being used in CDISCPILOT01 were provided by Eli Lilly and Company (Legacy Sponsor) for the purposes of this CDISC Pilot Project. The data were de-identified and documents were redacted prior to release to the CDISC Pilot Project team. De-identification included changing dates and shifting them into the future. All chronological relationships and sequences were maintained within the data elements for a subject (e.g., no change in the relationship of timing of adverse events with respect to dosing). The submission did not reproduce all of the Legacy Sponsor's analyses and reports. Instead only the more common elements of a submission were addressed. These included safety data, the primary efficacy endpoints and a few secondary efficacy endpoints. Deviations from the protocol-specified analyses are described in the statistical analysis plan created specifically for this study as part of the CDISC Pilot Project (Appendix 9).

8.   STUDY OBJECTIVES

The primary objectives of this study were:

- To determine if there is a statistically significant relationship (overall Type 1 error rate, $\alpha=0.05$) between the change in both the ADAS-Cog (11) and CIBIC+ scores, and drug dose (0, 50 cm^2 [54 mg], and 75 cm^2 [81 mg]).

- To document the safety profile of the xanomeline TTS.

A secondary objective of this study was:

- To assess the dose-dependent improvement in behavior. Improved scores on the Revised Neuropsychiatric Inventory (NPI-X) will indicate improvement in these areas.

9.   INVESTIGATIONAL PLAN

9.1.   Overall Study Design and Plan

This study was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. 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.

Xanomeline or placebo was administered daily in the morning, with the application of two adhesive patches, one 50 cm^2 in area, the other 25 cm^2 in area. Doses were measured in terms of the xanomeline base, and were 54 mg for the 50 cm^2 patch and 27 mg for the 25 cm^2 patch. Placebo was identical in appearance to the primary study material. The total doses being compared are therefore 0 (both patches placebo), 54 mg (large patch active drug, small patch placebo), and 81 mg (both patches active drug). The treatment groups referred to throughout this report will be "xanomeline high dose," "xanomeline low dose," and "placebo".

Subjects were males or females of non-childbearing potential, 50 years of age or older, had probable mild to moderate Alzheimer's disease according to the NINCDS-ADRDA criteria, and an MMSE score of 10 to 23. The duration of treatment was 26 weeks, with 24 weeks of active treatment. Approximately 300 subjects were to be enrolled and randomized equally to xanomeline high dose, xanomeline low dose, or placebo.

Subjects were assessed for efficacy using the Alzheimer's Disease Assessment Scale - Cognitive Subscale of 11 items [ADAS-Cog (11)], video-referenced Clinician's Interview-based Impression of Change (CIBIC+), and Revised Neuropsychiatric Inventory (NPI-X). Safety assessments include reporting of adverse events, laboratory values, and vital signs.

The schema for this study is illustrated in Figure 9-1. Additional study design details are described in the study protocol (Appendix 1).

Figure 9-1. Study Schema

9.2.   Discussion of Study Design, Including the Choice of Control Groups

This study was designed to evaluate the safety and efficacy of the low and high dose xanomeline relative to placebo in subjects with mild to moderate Alzheimer's disease. Subjects were randomized to 1 of 3 treatment groups: placebo, xanomeline low dose and xanomeline high dose. Two patches were administered to each subject in a double-blind fashion to minimize investigator and subject bias. Placebo was the control group used in this study.

9.3.   Selection of Study Population

Subjects were included in the study if they were males or females of non-childbearing potential, 50 years of age or older, had probable mild to moderate Alzheimer's disease according to the NINCDS-ADRDA criteria, had an MMSE score of 10 to 23, had a Hachinski Ischemic Scale score of ≤ 4, and CNS imaging compatible with Alzheimer's disease within the past year. Subjects were excluded from the study if they had previously participated in a xanomeline study, had used an investigational or approved Alzheimer's therapeutic medication within 30 days of prior to enrollment, serious illness requiring hospitalization within 3 months prior to screening, have certain concurrent or historical medical conditions, or were concurrently or historically using certain medications. Details of the inclusions and exclusion criteria are included in the study protocol (Appendix 1).

9.4.   Treatments

Subjects were randomized to 1 of the 3 treatment groups: placebo, xanomeline low or high dose. Xanomeline or placebo was administered daily in the morning, with the application of two adhesive patches, one 50 cm^2 in area, the other 25 cm^2 in area. Doses were measured in terms of the xanomeline base, and were 54 mg for the 50 cm^2 patch and 27 mg for the 25 cm^2 patch. Placebo was identical in appearance to the primary study material. Xanomeline high dose group received an active patch of each size and the xanomeline low dose received an active large patch and a placebo small patch. The total doses being compared are therefore 0 (both patches placebo), 54 mg (large patch active drug, small patch placebo), and 81 mg (both patches active drug). The treatment groups referred to throughout this report will be "xanomeline high dose," "xanomeline low dose," and "placebo".

9.5.   Efficacy and Safety Variables

Efficacy in this study was assessed using Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog), Video-referenced Clinician's Interview-based Impression of Change (CIBIC+), and Revised Neuropsychiatric Inventory (NPI-X). The ADAS-Cog is an established measure of cognitive function in Alzheimer's disease. This study will specifically use an 11-item subscale of the ADAS-Cog, denoted as ADAS-Cog (11). The CIBIC+ is an assessment of the global clinical status relative to baseline and utilizes semi-structured interviews with the subject and the caregiver. The NPI-X is an assessment of change in psychopathology in subjects with dementia and is administered to the designated caregiver. Methods for scoring the ADAS-Cog (11), CIBIC+, and NPI-X are noted in the statistical analysis plan (Appendix 9).

Safety in this study was assessed with the reporting of adverse events, laboratory measures, and vital signs. The list of laboratory measures is noted in the study protocol (Appendix 1).

The schedule of efficacy and safety assessments is listed in the study protocol (Appendix 1). Additional efficacy and safety assessments were utilized in this protocol, but were not included in this study report due to the nature of this CDISC Pilot Project.

9.6.   Data Quality Assurance

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

9.7.   Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1.   Statistical Methods

This section summarizes the statistical methods used to analyze the data for this report. 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. Additional details can be found in the statistical analysis plan (Appendix 9).

9.7.1.1.   Endpoints

The primary efficacy endpoints were:
- 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

The secondary efficacy endpoints were:
- Alzheimer's Disease Assessment Scale - Cognitive Subscale, total of 11 items [ADAS-Cog (11)] at Weeks 8 and 16
- Video-referenced Clinician's Interview-based Impression of Change (CIBIC+) at Weeks 8 and 16
- Mean Revised Neuropsychiatric Inventory (NPI-X) from Week 4 to Week 24

The safety endpoints were:
- Adverse events
- Vital signs (weight, standing and supine blood pressure, heart rate)
- Laboratory evaluations

9.7.1.2.   Disposition and Baseline Characteristics

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 following baseline characteristics were summarized by treatment group and across all treatment groups: age, age category (<65, 65-80, >80), sex, race, Mini-Mental State (MMSE), duration of Alzheimer's disease, years of education, weight, height, BMI, and BMI category (BMI<25, BMI 25-<30, BMI>=30). The treatment groups were compared by analysis of variance (ANOVA) for continuous variables and by Pearson's chi-square test for categorical variables.

9.7.1.3.   Efficacy

The primary analysis of the ADAS-Cog (11) at Week 24 used the efficacy population with LOCF imputation for any missing values at Week 24. An ANCOVA model was used with the baseline score, site, and treatment included as independent variables. Treatment was included as a continuous variable, and results for a test of dose response were produced. If the test for dose response was statistically significant, pairwise comparisons among the 3 groups were to be performed and evaluated at a significance level of 0.05. Similar analyses were performed at Weeks 8 and 16. Summary statistics were generated for each visit using the efficacy population with LOCF imputation.

A supportive analysis for the ADAS-Cog (11) used a likelihood-based repeated measures (MMRM) analysis. In this analysis for the change from baseline in the ADAS-Cog (11) at Week 24, the independent variables included in the model were the fixed, categorical effects of treatment, site, time (week), and treatment by time interaction along with the continuous effects of baseline ADAS-Cog (11) score and baseline ADAS-Cog (11) score by time interaction.

The primary analysis of CIBIC+ at Week 24 used the efficacy population with LOCF imputation for any missing values at Week 24. For this endpoint, an ANOVA model was used with site, and treatment included as independent variables. Treatment was included as a continuous variable, and results for a test of dose response were produced. If the test for dose response was statistically significant, pairwise comparisons among the 3 groups were to be performed and evaluated at a significance level of 0.05. Similar analyses were performed at Weeks 8 and 16.

The primary analysis of mean NPI-X total score from Week 4 to Week 24 used the efficacy population. This endpoint was calculated as the mean of all available total scores between Weeks 4 and 24, inclusive. For this endpoint, an ANCOVA model was used with the baseline score, site, and treatment included as independent variables. Treatment was included as a continuous variable, and results for a test of dose response were produced. If the test for dose response was statistically significant, pairwise comparisons among the 3 groups were to be performed and evaluated at a significance level of 0.05.

9.7.1.4.   Safety

Average daily dose and cumulative dose at end of study (Week 26 or early termination) 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.

Adverse events were coded according to MedDRA. Due to the nature of the CDISC Pilot Project, the higher level terms and higher level group terms of the MedDRA coding were masked. In addition, no numeric MedDRA codes are included in the databases. Treatment emergent adverse events and serious adverse events were summarized by SOC (system organ class) 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. A category of special events was created to identify the events that were considered dermatological events. These events were determined by a thorough review of blinded coded adverse event terms and all preferred terms that were considered to be dermatologic in nature, such as rash, pruritus, or dermatitis, were flagged as adverse events of special interest. The time to the first dermatological event was compared across the treatment groups using Kaplan-Meier methods. Graphical displays of the survival curves were produced.

Hematology and clinical chemistry values were summarized at each visit week, for each analyte, for each treatment group. Four assessments of abnormality were identified for each laboratory analyte:
  * Values outside the normal range
  * Values significantly beyond the normal range (i.e., outside the threshold range)
  * Values differing significantly from values at the previous scheduled visit,
  * Abnormal values as defined by Hy's Law

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. Two tables were provided – one defining abnormal as beyond normal range (i.e., below LLN or above ULN) and the other defining abnormal as a clinically significant change from the previous visit. 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 using sets of 3-by-3 matrices 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. Two variations of the modified Hy's Law criteria were used in the

assessment. The first considered subjects with transaminase (ALT or AST) elevations of greater than 1.5 times ULN as abnormal. The second further narrowed the assessment of abnormality to require total bilirubin elevations to be greater than 1.5 times ULN in addition to transaminase elevations of greater than 1.5 times ULN. In these tables a subject was categorized as normal or abnormal (i.e., outside the threshold range) at baseline. During the treatment phase, the most extreme value was used to categorize a subject as normal or abnormal during the treatment phase. The shift table shows the number of subjects whose on treatment categorization was the same or shifted from the baseline categorization. The treatment period was defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12). Cochran-Mantel-Haenszel (CMH) tests, stratifying by status at baseline, were performed.

Vital sign data (blood pressure supine, blood pressure standing 1 minute, blood pressure standing 3 minutes, heart rate supine, heart rate standing 1 minute, and heart rate standing 3 minutes) at baseline, week 24 and end of treatment (last visit on or before week 24 visit) was summarized by treatment group. Change from baseline was also summarized.

Weight data at baseline and Week 24 (with and without including early terminations) was summarized by treatment group. Change from baseline was also summarized.

The concomitant medication data were coded using a publicly available sample of WHO Drug. The data were matched to a preferred term and an anatomical class (ATC level 1). Drugs not matching those in the sample were considered "uncoded" for the purposes of this submission. Due to the nature of this CDISC Pilot Project, drugs were matched to only one class. The number and percent of subjects receiving each concomitant medication were summarized. Concomitant medications were reported by anatomical class and ingredient. Medications were sorted in descending order of total incidence across treatment groups for anatomical class and in descending order of total incidence for the ingredient within each anatomical class. If the total incidence for any two or more ingredients is equal, the events were presented in alphabetical order.

9.7.2.   Determination of Sample Size

Approximately 100 subjects were to be randomized to each of the 3 treatment groups. Previous experience with the oral formulation of xanomeline suggested that this sample size had 90% power to detect a 3.0 mean treatment difference in ADAS-Cog ($p < 0.05$, two-sided), based on a standard deviation of 6.5. Furthermore, this sample size had 80% power to detect a 0.36 mean treatment difference in CIBIC+ ($p < 0.05$, two-sided), based on a standard deviation of 0.9.

9.8.   Changes in Study Conduct or Planned Analyses

The protocol was amended 3 times. For the first 2 amendments, changes were made to the ambulatory ECG assessments. These changes included shortening the duration of the ambulatory ECG monitoring from 48 to 24 hours prior to visit 3, adding monitoring prior to visit 4, removing monitoring prior to visit 6, and subsequently removing the monitoring prior to visit 4. During the time the additional monitoring prior to visit 4 was required, a visit (designated as visit 3e) was added for the placement of the ambulatory ECG equipment. Other changes in the study conduct are not described in this study report due to the nature of this CDISC Pilot Project.
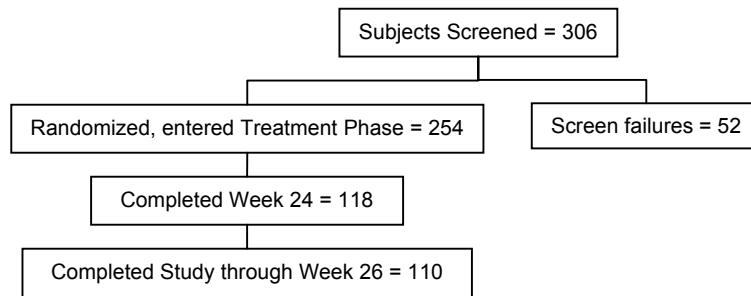
Changes to the protocol-specified analyses are described in the statistical analysis plan (Appendix 9). These changes included omission of secondary or sensitivity analyses, omission of some efficacy endpoints, omission of some safety endpoints, and the inclusion of additional types of analyses.

10.   STUDY SUBJECTS

10.1.   Disposition of Subjects

Table 14-1.01 provides a summary of the subjects in each analysis population. A total of 306 subjects have demographic information in the study tabulation database (Figure 10-1). Fifty-two (52) subjects were not randomized, and thus were screen failures. The remaining 254 subjects were randomized and entered the double-blind treatment phase. These subjects comprise the Intent-to-Treat population. 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.

Figure 10-1. Subject Disposition

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                        │  Subjects Screened = 306 │
                        └─────────────────────────┘
                                    │
              ┌─────────────────────┴──────────────────────┐
  ┌──────────────────────────────────────┐   ┌──────────────────────────┐
  │ Randomized, entered Treatment Phase   │   │  Screen failures = 52    │
  │              = 254                     │   └──────────────────────────┘
  └──────────────────────────────────────┘
              │
  ┌──────────────────────────────────────┐
  │      Completed Week 24 = 118          │
  └──────────────────────────────────────┘
              │
  ┌──────────────────────────────────────┐
  │ Completed Study through Week 26 = 110 │
  └──────────────────────────────────────┘
```

Table 14-1.03 summarizes the disposition of the population by site. The table provides the number of subjects randomized and completing Week 24, per treatment group, for each site. Of the 17 sites participating in the study, 7 met the pre-specified criteria for small sample sizes, requiring them to be grouped together for the purposes of analyses including site as a covariate, as shown in Table 14-1.03.

A total of 136 subjects prematurely discontinued from the study prior to Week 24. Table 14-1.02 provides a summary of the reasons for premature discontinuation for these subjects. There was a statistically significant association between the number of subjects discontinuing the study and the treatment group (p < 0.0001), with 30% of placebo subjects terminating early as compared to 67% of the xanomeline low dose subjects, and 64% of the xanomeline high dose subjects. 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).

10.2.   Protocol Deviations

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

11.   EFFICACY EVALUATION

11.1.   Data Sets Analyzed

Table 14-1.01 provides the summary of study populations analyzed in this protocol. Subjects were randomly assigned to treatment groups at Week 0 (Visit 3). All subjects who were randomized comprised the Intent-to-Treat (ITT) Population. A total of 254 subjects (86 in the placebo group; 84 in the xanomeline low dose group; 84 in the xanomeline high dose group) were randomized.

All subjects randomized and known to have taken at least one dose of randomized drug were included in the Safety Population. Of the 254 subjects randomized, all took a dose of the randomized study drug and were included in the Safety Population. Note that the first patches were applied at the randomization visit.

All subjects who were randomized and took at least one dose of randomized drug (i.e., were in the Safety Population), and have at least one post-baseline measure for both ADAS-Cog and CIBIC+ were included in the Efficacy Population. Twenty (20) of the subjects in Safety Population did not have a post-randomization ADAS-Cog assessment and a post-randomization CIBIC+ assessment, thus 234 subjects (79 placebo; 81 xanomeline low dose; 74 xanomeline high dose) comprised the Efficacy Population.

The 118 subjects (60 placebo; 28 xanomeline low dose; 30 xanomeline high dose) who were in the Efficacy Population and completed their Week 24 visit (Visit 12) comprised the Completers Population. Eight (8) subjects discontinued between Week 24 and Week 26, leaving 110 subjects (58 placebo; 25 xanomeline low dose; 27 xanomeline high dose) who completed the study.

11.2.   Demographics and Other Baseline Characteristics

11.2.1.   Demographic Characteristics

Table 14-2.01 summarizes demographic characteristics of age, sex, race and education level for all ITT subjects in the study. The study population was similar across all treatment groups (Table 11-1).

Table 11-1. Demographic Characteristics

	Placebo (N=86)	Xan Low (N=84)	Xan High (N=84)	Total (N=254)
Age (years), mean (range)	75.2 (52-89)	75.7 (51-88)	74.4 (56-88)	75.1 (51-89)
Gender (%)				
Male	38%	40%	52%	44%
Female	62%	60%	48%	56%
Race (%)				
White/Caucasian	87%	86%	85%	86%
Other	13%	14%	15%	14%
Education (years), mean (range)	12.6 (6-21)	13.2 (3-24)	12.5 (6-20)	12.8 (3-24)

Source: Table 14-2.01

11.2.2.   Baseline Characteristics

Table 14-2.01 summarizes the height, weight, and body mass index (BMI) data at randomization for all ITT subjects in the study. The height was similar across all treatment groups and ranged from 135.9 to 195.6 cm, with a mean of 163.9 cm. The weight at baseline differed across treatment groups (p-value = 0.003), with placebo subjects having a mean weight of 62.8 kg (SD 12.77; range 34.0-86.2), xanomeline low dose subjects having a mean weight of 67.3 kg (SD 14.12; range 45.4-106.1), and xanomeline high dose subjects having a mean weight of 70.0 kg (SD 14.65; range 41.7-108.0).

Table 14-2.01 also summarizes the duration of subjects' disease and the Mini-Mental State Examination (MMSE) score at screening.

The duration of subjects' disease was similar across all treatment groups and ranged from 2.2 to 183.1 months with a mean duration of 43.9 months. The percentage of subjects with disease duration of < one year was 5%, and the percentage of subjects with disease duration of ≥ one year was 95%.

The MMSE score at screening was similar across all treatment groups and ranged from 10 to 24, with a mean score of 18.1.

11.3.   Measurements of Treatment Compliance

Due to the nature of this CDISC Pilot Project, this section is not included in this study report.

11.4.   Efficacy Results

There are 2 co-primary efficacy endpoints in this study: the change from baseline in ADAS-Cog (11) at Week 24 and the CIBIC+ score at Week 24. Hypothesis testing for both of these endpoints considered whether there is a statistically significant dose response among the 3 treatment groups. The significance level for each of these endpoints is 0.05.

11.4.1.   ADAS-Cog (11)

Table 14-3.01 presents the summary statistics for baseline and Week 24 values for ADAS-Cog (11) and the change from baseline in ADAS-Cog (11) at Week 24. These results are based on the efficacy population with LOCF imputation. The mean scores across all 3 treatment groups are similar at baseline with the similar worsening in scores by Week 24. Accordingly, the dose response for the change from baseline at Week 24, adjusted for site and baseline score is not statistically significantly different from 0. Pairwise comparisons among the treatment groups are also presented in Table 14-3.01, but should not be considered since the dose response analysis was not statistically significant.

Similar analyses were performed at Weeks 8 and 16 (Table 14-3.03 and Table 14-3.05). Likewise, no dose response was seen at these earlier time points.

To check the robustness of the imputation method, a sensitivity analysis using only the observed values was performed (Table 14-3.07). Although the xanomeline low dose group had a smaller mean change from baseline at Week 24, the dose response in this analysis was also not statistically significantly different from 0.

Subgroup analyses by gender were also performed using the LOCF-imputed values (Table 14-3.08 and Table 14-3.09). The males in the xanomeline low dose group had a mean change from baseline that was higher than the other 2 groups, but the dose response was not statistically significantly. The dose response in the female subgroup was trending in a positive direction (p = 0.094) indicating that higher doses may result in smaller changes by Week 24. Mean (SD) changes from baseline at Week 24 for the placebo, xanomeline low dose, and xanomeline high dose were 3.0 (5.57), 1.7 (5.54), and 1.1 (4.77), respectively.

Summary statistics for the actual values and the change from baseline in ADAS-Cog (11) are presented in Table 14-3.10 for both the observed values by visit window and LOCF-imputed values.

A repeated measures analysis was performed on ADAS-Cog (11) using postbaseline changes from baseline (Table 14-3.11) to examine treatment effect over time. Covariates included in the model were treatment, site, time, treatment by time interaction, baseline

score, and baseline by time interaction. Adjusted means for the change from baseline at Week 24 were similar across the 3 treatment groups. Pairwise comparisons among the 3 treatment groups were not statistically significantly different.

11.4.2.   CIBIC+

Table 14-3.02 presents the summary statistics for the Week 24 values for CIBIC+. These results are based on the efficacy population with LOCF imputation. The mean scores across all 3 treatment groups are similar at Week 24. Accordingly, the dose response for the CIBIC+ score at Week 24, adjusted for site is not statistically significantly different from 0. Pairwise comparisons among the treatment groups are also presented in Table 14-3.02, but should not be considered since the dose response analysis was not statistically significant.

Similar analyses were performed at Weeks 8 and 16 (Table 14-3.04 and Table 14-3.06). Likewise, no dose response was seen at these earlier time points.

An analysis not specified in the protocol was performed considering CIBIC+ scores as a categorical variable (Table 14-3.13). This analysis used the LOCF-imputed values and compared treatment groups at Weeks 8, 16, and 24. Distributions of scores between the 3 treatment groups were not statistically significantly different.

11.4.3.   NPI-X

Table 14-3.12 presents the summary statistics for the baseline NPI-X score and for the mean of the observed values from Weeks 4 to 24, inclusive. The mean NPI-X value at baseline for the xanomeline high dose group was slightly larger than the other 2 groups. The dose response for the mean of the Week 4 through Week 24 values, adjusted for site and baseline value, was not statistically significantly different from 0. Pairwise comparisons among the treatment groups are also presented in Table 14-3.12, but should not be considered since the dose response analysis was not statistically significant.

11.5.   Efficacy Conclusions

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.

12.   SAFETY EVALUATION

12.1.   Extent of Exposure

For the purposes of this submission, planned exposure was summarized. It was assumed that while the subject was in the study the subject took the randomized drug as planned, with the first dose occurring on the date of randomization (Week 0), and the new dose levels occurring on the day following the Week 2 visit and the Week 24 visit. The date of last dose was that indicated on the CRF. If no date of last dose was available, the date of discontinuation was assumed to be the date of last dose.

A total of 254 subjects received randomized drug during the study. Eighty-six (86) subjects received placebo, 84 received xanomeline low dose and 84 received xanomeline high dose. The mean daily dose was 54.0 mg and 71.6 mg for the low dose and high dose treatment groups, respectively, as shown in Table 14-4.01.

12.2.   Adverse Events

12.2.1.   Brief Summary of Adverse Events

A summary of total adverse events across all body systems showed an increase in adverse events associated with randomized drug with over 90% of subjects receiving active therapy reporting at least one adverse event compared to 75.6% of subjects receiving placebo (Table 14-5.01). However, this difference is due largely to a disproportionate number of dermatologic type events that occurred in the xanomeline treatment groups. Therefore, with the exception of dermatologic irritation (discussed below), the overall adverse event profile does not suggest that there is a specific hazard associated with either dose of xanomeline.

The number of serious adverse events reported during this study were minimal (Table 14-5.02) and do not suggest that there is any pattern attributable to active therapy. There were 3 deaths observed during the course of the study, yet none of these were flagged as being serious events.

12.2.2.   Display of Adverse Events

The most commonly reported adverse events, those reported in $\geq$ 5% of subjects in any treatment group are summarized in Table 12-1 in the order that they appear in Table 14-5.01.

Table 12-1. Most Common AE's (≥ 5% Subjects in any Treatment Group)

	Placebo (N=86) n (%)	Xan Low Dose (N=84) n (%)	Xan High Dose (N=84) n (%)
Sinus Bradycardia	2 (2.3%)	7 (8.3%)*	8 (9.5%)*
Vomiting	3 (3.5%)	3 (3.6%)	7 (8.3%)
Nausea	3 (3.5%)	3 (3.6%)	6 (7.1%)
Diarrhoea	9 (10.5%)	4 (4.8%)	4 (4.8%)
Application Site Pruritus	6 (7.0%)	22 (26.2%)*	22 (26.2%) *
Application Site Erythema	3 (3.5%)	12 (14.3%)*	15 (17.9%)*
Application Site Irritation	3 (3.5%)	9 (10.7%)*	9 (10.7%)*
Application Site Dermatitis	5 (5.8%)	9 (10.7%)	7 (8.3%)
Application Site Vesicles	1 (1.2%)	4 (4.8%)	6 (7.1%)*
Fatigue	1 (1.2%)	5 (6.0%)*	5 (6.0%)*
Nasopharyngitis	2 (2.3%)	4 (4.8%)	6 (7.1%)
Upper Respiratory Tract Infection	6 (7.0%)	1 (1.2%)*	3 (3.6%)
Dizziness	2 (2.3%)	8 (9.5%)*	11 (13.1%)*
Headache	3 (3.5%)	3 (3.6%)	5 (6.0%)
Cough	1 (1.2%)	5 (6.0%)*	5 (6.0%)*
Pruritus	8 (9.3%)	21 (25.0%)*	26 (31.0%)*
Erythema	8 (9.3%)	14 (16.7%)	14 (16.7%)
Rash	5 (5.8%)	13 (15.5%)*	9 (10.7%)
Hyperhidrosis	2 (2.3%)	4 (4.8%)	8 (9.5%)*
Skin Irritation	3 (3.5%)	6 (7.1%)	5 (6.0%)
Blister	0	5 (6.0%) *	1 (1.2%)

Source: Table 14-5.01

* $p < 0.150$ versus placebo

12.2.3.   Analysis of Adverse Events

The adverse event profile of the treatment groups was generally similar across the treatment groups. With the exception of skin related adverse events, discussed below, the most commonly reported events (reported by $\geq$ 5% of subjects in any treatment group) were reported in numerous body systems and did not show a consistent treatment dependent pattern. There were noted differences ($p < 0.150$) between placebo and at least one of the active therapy groups in the incidence of sinus bradycardia (2.3% placebo, 8.3% low dose, and 9.5% high dose), fatigue (1.2% placebo, 6.0% xanomeline low dose, 6.0% xanomeline high dose), dizziness (2.3% placebo, 9.5% xanomeline low dose, 13.1% xanomeline high dose), cough (1.2% placebo, 6.0% xanomeline low dose, 6.0% xanomeline high dose), and hyperhiridosis (2.3% placebo, 4.8% xanomeline low dose, 9.5% xanomeline high dose). Upper respiratory tract infection was reported more frequently in the placebo group (7.0%) compared with the xanomeline low dose group (1.2%, $p < 0.150$) but not the xanomeline high dose group (3.6%).

12.3.   Analysis of Death, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.   Deaths

There were 3 deaths reported during the conduct of this study with 2 subjects in the placebo group and 1 subject randomized to xanomeline low dose. None of these deaths were recorded as serious adverse events yet two of the deaths were clearly of serious nature (myocardial infarction and sudden death) and the other death being a suicide. None of the deaths were judged related to treatment.

12.3.2.   Other Serious Adverse Events

There were a total of 3 serious adverse events reported in 3 individual subjects, 2 of whom were in the xanomeline high dose and 1 in the xanomeline low dose group (Table 14-5.02). All 3 events were events related to the nervous system. Due to the low numbers of serious adverse events, it is not possible to make any conclusions regarding the relationship of these events and treatment group.

12.3.3.   Dermatologic Adverse Events

A special category of dermatologic events was created prior to unblinding. This category combines all adverse events that were considered to be of dermatologic importance after a thorough medical review of the coded adverse events. The preferred terms listed in Table 12-2 were included in this category of special interest adverse events.

**Table 12-2. Preferred Terms Included in
Special Interest Category of Dermatologic Events**

System Organ Class	Preferred Term
General Disorders and Administration Site Conditions	Application Site Pruritus
	Application Site Erythema
	Application Site Irritation
	Application Site Dermatitis
	Application Site Vescicles
	Application Site Pain
	Application Site Perspiration
	Application Site Swelling
	Application Site Discharge
	Application Site Reaction
	Application Site Urticaria
	Application Site Bleeding
	Application Site Desquamation
	Application Site Discolouration
	Application Site Induration
	Application Site Warmth
Skin and Subcutaneous Tissue Disorders	Pruritus
	Erythema
	Rash
	Skin Irritation
	Rash Pruritic
	Actinic Keratosis
	Blister
	Pruritus Generalised
	Rash Maculo-papular
	Skin Odour Abnormal
	Urticaria
	Dermatitis Cintact
	Drug Eruption
	Rash Erythematous
	Skin Exfoliation
	Skin Ulcer

As shown on the table at the bottom of Figure 14-1, there was a disproportionate number of subjects in the xanomeline treatment groups who experienced a special interest dermatologic adverse event with 74% (n = 62) of xanomeline low dose and 73% (n = 61) of xanomeline high dose subjects with at least one event of special interest compared to 34% (n = 29) of placebo subjects. This high rate of dermatologic events most likely contributed to the larger proportion of subjects in the active treatment groups who discontinued the study due to an adverse event (Table 14-1.02).

An analysis of the time to the first dermatologic event indicated that the median time to first event was significantly different (p<0.0001) between treatment groups with a median time of 33 days in the xanomeline low dose group (95% CI: 27 – 48 days) and 36 days in the xanomeline high dose group (95% CI: 24 – 46 days) compared to placebo, in which the median time to first event was not estimable (Figure 14-1).

12.3.4.   Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Narratives for subjects who died while on-study are included below. Narratives for subjects who reported other serious adverse events or other significant adverse events are not included in this study report due to the nature of this CDISC Pilot Project.

Subject 01-701-1211, a 76-year-old woman with Alzheimer's dementia, began receiving xanomeline low dose on 15 November 2012. The subject was diagnosed with Alzheimer's dementia in 2010. The subject also had non-insulin dependent diabetes mellitus, which was considered to be mild in severity. The subject experienced sudden death on 14 January 2013. This death was considered by the investigator to be unrelated to study medication. No action was taken for this event and study medication was not discontinued prior to death. Eight other adverse events were reported for this subject yet none were classified as being serious and none appeared to contribute to the sudden death.

Subject 01-701-1445, a 75-year-old man with Alzheimer's dementia, began receiving placebo on 11 May 2014. The subject was diagnosed with Alzheimer's dementia in 2012. The subject also suffered from mild forms of non-insulin dependent diabetes mellitus, chronic obstructive pulmonary disease, and benign prostatic hyperplasia. This subject committed suicide on 31 October 2014. This death was considered by the investigator to be unrelated to study medication. No action was taken for this event and study medication was not discontinued prior to death. No other adverse events were reported by this subject.

Subject 01-701-1083, an 89-year-old woman with Alzheimer's dementia, began receiving placebo on 22 July 2013. The subject was diagnosed with Alzheimer's dementia in 2011. This subject had previous history of cardiovascular disease: implanted cardiac pacemaker, first degree atrioventricular block, and a history of myocardial infarction and

angina pectoris in 2006. The subject experienced a fatal myocardial infarction on 2 August 2013. This event required hospitalization. The event was considered by the investigator to be possibly related to study medication. No action was taken for this event and study medication was not discontinued prior to death. No other adverse events were reported by this subject.

12.4.   Clinical Laboratory Evaluation

Table 14-6.01 to Table 14-6.05 summarize the findings for the laboratory data analysis. Commonly used laboratory analytes (as defined by the CDISC coding document) that were measured with sufficient frequency were reported. Hematology analytes that meet this criterion are: hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte count, lymphocytes, monocytes, eosinophils, basophils, platelet count, and erythrocyte count. Clinical chemistry analytes that meet this criterion are: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT, GGPT, SGGT, YGGT), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), urea nitrogen, creatinine, uric acid, inorganic phosphorus, calcium, non-fasting glucose, total protein, albumin, cholesterol, and creatine phosphokinase. Urinalysis and other lab data were not summarized, but were included in the tabulation datasets.

The hematology and clinical chemistry measures were summarized for baseline and Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 26 (visits 1, 4, 5, 7, 8, 9, 10, 11, 12, and 13, respectively). The baseline values were those collected at Week -2 (visit 1). Table 14-6.01 presents summaries of these results by week. This table provides descriptive statistics (n, mean, and standard deviation) for the measured value in standard units as well as the change from baseline. The change from baseline laboratory value was calculated as the difference between the baseline lab value and the endpoint value (i.e., the value at the specified visit) or the end of treatment observation. These results are shown by treatment group.

Table 14-6.02 and Table 14-6.03 summarize each laboratory value, including the baseline value, as categorized with reference to the lab normal range as

- "L" - less than or equal to the lower limit of normal (LLN)

- "N" – Greater than the LLN and less than the upper limit of normal (ULN)

- "H" – Greater than or equal to the ULN

Laboratory values were assigned a flag of abnormal (high or low) if the value was outside the threshold range (defined as significantly beyond the normal range, i.e., > 1.5 times ULN or < 0.5 times LLN) or if the value was significantly different from the value observed at the preceding scheduled visit (i.e., absolute value of the change from

previous value is larger than the 50% of the normal range, LLN to ULN). Shift tables summarizing whether a subject's status changed from baseline at each week of treatment and during the treatment period are provided based on threshold ranges and changes based on Hy's Law. Two variations of the modified Hy's Law criteria were used in the assessment. The first considered subjects with transaminase (ALT or AST) elevations of greater than 1.5 times ULN as abnormal. The second further narrowed the assessment of abnormality to require total bilirubin elevations to be greater than 1.5 times ULN in addition to transaminase elevations of greater than 1.5 times ULN. In these tables subjects were categorized as normal or abnormal (i.e., outside the threshold range) at baseline. During the treatment phase, the most extreme value was used to categorize a subject as normal or abnormal during the treatment phase. The shift table shows the number of subjects whose on treatment categorization was the same or shifted from the baseline categorization. The treatment phase is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).

The number of subjects with no abnormal measure during treatment and those with at least one abnormal measure during treatment are summarized for each lab analyte. Table 14-6.02 provides an analysis with abnormal as beyond normal range (i.e., below LLN or above ULN). Table 14-6.03 provides the analysis based on abnormal as a clinically significant change from the previous visit.

As shown in Table 14-6.02, only three laboratory analytes were statistically significantly associated with treatment group: albumin ($p = 0.042$), urea nitrogen ($p = 0.023$), and eosinophils ($p = 0.001$). There were four additional analytes that were nearly significant: chloride ($p = 0.058$), hematocrit ($p = 0.052$), hemoglobin ($p = 0.093$), and MCV ($p = 0.077$). Albumin was more often lower than normal range for subjects in the placebo and xanomeline low dose groups. Subjects in the xanomeline treatment groups had statistically significantly more values above the normal range than subjects in the placebo group for urea nitrogen [placebo=9 (11%), xanomeline low dose group =22 (27%), xanomeline high dose group=12 (15%)] and eosinophils [placebo=0, xanomeline low dose group =11 (13%), xanomeline high dose group=7 (9%)].

Table 14-6.03 shows the number of clinically significant changes from previous visit by treatment group for each analyte. The association between clinically significant change from the previous visit and treatment was statistically significant for aspartate aminotransferase ($p = 0.045$) and eosinophils ($p = 0.010$). Nearly significant were protein ($p = 0.062$) and monocytes ($p = 0.081$).

Table 14-6.04 summarizes shifts from baseline by week in terms of abnormality based on threshold range. The data in this table were summarized using sets of 3-by-3 tables comparing baseline and on drug categorization for each treatment group for each week for each laboratory analyte. Because no subjects were abnormally low at baseline, only the normal at baseline and high at baseline data are shown.

In Table 14-6.05, a CMH test, stratifying by status at baseline, is shown. This test was performed to assess the association of significant shifts from baseline for each analyte with treatment group. The number of subjects with no abnormal measure during treatment and those with at least one abnormal measure during treatment was summarized for each lab analyte. Nineteen of the 30 analytes could not be analyzed because they had less than two non-missing levels. Of the 11 remaining analytes, only shifts from baseline to treatment phase for eosinophils were statistically significantly related to treatment group (p = 0.044). For eosinophils, the number of subjects in each group that showed a shift from normal to high were 0 in the placebo group, 5 (6%) in the xanomeline low dose group, and 6 (8%) in the xanomeline high dose group.

Finally, Table 14-6.06 reports the results of the Hy's Law analysis. Of the cases where transaminase was greater than 1.5 times ULN, 3 subjects in the placebo group, 1 in the xanomeline low dose, and 3 in the xanomeline high dose shifted from normal at baseline to above normal during treatment. In addition, 2 subjects in the placebo group and 1 in the xanomeline low dose group had an elevated transaminase at baseline that remained high during treatment, and 1 subject in the xanomeline low dose group had an elevated transaminase at baseline that became normal during treatment. There were no subjects in the xanomeline treatment groups and 1 subject in the placebo group who had both transaminase levels greater than 1.5 times ULN and total bilirubin greater than 1.5 times ULN. A CMH test for an association with treatment group was not statistically significant for either Hy's law assessment.

12.5.   Vital Signs and Weight

Vital signs and weight were to be collected for all subjects at each visit. For the purposes of this submission, vital signs were summarized only for baseline and Week 24 and end of treatment. End of treatment is defined to be the last on-treatment assessment of the specified measure.

12.5.1.   Vital Signs Summary

Table 14-7.01 presents a summary of the vital sign data (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse) collected at baseline (Week 0), Week 24, and end of treatment.

Table 14-7.02 summarizes the changes in vital signs at Week 24 and end of treatment as compared to values at the baseline visit (Week 0).

Table 12-3 presents summary statistics for SBP, DBP, and pulse after standing for 3 minutes. These assessments are representative of the vitals taken at other positions and time points in terms of the relationships among treatment groups. Measurements were also taken after the subject had been lying down for 5 minutes and after the subject had

been standing for 1 minute. The largest change from baseline occurred in the assessments taken after the subject had been standing for 3 minutes.

Vital sign values at baseline were comparable across treatment groups. Changes from baseline, at the Week 24 and end of treatment assessments, were generally small decreases.

Table 12-3. Summary of Change from Baseline in Vital Signs

Parameter	Treatment Group					
	Placebo (N=86)		Xan Low (N=84)		Xan high (N=84)	
	n	Mean	n	Mean	n	Mean
SBP (mmHg) after standing for 3 minutes						
Baseline	85	136.5	84	136.4	84	138.8
Change at Week 24	58	-1.0	27	-0.1	30	-9.0
Change at End of Treatment	83	-2.5	83	-3.5	81	-8.3
DBP (mmHg) after standing for 3 minutes						
Baseline	85	77.7	84	76.6	84	79.6
Change at Week 24	58	-2.3	27	-1.6	30	-2.1
Change at End of Treatment	83	-2.7	83	-1.8	81	-2.6
Pulse (BPM) after standing for 3 minutes						
Baseline	85	74.6	84	72.3	84	74.0
Change at Week 24	58	-1.5	27	-2.1	30	-2.7
Change at End of Treatment	83	-1.0	83	-0.7	81	-1.9

Source: Table 14-7.01 and Table 14-7.02

12.5.2.   Weight Summary

Table 14-7.03 presents a summary of the weight data collected at baseline (Week 0), Week 24, and end of treatment. It also summarizes the changes in weight at Week 24 and end of treatment as compared to values at the baseline visit (Week 0).

As mentioned in Section 11.2.2, weight at baseline differed across treatment groups. Changes from baseline, at the Week 24 and end of treatment assessments, however, were generally small with no treatment-related pattern of increases or decreases (Table 12-4).

Table 12-4. Summary of Change from Baseline in Weight

	Treatment Group					
	Placebo (N=86)		Xan Low (N=84)		Xan high (N=84)	
Parameter	N	Mean	n	Mean	n	Mean
Weight (kg)						
Baseline	86	62.8	83	67.3	84	70.0
Change at Week 24	59	0.1	27	-0.3	30	1.0
Change at End of Treatment	84	0.2	83	-0.4	81	0.1

Source: Table 14-7.03

12.6.   Concomitant Medications

Table 14-7.04 shows that use of concomitant medications was similar across the 3 treatment groups. Concomitant medications were taken by 77 (90%), 74 (88%), and 78 (93%) subjects in the placebo, xanomeline low dose, and xanomeline high dose groups, respectively.

The most common concomitant medication (based on coded term) used by xanomeline subjects in this study was hydrocortisone, which was taken by 2 (2%), 13 (15%), and 8 (10%) subjects in the placebo, xanomeline low dose, and xanomeline high dose groups, respectively.

12.7.   Safety Conclusions

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.

13. DISCUSSION OF STUDY RESULTS AND 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.

14.   SUMMARY TABLES AND FIGURES

<p style="text-align:center; color:blue;">*Table 14-1.01*</p>
<p style="text-align:center; color:blue;">*Summary of Populations*</p>

	Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)	Total (N=254)
Intent-To-Treat (ITT)	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Safety	86 (100%)	84 (100%)	84 (100%)	254 (100%)
Efficacy	79 (92%)	81 (96%)	74 (88%)	234 (92%)
Complete Week 24	60 (70%)	28 (33%)	30 (36%)	118 (46%)
Complete Study	58 (67%)	25 (30%)	27 (32%)	110 (43%)

Table 14-1.02
Summary of End of Study Data

	Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)	Total (N=254)	p-value[1]
Completion Status:					
Completed Week 24	60 (70%)	28 (33%)	30 (36%)	118 (46%)	<.0001
Early Termination (prior to Week 24)	26 (30%)	56 (67%)	54 (64%)	136 (54%)	
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Reason for Early Termination (prior to Week 24):					
Adverse Event	8 (9%)	44 (52%)	39 (46%)	91 (36%)	<.0001
Death	1 (1%)	1 (1%)	0 (0%)	2 (1%)	
Lack of Efficacy[2]	3 (3%)	0 (0%)	1 (1%)	4 (2%)	0.3281
Lost to Follow-up	1 (1%)	0 (0%)	0 (0%)	1 (0%)	
Subject decided to withdraw	9 (10%)	8 (10%)	8 (10%)	25 (10%)	
Physician decided to withdraw subject	1 (1%)	0 (0%)	2 (2%)	3 (1%)	
Protocol criteria not met	1 (1%)	0 (0%)	2 (2%)	3 (1%)	
Protocol violation	1 (1%)	1 (1%)	1 (1%)	3 (1%)	
Sponsor decision	1 (1%)	2 (2%)	1 (1%)	4 (2%)	
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

[1] Fisher's exact test.
[2] Based on either patient/caregiver perception or physician perception.

Table 14-1.03
Summary of Number of Subjects By Site

		Placebo (N=86)			Xanomeline Low Dose (N=84)			Xanomeline High Dose (N=84)			Total (N=254)		
Pooled Id	Site Id	ITT	Eff	Com	ITT	Eff	Com	ITT	Eff	Com	ITT	Eff	Com
701	701	14	14	11	13	13	5	14	14	7	41	41	23
703	703	6	5	4	6	5	1	6	5	2	18	15	7
704	704	9	9	5	8	7	3	8	8	0	25	24	8
705	705	5	3	2	5	5	3	6	4	1	16	12	6
708	708	9	9	7	8	8	2	8	5	2	25	22	11
709	709	7	7	5	7	6	2	7	7	3	21	20	10
710	710	11	8	6	10	10	2	10	8	5	31	26	13
713	713	3	3	3	3	3	2	3	2	2	9	8	7
716	716	8	8	7	8	8	3	8	8	3	24	24	13
718	718	4	4	3	5	5	1	4	4	1	13	13	5
900	702	0	0	0	1	1	0	0	0	0	1	1	0
900	706	1	1	1	1	1	0	1	1	0	3	3	1
900	707	1	1	1	1	1	0	0	0	0	2	2	1
900	711	1	1	1	1	1	0	2	1	0	4	3	1
900	714	2	2	2	2	2	1	2	2	1	6	6	4
900	715	3	2	2	3	3	1	2	2	0	8	7	3
900	717	2	2	0	2	2	2	3	3	3	7	7	5
TOTAL		86	79	60	84	81	28	84	74	30	254	234	118

Note: ITT: Number of subjects in the ITT population, Eff: Number of subjects in the Efficacy population;
Com: Number of subjects completing Week 24.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\adsl4.sas   21:02 Monday, June 26, 2006

Table 14-2.01
Summary of Demographic and Baseline Characteristics

		Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)	Total (N=254)	p-value [1]
Age (y)	n	86	84	84	254	0.5934
	Mean	75.2	75.7	74.4	75.1	
	SD	8.59	8.29	7.89	8.25	
	Median	76.0	77.5	76.0	77.0	
	Min	52.0	51.0	56.0	51.0	
	Max	89.0	88.0	88.0	89.0	
	<65 yrs	14 (16%)	8 (10%)	11 (13%)	33 (13%)	0.1439
	65-80 yrs	42 (49%)	47 (56%)	55 (65%)	144 (57%)	
	>80 yrs	30 (35%)	29 (35%)	18 (21%)	77 (30%)	
Sex	n	86	84	84	254	0.1409
	Male	33 (38%)	34 (40%)	44 (52%)	111 (44%)	
	Female	53 (62%)	50 (60%)	40 (48%)	143 (56%)	
Race (Origin)	n	86	84	84	254	0.6477
	Caucasian	75 (87%)	72 (86%)	71 (85%)	218 (86%)	
	African Descent	8 (9%)	6 (7%)	9 (11%)	23 (9%)	
	Hispanic	3 (3%)	6 (7%)	3 (4%)	12 (5%)	
	Other	0	0	1 (1%)	1 (<1%)	
MMSE	n	86	84	84	254	0.5947
	Mean	18.0	17.9	18.5	18.1	
	SD	4.27	4.22	4.16	4.21	
	Median	19.5	18.0	20.0	19.0	

[1] P-values are results of ANOVA treatment group comparison for continuous variable and Pearson's chi-square test for categorical variables.
NOTE: Duration of disease is computed as months between date of enrollment and date of onset of the first definite symptoms of Alzheimer's disease.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\adsl3.sas   21:02 Monday, June 26, 2006

Population: Intent-to-Treat

Table 14-2.01
Summary of Demographic and Baseline Characteristics

		Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)	Total (N=254)	p-value [1]
	Min	10.0	10.0	10.0	10.0	
	Max	23.0	24.0	24.0	24.0	
Duration of disease	n	86	84	84	254	0.1530
	Mean	42.7	48.7	40.5	43.9	
	SD	30.24	29.58	24.69	28.40	
	Median	35.3	40.3	36.0	36.3	
	Min	7.2	7.8	2.2	2.2	
	Max	183.1	130.8	135.0	183.1	
	<12 months	5 (6%)	3 (4%)	4 (5%)	12 (5%)	0.7885
	>=12 months	81 (94%)	81 (96%)	80 (95%)	242 (95%)	
Years of education	n	86	84	84	254	0.3875
	Mean	12.6	13.2	12.5	12.8	
	SD	2.95	4.15	2.92	3.38	
	Median	12.0	12.0	12.0	12.0	
	Min	6.0	3.0	6.0	3.0	
	Max	21.0	24.0	20.0	24.0	
Baseline weight(kg)	n	86	83	84	253	0.0030
	Mean	62.8	67.3	70.0	66.6	
	SD	12.77	14.12	14.65	14.13	
	Median	60.6	64.9	69.2	66.7	
	Min	34.0	45.4	41.7	34.0	
	Max	86.2	106.1	108.0	108.0	

[1] P-values are results of ANOVA treatment group comparison for continuous variable and Pearson's chi-square test for categorical variables.
NOTE: Duration of disease is computed as months between date of enrollment and date of onset of the first definite symptoms of Alzheimer's disease.
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Table 14-2.01
Summary of Demographic and Baseline Characteristics

		Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)	Total (N=254)	p-value [1]
Baseline height(cm)	n	86	84	84	254	0.1262
	Mean	162.6	163.4	165.8	163.9	
	SD	11.52	10.42	10.13	10.76	
	Median	162.6	162.6	165.1	162.9	
	Min	137.2	135.9	146.1	135.9	
	Max	185.4	195.6	190.5	195.6	
Baseline BMI	n	86	83	84	253	0.0133
	Mean	23.6	25.1	25.3	24.7	
	SD	3.67	4.27	4.16	4.09	
	Median	23.4	24.3	24.8	24.2	
	Min	15.1	17.7	13.7	13.7	
	Max	33.3	40.1	34.5	40.1	
	<25	59 (69%)	47 (56%)	44 (52%)	150 (59%)	0.2326
	25-<30	21 (24%)	27 (32%)	28 (33%)	76 (30%)	
	>=30	6 (7%)	10 (12%)	12 (14%)	28 (11%)	

[1] P-values are results of ANOVA treatment group comparison for continuous variable and Pearson's chi-square test for categorical variables.
NOTE: Duration of disease is computed as months between date of enrollment and date of onset of the first definite symptoms of Alzheimer's disease.
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Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 24			
n	79	81	74
Mean (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.48)
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;62)
Change from Baseline			
n	79	81	74
Mean (SD)	2.5 (5.80)	2.0 (5.55)	1.5 (4.26)
Median (Range)	2.0 (-11;16)	2.0 (-11;17)	1.0 (-7;13)
p-value(Dose Response) [1][2]			0.245
p-value(Xan - Placebo) [1][3]		0.569	0.233
Diff of LS Means (SE)		-0.5 (0.82)	-1.0 (0.84)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value(Xan High - Xan Low)[1][3]			0.520
Diff of LS Means (SE)			-0.5 (0.84)
95% CI			(-2.2;1.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
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Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Week 24			
n	79	81	74
Mean (SD)	4.3 (0.77)	4.2 (0.79)	4.3 (0.81)
Median (Range)	4.0 (2;6)	4.0 (2;6)	4.0 (3;6)
p-value(Dose Response) [1][2]			0.960
p-value(Xan - Placebo) [1][3]		0.489	0.799
Diff of LS Means (SE)		-0.1 (0.13)	0.0 (0.13)
95% CI		(-0.3;0.2)	(-0.2;0.3)
p-value(Xan High - Xan Low)[1][3]			0.349
Diff of LS Means (SE)			0.1 (0.13)
95% CI			(-0.1;0.4)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Table 14-3.03
ADAS Cog (11) - Change from Baseline to Week 8 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 8			
n	79	81	74
Mean (SD)	25.0 (13.10)	26.2 (12.98)	22.3 (12.41)
Median (Range)	22.0 (5;62)	25.0 (5;62)	19.0 (2;62)
Change from Baseline			
n	79	81	74
Mean (SD)	0.8 (4.81)	1.8 (4.14)	1.0 (3.62)
Median (Range)	1.0 (-12;16)	2.0 (-12;14)	1.0 (-8;13)
p-value(Dose Response) [1][2]			0.497
p-value(Xan - Placebo) [1][3]		0.099	0.751
Diff of LS Means (SE)		1.1 (0.65)	0.2 (0.67)
95% CI		(-0.2;2.4)	(-1.1;1.5)
p-value(Xan High - Xan Low) [1][3]			0.195
Diff of LS Means (SE)			-0.9 (0.66)
95% CI			(-2.2;0.4)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.

[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.

[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

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Table 14-3.04
CIBIC+ - Summary at Week 8 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Week 8			
n	77	81	73
Mean (SD)	3.9 (0.73)	4.0 (0.72)	4.1 (0.75)
Median (Range)	4.0 (2;6)	4.0 (2;6)	4.0 (2;6)
p-value(Dose Response) [1][2]			0.167
p-value(Xan - Placebo) [1][3]		0.754	0.128
Diff of LS Means (SE)		0.0 (0.12)	0.2 (0.12)
95% CI		(-0.2;0.3)	(-0.1;0.4)
p-value(Xan High - Xan Low) [1][3]			0.218
Diff of LS Means (SE)			0.1 (0.12)
95% CI			(-0.1;0.4)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
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Table 14-3.05
ADAS Cog (11) - Change from Baseline to Week 16 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 16			
n	79	81	74
Mean (SD)	26.1 (14.16)	26.0 (13.05)	22.5 (12.33)
Median (Range)	23.0 (5;63)	25.0 (5;62)	20.0 (4;62)
Change from Baseline			
n	79	81	74
Mean (SD)	2.0 (5.89)	1.6 (4.10)	1.2 (4.33)
Median (Range)	2.0 (-17;23)	2.0 (-9;14)	1.0 (-11;13)
p-value(Dose Response) [1][2]			0.412
p-value(Xan - Placebo) [1][3]		0.724	0.392
Diff of LS Means (SE)		-0.3 (0.77)	-0.7 (0.79)
95% CI		(-1.8;1.2)	(-2.2;0.9)
p-value(Xan High - Xan Low) [1][3]			0.606
Diff of LS Means (SE)			-0.4 (0.78)
95% CI			(-1.9;1.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
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Table 14-3.06
CIBIC+ - Summary at Week 16 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Week 16			
n	79	81	74
Mean (SD)	4.2 (0.70)	4.0 (0.77)	4.0 (0.75)
Median (Range)	4.0 (3;6)	4.0 (2;6)	4.0 (2;5)
p-value(Dose Response) [1][2]			0.214
p-value(Xan - Placebo) [1][3]		0.219	0.272
Diff of LS Means (SE)		-0.1 (0.12)	-0.1 (0.12)
95% CI		(-0.4;0.1)	(-0.4;0.1)
p-value(Xan High - Xan Low) [1][3]			0.916
Diff of LS Means (SE)			0.0 (0.12)
95% CI			(-0.2;0.2)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
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Table 14-3.07
ADAS Cog (11) - Change from Baseline to Week 24 - Completers at Wk 24-Observed Cases-Windowed

	Placebo (N=60)	Xanomeline Low Dose (N=28)	Xanomeline High Dose (N=30)
Baseline			
n	59	27	30
Mean (SD)	23.2 (11.74)	24.0 (13.89)	20.5 (11.50)
Median (Range)	21.0 (5;51)	20.0 (5;57)	18.0 (3;49)
Week 24			
n	59	27	30
Mean (SD)	25.3 (13.32)	24.1 (11.87)	21.8 (12.60)
Median (Range)	23.0 (5;58)	22.0 (8;51)	18.5 (3;44)
Change from Baseline			
n	59	27	30
Mean (SD)	2.1 (5.89)	0.1 (5.86)	1.3 (4.51)
Median (Range)	2.0 (-11;16)	1.0 (-11;12)	1.0 (-7;13)
p-value(Dose Response) [1][2]			0.234
p-value(Xan - Placebo) [1][3]		0.105	0.461
Diff of LS Means (SE)		-2.1 (1.26)	-0.9 (1.22)
95% CI		(-4.6;0.4)	(-3.3;1.5)
p-value(Xan High - Xan Low) [1][3]			0.430
Diff of LS Means (SE)			1.2 (1.47)
95% CI			(-1.8;4.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Note that only assessments falling within the assessment window are included in the summary for a visit.
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Table 14-3.08

ADAS Cog (11) - Change from Baseline to Week 24 in Male Subjects - LOCF

	Placebo (N=33)	Xanomeline Low Dose (N=34)	Xanomeline High Dose (N=39)
Baseline			
n	33	34	39
Mean (SD)	22.8 (13.45)	23.3 (14.03)	20.8 (11.11)
Median (Range)	19.0 (5;61)	21.5 (7;57)	17.0 (3;51)
Week 24			
n	33	34	39
Mean (SD)	24.7 (13.89)	25.7 (14.72)	22.7 (12.32)
Median (Range)	20.0 (5;62)	24.0 (6;57)	21.0 (3;51)
Change from Baseline			
n	33	34	39
Mean (SD)	1.9 (6.14)	2.5 (5.61)	1.8 (3.77)
Median (Range)	1.0 (-11;16)	1.0 (-6;14)	1.0 (-7;13)
p-value(Dose Response) [1][2]			0.873
p-value(Xan - Placebo) [1][3]		0.712	0.915
Diff of LS Means (SE)		0.5 (1.30)	0.1 (1.25)
95% CI		(-2.1;3.1)	(-2.4;2.6)
p-value(Xan High - Xan Low) [1][3]			0.783
Diff of LS Means (SE)			-0.3 (1.26)
95% CI			(-2.9;2.2)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff1.sas   21:05 Monday, June 26, 2006

Table 14-3.09
ADAS Cog (11) - Change from Baseline to Week 24 in Female Subjects - LOCF

	Placebo (N=46)	Xanomeline Low Dose (N=47)	Xanomeline High Dose (N=35)
Baseline			
n	46	47	35
Mean (SD)	25.1 (11.25)	25.2 (12.15)	21.8 (12.54)
Median (Range)	23.5 (5;51)	21.0 (5;55)	18.0 (5;57)
Week 24			
n	46	47	35
Mean (SD)	28.1 (13.70)	26.9 (12.09)	22.9 (12.84)
Median (Range)	24.0 (8;59)	25.0 (8;62)	19.0 (4;62)
Change from Baseline			
n	46	47	35
Mean (SD)	3.0 (5.57)	1.7 (5.54)	1.1 (4.77)
Median (Range)	3.0 (-8;16)	2.0 (-11;17)	0.0 (-7;13)
p-value(Dose Response) [1][2]			0.094
p-value(Xan - Placebo) [1][3]		0.160	0.135
Diff of LS Means (SE)		-1.6 (1.10)	-1.8 (1.20)
95% CI		(-3.7;0.6)	(-4.2;0.6)
p-value(Xan High - Xan Low) [1][3]			0.843
Diff of LS Means (SE)			-0.2 (1.21)
95% CI			(-2.6;2.2)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff1.sas   21:05 Monday, June 26, 2006

Table 14-3.10
ADAS Cog (11) - Mean and Mean Change from Baseline over Time

								Bsln	Bsln	---Change from baseline---				
		nc	Mean	Std	Med.	Min.	Max.	Mean	Std	Mean	Std	Med.	Min.	Max.
Placebo	Baseline	79	24.1	12.19	21.0	5	61							
	Week 8 (Windowed)	79	25.0	13.10	22.0	5	62	24.1	12.19	0.8	4.81	1.0	-12	16
	Week 16 (Windowed)	68	25.1	13.42	21.0	5	63	23.4	11.32	1.7	5.92	2.0	-17	23
	Week 24 (Windowed)	65	25.7	13.90	23.0	5	59	23.6	12.13	2.1	5.99	2.0	-11	16
	Week 8 LOCF	79	25.0	13.10	22.0	5	62	24.1	12.19	0.8	4.81	1.0	-12	16
	Week 16 LOCF	79	26.1	14.16	23.0	5	63	24.1	12.19	2.0	5.89	2.0	-17	23
	Week 24 LOCF	79	26.7	13.79	24.0	5	62	24.1	12.19	2.5	5.80	2.0	-11	16
Xan.Low	Baseline	81	24.4	12.92	21.0	5	57							
	Week 8 (Windowed)	81	26.2	12.98	25.0	5	62	24.4	12.92	1.8	4.14	2.0	-12	14
	Week 16 (Windowed)	42	26.2	12.23	25.0	8	53	25.0	12.52	1.2	4.33	1.0	-8	13
	Week 24 (Windowed)	49	25.6	13.81	24.0	7	57	24.4	13.76	1.3	6.05	1.0	-11	17
	Week 8 LOCF	81	26.2	12.98	25.0	5	62	24.4	12.92	1.8	4.14	2.0	-12	14
	Week 16 LOCF	81	26.0	13.05	25.0	5	62	24.4	12.92	1.6	4.10	2.0	-9	14
	Week 24 LOCF	81	26.4	13.18	25.0	6	62	24.4	12.92	2.0	5.55	2.0	-11	17
Xan.High	Baseline	74	21.3	11.74	18.0	3	57							
	Week 8 (Windowed)	74	22.3	12.41	19.0	2	62	21.3	11.74	1.0	3.62	1.0	-8	13
	Week 16 (Windowed)	40	21.9	12.39	19.5	4	49	21.1	11.79	0.8	4.92	1.0	-11	10
	Week 24 (Windowed)	41	21.8	12.38	19.0	3	45	20.1	11.13	1.7	4.74	1.0	-7	13
	Week 8 LOCF	74	22.3	12.41	19.0	2	62	21.3	11.74	1.0	3.62	1.0	-8	13
	Week 16 LOCF	74	22.5	12.33	20.0	4	62	21.3	11.74	1.2	4.33	1.0	-11	13
	Week 24 LOCF	74	22.8	12.48	20.0	3	62	21.3	11.74	1.5	4.26	1.0	-7	13

Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
LS Means (SE)	1.6 (0.49)	1.5 (0.52)	1.1 (0.56)
p-value(Xan - Placebo)		0.955	0.556
Diff of LS Means (SE)		-0.0 (0.70)	-0.4 (0.72)
95% CI		(-1.4;1.3)	(-1.9;1.0)
p-value(Xan High - Xan Low)			0.606
Diff of LS Means (SE)			-0.4 (0.75)
95% CI			(-1.9;1.1)

Note: The change from baseline is calculated as the post-baseline score minus the baseline score. The covariates included in the MMRM model are treatment, site group, time and treatment by time interaction, baseline ADAS-Cog (11) score, and baseline ADAS-Cog (11) score by time interaction.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff_mmrm.sas   21:06 Monday, June 26, 2006

Table 14-3.12
Mean NPI-X Total Score from Week 4 through Week 24 - Windowed

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	9.5 (12.10)	8.7 (9.82)	11.9 (13.70)
Median (Range)	5.0 (0;66)	4.0 (0;32)	8.0 (0;61)
Mean of Weeks 4-24			
n	78	75	69
Mean (SD)	9.3 (11.18)	9.1 (12.10)	9.6 (11.60)
Median (Range)	5.5 (0;65)	3.8 (0;51)	4.4 (0;46)
p-value(Dose Response) [1][2]			0.637
p-value(Xan - Placebo) [1][3]		0.760	0.517
Diff of LS Means (SE)		0.3 (1.13)	-0.7 (1.15)
95% CI		(-1.9;2.6)	(-3.0;1.5)
p-value(Xan High - Xan Low) [1][3]			0.350
Diff of LS Means (SE)			-1.1 (1.17)
95% CI			(-3.4;1.2)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff1.sas   21:05 Monday, June 26, 2006

Table 14-3.13
CIBIC+ - Categorical Analysis - LOCF

	Assessment	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)	p-value [1]
Week 8	n	77	81	73	0.2727
	Marked improvement	0	0	0	
	Moderate improvement	1 (1%)	2 (2%)	1 (1%)	
	Minimal improvement	19 (25%)	16 (20%)	13 (18%)	
	No Change	45 (58%)	48 (59%)	38 (52%)	
	Minimal worsening	10 (13%)	14 (17%)	20 (27%)	
	Moderate worsening	2 (3%)	1 (1%)	1 (1%)	
	Marked worsening	0	0	0	
Week 16	n	79	81	74	0.4003
	Marked improvement	0	0	0	
	Moderate improvement	0	3 (4%)	2 (3%)	
	Minimal improvement	12 (15%)	12 (15%)	13 (18%)	
	No Change	41 (52%)	46 (57%)	39 (53%)	
	Minimal worsening	25 (32%)	19 (23%)	20 (27%)	
	Moderate worsening	1 (1%)	1 (1%)	0	
	Marked worsening	0	0	0	
Week 24	n	79	81	74	0.6180
	Marked improvement	0	0	0	
	Moderate improvement	1 (1%)	1 (1%)	0	
	Minimal improvement	9 (11%)	14 (17%)	11 (15%)	
	No Change	38 (48%)	37 (46%)	33 (45%)	
	Minimal worsening	28 (35%)	27 (33%)	25 (34%)	
	Moderate worsening	3 (4%)	2 (2%)	5 (7%)	
	Marked worsening	0	0	0	

[1] Overall comparison of treatments using CMH test (Pearson Chi-Square), controlling for site group.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtf_eff_cat.sas   21:06 Monday, June 26, 2006

Table 14-4.01
Summary of Planned Exposure to Study Drug, as of End of Study

		Completers at Week 24			Safety Population [1]		
		Placebo (N=60)	Xanomeline Low Dose (N=28)	Xanomeline High Dose (N=30)	Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)
Average daily dose (mg)	n	60	28	30	86	84	84
	mean	0.0	54.0	77.0	0.0	54.0	71.6
	std	0.00	0.00	0.58	0.00	0.00	8.11
	median	0.0	54.0	76.9	0.0	54.0	75.1
	min	0.0	54.0	76.1	0.0	54.0	54.0
	max	0.0	54.0	78.6	0.0	54.0	78.6
Cumulative dose at end of study [2]	n	60	28	30	86	84	84
	mean	0.0	9918.6	14089.5	0.0	5347.3	7551.0
	std	0.00	603.84	481.01	0.00	3680.35	5531.04
	median	0.0	9936.0	14080.5	0.0	4455.0	5778.0
	min	0.0	7884.0	12960.0	0.0	108.0	54.0
	max	0.0	11448.0	15417.0	0.0	11448.0	15417.0

[1] Includes completers and early terminators.
[2] End of Study refers to week 26/Early Termination.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\adsl12.sas   21:02 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
ANY BODY SYSTEM	65 (75.6%)	[281]	77 (91.7%)	[412]	76 (90.5%)	[433]	0.007*	0.014*
CARDIAC DISORDERS	12 (14.0%)	[26]	13 (15.5%)	[30]	15 (17.9%)	[30]	0.831	0.534
SINUS BRADYCARDIA	2 (2.3%)	[2]	7 (8.3%)	[10]	8 (9.5%)	[12]	0.097*	0.056*
MYOCARDIAL INFARCTION	4 (4.7%)	[4]	2 (2.4%)	[4]	4 (4.8%)	[8]	0.682	>0.99
ATRIAL FIBRILLATION	1 (1.2%)	[1]	1 (1.2%)	[1]	3 (3.6%)	[5]	>0.99	0.365
ATRIAL FLUTTER	0		1 (1.2%)	[1]	1 (1.2%)	[2]	0.494	0.494
CARDIAC DISORDER	0		0		1 (1.2%)	[1]		0.494
SUPRAVENTRICULAR EXTRASYSTOLES	1 (1.2%)	[2]	1 (1.2%)	[2]	1 (1.2%)	[1]	>0.99	>0.99
VENTRICULAR EXTRASYSTOLES	0		2 (2.4%)	[4]	1 (1.2%)	[1]	0.243	0.494
ATRIAL HYPERTROPHY	1 (1.2%)	[2]	0		0		>0.99	>0.99
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (1.2%)	[1]	1 (1.2%)	[1]	0		>0.99	>0.99
ATRIOVENTRICULAR BLOCK SECOND DEGREE	1 (1.2%)	[1]	0		0		>0.99	>0.99
BRADYCARDIA	1 (1.2%)	[4]	0		0		>0.99	>0.99
BUNDLE BRANCH BLOCK LEFT	1 (1.2%)	[1]	0		0		>0.99	>0.99
BUNDLE BRANCH BLOCK RIGHT	1 (1.2%)	[2]	1 (1.2%)	[1]	0		>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Population: Safety

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values	
							Placebo vs.	Placebo vs.
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]	Low Dose	High Dose
CARDIAC FAILURE CONGESTIVE	1 (1.2%)	[1]	0		0		>0.99	>0.99
PALPITATIONS	0		2 (2.4%)	[2]	0		0.243	
SINUS ARRHYTHMIA	1 (1.2%)	[2]	0		0		>0.99	>0.99
SUPRAVENTRICULAR TACHYCARDIA	0		1 (1.2%)	[2]	0		0.494	
TACHYCARDIA	1 (1.2%)	[2]	0		0		>0.99	>0.99
VENTRICULAR HYPERTROPHY	1 (1.2%)	[1]	0		0		>0.99	>0.99
WOLFF-PARKINSON-WHITE SYNDROME	0		1 (1.2%)	[2]	0		0.494	
CONGENITAL, FAMILIAL AND GENETIC DISORDE	0		1 (1.2%)	[1]	2 (2.4%)	[2]	0.494	0.243
VENTRICULAR SEPTAL DEFECT	0		1 (1.2%)	[1]	2 (2.4%)	[2]	0.494	0.243
EAR AND LABYRINTH DISORDERS	1 (1.2%)	[2]	2 (2.4%)	[2]	1 (1.2%)	[1]	0.618	>0.99
VERTIGO	0		1 (1.2%)	[1]	1 (1.2%)	[1]	0.494	0.494
CERUMEN IMPACTION	0		1 (1.2%)	[1]	0		0.494	
EAR PAIN	1 (1.2%)	[2]	0		0		>0.99	>0.99
EYE DISORDERS	2 (2.3%)	[5]	2 (2.4%)	[2]	1 (1.2%)	[2]	>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
VISION BLURRED	0		1 (1.2%)	[1]	1 (1.2%)	[2]	0.494	0.494
CONJUNCTIVAL HAEMORRHAGE	0		1 (1.2%)	[1]	0		0.494	
CONJUNCTIVITIS	1 (1.2%)	[2]	0		0		>0.99	>0.99
EYE ALLERGY	1 (1.2%)	[1]	0		0		>0.99	>0.99
EYE PRURITUS	1 (1.2%)	[1]	0		0		>0.99	>0.99
EYE SWELLING	1 (1.2%)	[1]	0		0		>0.99	>0.99
GASTROINTESTINAL DISORDERS	17 (19.8%)	[26]	14 (16.7%)	[22]	20 (23.8%)	[36]	0.692	0.58
VOMITING	3 (3.5%)	[3]	3 (3.6%)	[4]	7 (8.3%)	[9]	>0.99	0.209
NAUSEA	3 (3.5%)	[3]	3 (3.6%)	[5]	6 (7.1%)	[13]	>0.99	0.326
DIARRHOEA	9 (10.5%)	[10]	4 (4.8%)	[5]	4 (4.8%)	[4]	0.248	0.248
SALIVARY HYPERSECRETION	0		0		4 (4.8%)	[5]		0.058*
ABDOMINAL DISCOMFORT	0		0		1 (1.2%)	[1]		0.494
ABDOMINAL PAIN	1 (1.2%)	[1]	3 (3.6%)	[3]	1 (1.2%)	[2]	0.365	>0.99
GASTROINTESTINAL HAEMORRHAGE	0		0		1 (1.2%)	[1]		0.494
STOMACH DISCOMFORT	0		0		1 (1.2%)	[1]		0.494
CONSTIPATION	1 (1.2%)	[1]	0		0		>0.99	>0.99
DYSPEPSIA	1 (1.2%)	[2]	1 (1.2%)	[2]	0		>0.99	>0.99
DYSPHAGIA	0		1 (1.2%)	[1]	0		0.494	
FLATULENCE	1 (1.2%)	[2]	0		0		>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
GASTROOESOPHAGEAL REFLUX DISEASE	1 (1.2%)	[1]	0		0		>0.99	>0.99
GLOSSITIS	1 (1.2%)	[1]	0		0		>0.99	>0.99
HIATUS HERNIA	1 (1.2%)	[2]	0		0		>0.99	>0.99
RECTAL HAEMORRHAGE	0		1 (1.2%)	[2]	0		0.494	
GENERAL DISORDERS AND ADMINISTRATION SIT	21 (24.4%)	[46]	47 (56.0%)	[118]	40 (47.6%)	[124]	0.000*	0.002*
APPLICATION SITE PRURITUS	6 (7.0%)	[10]	22 (26.2%)	[32]	22 (26.2%)	[35]	0.001*	0.001*
APPLICATION SITE ERYTHEMA	3 (3.5%)	[3]	12 (14.3%)	[20]	15 (17.9%)	[23]	0.015*	0.003*
APPLICATION SITE IRRITATION	3 (3.5%)	[7]	9 (10.7%)	[18]	9 (10.7%)	[16]	0.078*	0.078*
APPLICATION SITE DERMATITIS	5 (5.8%)	[9]	9 (10.7%)	[15]	7 (8.3%)	[12]	0.277	0.563
APPLICATION SITE VESICLES	1 (1.2%)	[2]	4 (4.8%)	[5]	6 (7.1%)	[6]	0.208	0.062*
FATIGUE	1 (1.2%)	[2]	5 (6.0%)	[5]	5 (6.0%)	[5]	0.115*	0.115*
APPLICATION SITE PAIN	0		0		2 (2.4%)	[2]		0.243
APPLICATION SITE PERSPIRATION	0		0		2 (2.4%)	[3]		0.243
APPLICATION SITE SWELLING	0		1 (1.2%)	[1]	2 (2.4%)	[3]	0.494	0.243
CHEST DISCOMFORT	0		0		2 (2.4%)	[2]		0.243

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86) n(%)	[AEs]	Xanomeline Low (N=84) n(%)	[AEs]	Xanomeline High (N=84) n(%)	[AEs]	Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
CHEST PAIN	0		0		2 (2.4%)	[2]		0.243
MALAISE	0		1 (1.2%)	[2]	2 (2.4%)	[3]	0.494	0.243
OEDEMA PERIPHERAL	2 (2.3%)	[3]	1 (1.2%)	[1]	2 (2.4%)	[3]	>0.99	>0.99
APPLICATION SITE DISCHARGE	0		0		1 (1.2%)	[1]		0.494
APPLICATION SITE REACTION	1 (1.2%)	[2]	0		1 (1.2%)	[1]	>0.99	>0.99
APPLICATION SITE URTICARIA	0		2 (2.4%)	[2]	1 (1.2%)	[1]	0.243	0.494
ASTHENIA	1 (1.2%)	[2]	0		1 (1.2%)	[1]	>0.99	>0.99
CHILLS	1 (1.2%)	[3]	1 (1.2%)	[2]	1 (1.2%)	[1]	>0.99	>0.99
FEELING ABNORMAL	0		0		1 (1.2%)	[1]		0.494
FEELING COLD	0		0		1 (1.2%)	[1]		0.494
PAIN	0		1 (1.2%)	[2]	1 (1.2%)	[1]	0.494	0.494
PYREXIA	2 (2.3%)	[2]	0		1 (1.2%)	[1]	0.497	>0.99
APPLICATION SITE BLEEDING	0		1 (1.2%)	[1]	0		0.494	
APPLICATION SITE DESQUAMATION	0		1 (1.2%)	[1]	0		0.494	
APPLICATION SITE DISCOLOURATION	0		1 (1.2%)	[1]	0		0.494	
APPLICATION SITE INDURATION	1 (1.2%)	[1]	0		0		>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
APPLICATION SITE WARMTH	0		1 (1.2%)	[2]	0		0.494	
INFLAMMATION	0		1 (1.2%)	[1]	0		0.494	
OEDEMA	0		2 (2.4%)	[2]	0		0.243	
SECRETION DISCHARGE	0		1 (1.2%)	[2]	0		0.494	
SUDDEN DEATH	0		1 (1.2%)	[1]	0		0.494	
SWELLING	0		1 (1.2%)	[1]	0		0.494	
ULCER	0		1 (1.2%)	[1]	0		0.494	
HEPATOBILIARY DISORDERS	1 (1.2%)	[1]	0		0		>0.99	>0.99
HYPERBILIRUBINAEMIA	1 (1.2%)	[1]	0		0		>0.99	>0.99
IMMUNE SYSTEM DISORDERS	0		1 (1.2%)	[2]	0		0.494	
HYPERSENSITIVITY	0		1 (1.2%)	[2]	0		0.494	
INFECTIONS AND INFESTATIONS	16 (18.6%)	[35]	9 (10.7%)	[16]	13 (15.5%)	[20]	0.194	0.685
NASOPHARYNGITIS	2 (2.3%)	[4]	4 (4.8%)	[9]	6 (7.1%)	[8]	0.441	0.166
UPPER RESPIRATORY TRACT INFECTION	6 (7.0%)	[12]	1 (1.2%)	[2]	3 (3.6%)	[5]	0.117*	0.496
CYSTITIS	1 (1.2%)	[1]	0		1 (1.2%)	[1]	>0.99	>0.99
HORDEOLUM	0		0		1 (1.2%)	[1]		0.494
INFLUENZA	1 (1.2%)	[2]	1 (1.2%)	[1]	1 (1.2%)	[1]	>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
LOWER RESPIRATORY TRACT INFECTION	0		0		1 (1.2%)	[2]		0.494
RHINITIS	0		0		1 (1.2%)	[1]		0.494
URINARY TRACT INFECTION	2 (2.3%)	[4]	0		1 (1.2%)	[1]	0.497	>0.99
BRONCHITIS	1 (1.2%)	[1]	0		0		>0.99	>0.99
CELLULITIS	0		1 (1.2%)	[1]	0		0.494	
CERVICITIS	1 (1.2%)	[2]	0		0		>0.99	>0.99
EAR INFECTION	2 (2.3%)	[4]	0		0		0.497	0.497
GASTROENTERITIS VIRAL	1 (1.2%)	[1]	0		0		>0.99	>0.99
LOCALISED INFECTION	1 (1.2%)	[2]	0		0		>0.99	>0.99
PNEUMONIA	0		1 (1.2%)	[2]	0		0.494	
VAGINAL MYCOSIS	1 (1.2%)	[2]	0		0		>0.99	>0.99
VIRAL INFECTION	0		1 (1.2%)	[1]	0		0.494	
INJURY, POISONING AND PROCEDURAL COMPLIC	4 (4.7%)	[9]	5 (6.0%)	[12]	5 (6.0%)	[8]	0.745	0.745
CONTUSION	1 (1.2%)	[1]	1 (1.2%)	[3]	2 (2.4%)	[3]	>0.99	0.618
HIP FRACTURE	1 (1.2%)	[2]	0		2 (2.4%)	[2]	>0.99	0.618
EXCORIATION	2 (2.3%)	[3]	1 (1.2%)	[2]	1 (1.2%)	[1]	>0.99	>0.99
FACIAL BONES FRACTURE	0		0		1 (1.2%)	[1]		0.494
FALL	1 (1.2%)	[2]	2 (2.4%)	[2]	1 (1.2%)	[1]	0.618	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
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Population: Safety

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86) n(%)	[AEs]	Xanomeline Low (N=84) n(%)	[AEs]	Xanomeline High (N=84) n(%)	[AEs]	Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
JOINT DISLOCATION	0		1 (1.2%)	[1]	0		0.494	
SKIN LACERATION	1 (1.2%)	[1]	2 (2.4%)	[2]	0		0.618	>0.99
WOUND	0		1 (1.2%)	[2]	0		0.494	
INVESTIGATIONS	10 (11.6%)	[19]	6 (7.1%)	[7]	6 (7.1%)	[8]	0.432	0.432
BIOPSY	0		0		1 (1.2%)	[1]		0.494
BIOPSY PROSTATE	0		0		1 (1.2%)	[1]		0.494
BLOOD CHOLESTEROL INCREASED	0		0		1 (1.2%)	[1]		0.494
BLOOD GLUCOSE INCREASED	0		1 (1.2%)	[1]	1 (1.2%)	[2]	0.494	0.494
ELECTROCARDIOGRAM T WAVE INVERSION	2 (2.3%)	[3]	1 (1.2%)	[1]	1 (1.2%)	[1]	>0.99	>0.99
WEIGHT DECREASED	0		0		1 (1.2%)	[2]		0.494
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (1.2%)	[1]	0		0		>0.99	>0.99
BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (1.2%)	[2]	0		0		>0.99	>0.99
BLOOD URINE PRESENT	1 (1.2%)	[1]	0		0		>0.99	>0.99
BODY TEMPERATURE INCREASED	0		1 (1.2%)	[1]	0		0.494	
CYSTOSCOPY	1 (1.2%)	[1]	0		0		>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
ELECTROCARDIOGRAM ST SEGMENT DEPRESSIO	4 (4.7%)	[4]	1 (1.2%)	[2]	0		0.368	0.121*
ELECTROCARDIOGRAM T WAVE AMPLITUDE DEC	1 (1.2%)	[1]	1 (1.2%)	[1]	0		>0.99	>0.99
HEART RATE INCREASED	1 (1.2%)	[2]	0		0		>0.99	>0.99
HEART RATE IRREGULAR	1 (1.2%)	[4]	0		0		>0.99	>0.99
NASAL MUCOSA BIOPSY	0		1 (1.2%)	[1]	0		0.494	
METABOLISM AND NUTRITION DISORDERS	6 (7.0%)	[8]	1 (1.2%)	[1]	2 (2.4%)	[4]	0.117*	0.278
DECREASED APPETITE	1 (1.2%)	[2]	0		1 (1.2%)	[2]	>0.99	>0.99
INCREASED APPETITE	1 (1.2%)	[2]	0		1 (1.2%)	[2]	>0.99	>0.99
DEHYDRATION	1 (1.2%)	[1]	0		0		>0.99	>0.99
DIABETES MELLITUS	1 (1.2%)	[1]	0		0		>0.99	>0.99
FOOD CRAVING	1 (1.2%)	[1]	1 (1.2%)	[1]	0		>0.99	>0.99
HYPONATRAEMIA	1 (1.2%)	[1]	0		0		>0.99	>0.99
MUSCULOSKELETAL AND CONNECTIVE TISSUE DI	4 (4.7%)	[6]	7 (8.3%)	[10]	7 (8.3%)	[10]	0.367	0.367
BACK PAIN	1 (1.2%)	[2]	1 (1.2%)	[1]	3 (3.6%)	[4]	>0.99	0.365
ARTHRALGIA	1 (1.2%)	[1]	2 (2.4%)	[4]	1 (1.2%)	[1]	0.618	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
ARTHRITIS	0		0		1 (1.2%)	[1]		0.494
FLANK PAIN	0		0		1 (1.2%)	[1]		0.494
MUSCLE SPASMS	0		1 (1.2%)	[1]	1 (1.2%)	[2]	0.494	0.494
MYALGIA	0		0		1 (1.2%)	[1]		0.494
MUSCULAR WEAKNESS	0		1 (1.2%)	[2]	0		0.494	
PAIN IN EXTREMITY	1 (1.2%)	[1]	0		0		>0.99	>0.99
SHOULDER PAIN	1 (1.2%)	[2]	2 (2.4%)	[2]	0		0.618	>0.99
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIF	0		2 (2.4%)	[3]	1 (1.2%)	[1]	0.243	0.494
PROSTATE CANCER	0		0		1 (1.2%)	[1]		0.494
COLON CANCER	0		1 (1.2%)	[1]	0		0.494	
MALIGNANT FIBROUS HISTIOCYTOMA	0		1 (1.2%)	[2]	0		0.494	
NERVOUS SYSTEM DISORDERS	8 (9.3%)	[11]	20 (23.8%)	[40]	25 (29.8%)	[41]	0.013*	0.001*
DIZZINESS	2 (2.3%)	[3]	8 (9.5%)	[13]	11 (13.1%)	[15]	0.056*	0.009*
HEADACHE	3 (3.5%)	[3]	3 (3.6%)	[4]	5 (6.0%)	[8]	>0.99	0.493
SYNCOPE	0		4 (4.8%)	[6]	3 (3.6%)	[4]	0.058*	0.118*
BURNING SENSATION	0		0		2 (2.4%)	[2]		0.243
AMNESIA	0		0		1 (1.2%)	[2]		0.494

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
COGNITIVE DISORDER	0		0		1 (1.2%)	[1]		0.494
HYPERSOMNIA	0		0		1 (1.2%)	[1]		0.494
LETHARGY	0		1 (1.2%)	[1]	1 (1.2%)	[1]	0.494	0.494
PARAESTHESIA	0		0		1 (1.2%)	[1]		0.494
PAROSMIA	0		0		1 (1.2%)	[2]		0.494
PARTIAL SEIZURES WITH SECONDARY GENERA	0		0		1 (1.2%)	[1]		0.494
SOMNOLENCE	2 (2.3%)	[3]	3 (3.6%)	[5]	1 (1.2%)	[1]	0.68	>0.99
SYNCOPE VASOVAGAL	0		0		1 (1.2%)	[1]		0.494
TRANSIENT ISCHAEMIC ATTACK	0		2 (2.4%)	[3]	1 (1.2%)	[1]	0.243	0.494
BALANCE DISORDER	0		1 (1.2%)	[3]	0		0.494	
COMPLEX PARTIAL SEIZURES	0		1 (1.2%)	[1]	0		0.494	
COORDINATION ABNORMAL	0		1 (1.2%)	[1]	0		0.494	
HEMIANOPIA HOMONYMOUS	0		1 (1.2%)	[1]	0		0.494	
PARAESTHESIA ORAL	0		1 (1.2%)	[1]	0		0.494	
PARKINSON'S DISEASE	1 (1.2%)	[1]	0		0		>0.99	>0.99
PSYCHOMOTOR HYPERACTIVITY	1 (1.2%)	[1]	0		0		>0.99	>0.99
STUPOR	0		1 (1.2%)	[1]	0		0.494	
PSYCHIATRIC DISORDERS	10 (11.6%)	[12]	10 (11.9%)	[14]	8 (9.5%)	[11]	>0.99	0.804

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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values	
							Placebo vs.	Placebo vs.
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]	Low Dose	High Dose
INSOMNIA	2 (2.3%)	[3]	0		2 (2.4%)	[2]	0.497	>0.99
AGITATION	2 (2.3%)	[2]	2 (2.4%)	[2]	1 (1.2%)	[1]	>0.99	>0.99
CONFUSIONAL STATE	2 (2.3%)	[2]	3 (3.6%)	[3]	1 (1.2%)	[1]	0.68	>0.99
DELIRIUM	0		0		1 (1.2%)	[1]		0.494
DELUSION	1 (1.2%)	[1]	0		1 (1.2%)	[1]	>0.99	>0.99
HALLUCINATION	0		0		1 (1.2%)	[1]		0.494
HALLUCINATION, VISUAL	0		0		1 (1.2%)	[1]		0.494
LIBIDO DECREASED	0		0		1 (1.2%)	[1]		0.494
LISTLESS	0		0		1 (1.2%)	[1]		0.494
NIGHTMARE	0		0		1 (1.2%)	[1]		0.494
ANXIETY	0		3 (3.6%)	[4]	0		0.118*	
COMPLETED SUICIDE	1 (1.2%)	[1]	0		0		>0.99	>0.99
DEPRESSED MOOD	0		1 (1.2%)	[2]	0		0.494	
DISORIENTATION	1 (1.2%)	[1]	0		0		>0.99	>0.99
IRRITABILITY	1 (1.2%)	[2]	1 (1.2%)	[1]	0		>0.99	>0.99
RESTLESSNESS	0		1 (1.2%)	[2]	0		0.494	
RENAL AND URINARY DISORDERS	4 (4.7%)	[5]	3 (3.6%)	[3]	3 (3.6%)	[4]	>0.99	>0.99
CALCULUS URETHRAL	0		0		1 (1.2%)	[1]		0.494
MICTURITION URGENCY	1 (1.2%)	[1]	1 (1.2%)	[1]	1 (1.2%)	[2]	>0.99	>0.99
NEPHROLITHIASIS	1 (1.2%)	[1]	0		1 (1.2%)	[1]	>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
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Population: Safety

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86) n(%)	[AEs]	Xanomeline Low (N=84) n(%)	[AEs]	Xanomeline High (N=84) n(%)	[AEs]	Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
DYSURIA	1 (1.2%)	[1]	1 (1.2%)	[1]	0		>0.99	>0.99
INCONTINENCE	0		1 (1.2%)	[1]	0		0.494	
POLLAKIURIA	1 (1.2%)	[2]	0		0		>0.99	>0.99
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (2.3%)	[4]	0		1 (1.2%)	[1]	0.497	>0.99
BENIGN PROSTATIC HYPERPLASIA	1 (1.2%)	[2]	0		1 (1.2%)	[1]	>0.99	>0.99
PELVIC PAIN	1 (1.2%)	[2]	0		0		>0.99	>0.99
RESPIRATORY, THORACIC AND MEDIASTINAL DI	8 (9.3%)	[12]	9 (10.7%)	[14]	10 (11.9%)	[22]	0.803	0.626
COUGH	1 (1.2%)	[1]	5 (6.0%)	[7]	5 (6.0%)	[7]	0.115*	0.115*
NASAL CONGESTION	3 (3.5%)	[3]	1 (1.2%)	[1]	3 (3.6%)	[4]	0.621	>0.99
EPISTAXIS	0		1 (1.2%)	[1]	2 (2.4%)	[2]	0.494	0.243
ALLERGIC GRANULOMATOUS ANGIITIS	0		0		1 (1.2%)	[1]		0.494
DYSPNOEA	1 (1.2%)	[1]	1 (1.2%)	[1]	1 (1.2%)	[1]	>0.99	>0.99
PHARYNGEAL ERYTHEMA	0		0		1 (1.2%)	[2]		0.494
PHARYNGOLARYNGEAL PAIN	0		1 (1.2%)	[1]	1 (1.2%)	[1]	0.494	0.494
PRODUCTIVE COUGH	0		0		1 (1.2%)	[1]		0.494

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
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Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
RESPIRATORY TRACT CONGESTION	0		0		1 (1.2%)	[1]		0.494
RHINORRHOEA	0		1 (1.2%)	[2]	1 (1.2%)	[2]	0.494	0.494
DYSPHONIA	0		1 (1.2%)	[1]	0		0.494	
EMPHYSEMA	1 (1.2%)	[1]	0		0		>0.99	>0.99
HAEMOPTYSIS	1 (1.2%)	[2]	0		0		>0.99	>0.99
POSTNASAL DRIP	1 (1.2%)	[2]	0		0		>0.99	>0.99
RALES	1 (1.2%)	[2]	0		0		>0.99	>0.99
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	20 (23.3%)	[45]	39 (46.4%)	[111]	40 (47.6%)	[104]	0.002*	0.001*
PRURITUS	8 (9.3%)	[11]	21 (25.0%)	[31]	26 (31.0%)	[38]	0.008*	0.000*
ERYTHEMA	8 (9.3%)	[12]	14 (16.7%)	[22]	14 (16.7%)	[22]	0.175	0.175
RASH	5 (5.8%)	[9]	13 (15.5%)	[18]	9 (10.7%)	[15]	0.048*	0.277
HYPERHIDROSIS	2 (2.3%)	[2]	4 (4.8%)	[5]	8 (9.5%)	[10]	0.441	0.056*
SKIN IRRITATION	3 (3.5%)	[4]	6 (7.1%)	[13]	5 (6.0%)	[8]	0.326	0.493
RASH PRURITIC	0		1 (1.2%)	[2]	2 (2.4%)	[3]	0.494	0.243
ACTINIC KERATOSIS	0		0		1 (1.2%)	[1]		0.494
BLISTER	0		5 (6.0%)	[8]	1 (1.2%)	[2]	0.028*	0.494
PRURITUS GENERALISED	0		1 (1.2%)	[4]	1 (1.2%)	[1]	0.494	0.494
RASH MACULO-PAPULAR	0		0		1 (1.2%)	[1]		0.494

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo (N=86)		Xanomeline Low (N=84)		Xanomeline High (N=84)		Fisher's Exact p-values	
							Placebo vs.	Placebo vs.
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]	Low Dose	High Dose
SKIN ODOUR ABNORMAL	0		0		1 (1.2%) [1]			0.494
URTICARIA	0		1 (1.2%) [3]		1 (1.2%) [2]		0.494	0.494
ALOPECIA	1 (1.2%) [1]		0		0		>0.99	>0.99
COLD SWEAT	1 (1.2%) [3]		0		0		>0.99	>0.99
DERMATITIS CONTACT	0		1 (1.2%) [2]		0		0.494	
DRUG ERUPTION	1 (1.2%) [1]		0		0		>0.99	>0.99
RASH ERYTHEMATOUS	0		1 (1.2%) [1]		0		0.494	
SKIN EXFOLIATION	0		1 (1.2%) [2]		0		0.494	
SKIN ULCER	1 (1.2%) [2]		0		0		>0.99	>0.99
SOCIAL CIRCUMSTANCES	0		0		1 (1.2%) [1]			0.494
ALCOHOL USE	0		0		1 (1.2%) [1]			0.494
SURGICAL AND MEDICAL PROCEDURES	2 (2.3%) [2]		1 (1.2%) [1]		2 (2.4%) [2]		>0.99	>0.99
ACROCHORDON EXCISION	0		0		1 (1.2%) [1]			0.494
SKIN LESION EXCISION	0		0		1 (1.2%) [1]			0.494
CATARACT OPERATION	1 (1.2%) [1]		1 (1.2%) [1]		0		>0.99	>0.99
EYE LASER SURGERY	1 (1.2%) [1]		0		0		>0.99	>0.99
VASCULAR DISORDERS	3 (3.5%) [7]		3 (3.6%) [3]		1 (1.2%) [1]		>0.99	0.621

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.01
Incidence of Treatment Emergent Adverse Events by Treatment Group

| System Organ Class/ Preferred Term | Placebo (N=86) | | Xanomeline Low (N=84) | | Xanomeline High (N=84) | | Fisher's Exact p-values | |
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]	Placebo vs. Low Dose	Placebo vs. High Dose
WOUND HAEMORRHAGE	0		0		1 (1.2%)	[1]		0.494
HOT FLUSH	0		1 (1.2%)	[1]	0		0.494	
HYPERTENSION	1 (1.2%)	[2]	1 (1.2%)	[1]	0		>0.99	>0.99
HYPOTENSION	2 (2.3%)	[3]	1 (1.2%)	[1]	0		>0.99	0.497
ORTHOSTATIC HYPOTENSION	1 (1.2%)	[2]	0		0		>0.99	>0.99

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\aetable.sas   21:41 Monday, June 26, 2006

Table 14-5.02
Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

System Organ Class/ Preferred Term	Placebo ((N=86)		Xanomeline Low (N=84)		XanomelineHigh (N=84)		Fisher's Exact p-values Placebo vs. Low Dose	Placebo vs. High Dose
	n(%)	[AEs]	n(%)	[AEs]	n(%)	[AEs]		
ANY BODY SYSTEM	0		1 (1.2%)	[1]	2 (2.4%)	[2]	0.494	0.243
NERVOUS SYSTEM DISORDERS	0		1 (1.2%)	[1]	2 (2.4%)	[2]	0.494	0.243
SYNCOPE	0		1 (1.2%)	[1]	1 (1.2%)	[1]	0.494	0.494
PARTIAL SEIZURES WITH SECONDARY GENERA	0		0		1 (1.2%)	[1]		0.494

Note: Treatment emergent events are defined as events which start on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group. An asterisk is appended to p-values that are less than 0.15.
Note: The column [AE] represents the total number of times an event was recorded.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\saetable.sas   21:44 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)		

CHEMISTRY

ALANINE AMINOTRANSFERASE

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	86	17.6 (9.22)		82	18.0 (8.72)		84	19.2 (10.05)	
Wk 2	83	18.0 (12.53)	0.2 (7.90)	80	20.9 (10.55)	2.8 (8.18)	78	21.0 (8.87)	1.6 (6.83)
Wk 4	79	18.7 (12.91)	0.7 (8.66)	72	17.5 (7.66)	-0.7 (5.08)	72	21.3 (9.51)	2.1 (7.08)
Wk 6	73	17.0 (9.92)	-0.3 (7.78)	62	17.0 (7.98)	-0.8 (4.87)	66	21.2 (9.49)	1.6 (6.11)
Wk 8	72	16.7 (9.34)	-1.1 (5.05)	60	17.6 (7.86)	0.2 (5.45)	56	22.8 (17.49)	3.2 (17.24)
Wk 12	67	18.0 (9.16)	0.0 (8.07)	51	18.5 (12.68)	0.1 (9.27)	50	21.0 (10.18)	0.7 (8.74)
Wk 16	68	17.1 (7.39)	-0.8 (7.94)	42	17.3 (7.51)	0.7 (5.80)	37	19.6 (7.61)	-0.3 (7.58)
Wk 20	65	16.1 (6.56)	-1.9 (7.49)	30	16.7 (6.33)	0.9 (4.77)	31	19.6 (6.82)	-0.3 (8.63)
Wk 24	57	17.9 (15.61)	-0.3 (16.62)	26	18.2 (9.17)	1.6 (5.66)	30	21.0 (8.70)	0.2 (8.25)
Wk 26	57	16.0 (5.98)	-2.1 (7.70)	25	17.8 (9.51)	1.5 (6.26)	27	18.9 (7.02)	-2.0 (7.01)
End[1]	84	18.1 (16.74)	0.4 (15.40)	82	18.3 (8.26)	0.3 (7.25)	80	19.5 (7.44)	0.1 (8.08)

ALBUMIN

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	86	39.8 (2.81)		82	39.8 (2.56)		84	40.3 (2.84)	
Wk 2	83	38.9 (3.11)	-1.0 (2.49)	80	38.7 (3.17)	-1.1 (2.71)	78	38.9 (2.76)	-1.4 (2.59)
Wk 4	79	38.8 (3.29)	-1.0 (2.69)	72	38.6 (2.80)	-1.2 (2.66)	72	39.1 (3.05)	-1.3 (2.70)
Wk 6	73	39.1 (2.56)	-1.0 (2.25)	62	38.4 (2.60)	-1.2 (2.49)	66	39.5 (2.76)	-1.0 (2.60)
Wk 8	72	39.8 (3.51)	-0.4 (2.70)	60	39.1 (2.93)	-0.5 (2.73)	56	39.8 (2.33)	-0.9 (2.21)
Wk 12	67	39.5 (3.49)	-0.5 (2.31)	51	38.9 (2.18)	-0.9 (2.19)	50	39.8 (2.45)	-0.6 (2.77)
Wk 16	68	40.4 (3.02)	0.4 (2.45)	42	39.1 (2.98)	-0.4 (2.78)	37	39.9 (1.92)	-0.7 (2.76)
Wk 20	65	39.6 (3.47)	-0.5 (2.86)	30	38.6 (2.66)	-1.2 (2.55)	31	39.6 (1.85)	-1.4 (2.86)
Wk 24	57	39.7 (3.34)	-0.2 (2.88)	26	40.4 (2.52)	0.4 (2.40)	30	40.5 (2.10)	-0.5 (2.65)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Wk 26	57	39.8 (	3.02)	0.0 (	2.26)	25	39.2 (	2.39)	-1.0 (	2.85)	27	40.0 (	2.26)	-1.2 (	2.78)
End[1]	84	39.6 (	3.32)	-0.2 (	2.69)	82	39.2 (	2.97)	-0.5 (	2.64)	80	39.8 (	2.48)	-0.6 (	2.64)

ALKALINE PHOSPHATASE

Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Bsln	86	77.7 (	58.11)			81	73.3 (	20.72)			83	71.0 (	38.85)		
Wk 2	84	77.7 (	69.50)	0.1 (	15.51)	80	73.0 (	21.87)	0.3 (	10.25)	78	72.2 (	40.22)	-0.1 (	8.09)
Wk 4	82	78.0 (	69.43)	0.4 (	14.16)	72	73.2 (	23.17)	-0.3 (	11.12)	72	71.3 (	40.65)	-0.7 (	6.88)
Wk 6	75	68.4 (	21.53)	-0.4 (	10.40)	64	72.7 (	23.15)	-1.0 (	10.83)	67	71.5 (	43.40)	-0.2 (	12.65)
Wk 8	73	70.0 (	27.15)	-0.0 (	10.67)	60	72.9 (	23.84)	0.5 (	14.09)	56	74.0 (	45.60)	0.8 (	13.54)
Wk 12	67	72.1 (	32.73)	1.8 (	17.18)	52	69.5 (	20.55)	-1.5 (	9.41)	50	71.9 (	46.65)	-1.7 (	8.53)
Wk 16	68	70.6 (	29.49)	0.3 (	16.98)	42	69.5 (	19.43)	-1.7 (	8.61)	37	74.7 (	54.78)	-1.4 (	8.29)
Wk 20	65	72.6 (	37.41)	1.9 (	25.77)	31	70.6 (	22.20)	-2.2 (	9.90)	31	73.5 (	55.23)	-2.7 (	8.35)
Wk 24	56	80.6 (	68.06)	10.1 (	58.71)	27	72.0 (	21.80)	-0.4 (	8.93)	30	64.4 (	17.63)	-2.4 (	7.44)
Wk 26	57	81.0 (	79.33)	10.1 (	72.41)	25	68.6 (	21.08)	-4.1 (	10.74)	27	61.9 (	16.60)	-3.9 (	7.65)
End[1]	84	84.6 (	84.86)	7.1 (	49.37)	82	71.6 (	23.80)	-1.1 (	13.09)	80	70.3 (	37.91)	-1.6 (	12.00)

ASPARTATE AMINOTRANSFERASE

Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Bsln	86	23.2 (	7.50)			82	23.4 (	8.24)			84	23.1 (	6.61)		
Wk 2	83	23.6 (	12.35)	0.2 (	8.96)	80	24.7 (	8.06)	1.6 (	6.53)	78	23.4 (	5.20)	0.4 (	5.63)
Wk 4	79	23.9 (	14.93)	0.5 (	11.33)	72	22.3 (	6.75)	-1.4 (	6.40)	72	23.8 (	5.85)	0.6 (	5.75)
Wk 6	73	22.0 (	6.40)	-0.9 (	6.38)	62	22.1 (	6.11)	-0.4 (	4.19)	66	24.1 (	7.84)	0.4 (	6.10)
Wk 8	72	22.3 (	7.05)	-1.1 (	4.84)	60	22.7 (	5.95)	0.3 (	4.02)	56	25.7 (	13.33)	1.6 (	13.98)
Wk 12	67	22.8 (	7.64)	-0.6 (	7.06)	51	24.2 (	15.87)	1.5 (	12.39)	50	23.3 (	6.11)	-1.2 (	6.26)
Wk 16	68	22.8 (	6.42)	-0.6 (	6.43)	42	22.4 (	10.34)	0.6 (	7.62)	37	23.1 (	5.78)	-0.7 (	4.17)
Wk 20	65	21.9 (	5.90)	-1.6 (	6.07)	30	20.7 (	5.74)	0.4 (	4.60)	31	24.0 (	6.90)	-0.3 (	6.18)
Wk 24	57	25.2 (	21.02)	1.2 (	20.43)	26	22.4 (	10.78)	2.1 (	6.58)	30	24.4 (	7.29)	-0.2 (	5.48)
Wk 26	57	21.5 (	6.99)	-2.5 (	7.29)	25	22.1 (	11.85)	1.4 (	7.69)	27	21.6 (	5.71)	-3.1 (	4.17)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   *21:05 Monday, June 26, 2006*

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High			
				Change from Bsln					Change from Bsln					Change from Bsln	
Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
End[1]	84	25.1	(21.33)	1.8	(19.03)	82	23.2	(8.21)	-0.3	(8.06)	80	22.7	(6.13)	-0.4	(6.36)
BILIRUBIN															
Bsln	86	9.7	(3.96)			82	9.4	(4.01)			84	11.0	(5.35)		
Wk 2	83	10.8	(12.26)	1.1	(10.29)	79	9.4	(4.16)	-0.0	(3.08)	78	10.4	(3.94)	-0.6	(3.62)
Wk 4	79	11.1	(13.57)	1.4	(11.65)	71	9.2	(3.84)	-0.3	(2.70)	72	10.9	(5.62)	-0.3	(3.07)
Wk 6	73	9.6	(3.78)	0.1	(2.88)	62	9.5	(4.03)	-0.0	(2.99)	66	10.9	(4.89)	-0.6	(3.18)
Wk 8	72	9.4	(3.89)	-0.4	(3.43)	60	9.6	(4.72)	0.5	(3.11)	56	10.8	(5.21)	-0.7	(3.21)
Wk 12	67	9.5	(3.56)	-0.1	(2.83)	51	8.8	(4.15)	0.1	(2.64)	50	11.5	(6.16)	-0.3	(4.78)
Wk 16	68	10.0	(3.63)	0.2	(2.68)	42	8.8	(3.91)	0.4	(2.14)	37	11.6	(4.89)	-0.7	(4.28)
Wk 20	65	10.1	(5.19)	0.3	(3.58)	30	8.8	(4.51)	0.3	(2.82)	31	11.8	(8.69)	-0.2	(6.41)
Wk 24	55	9.4	(3.39)	0.1	(2.75)	25	10.1	(4.44)	1.1	(2.84)	30	12.3	(6.52)	-0.6	(2.89)
Wk 26	57	10.0	(4.73)	0.4	(3.57)	25	10.2	(6.21)	1.4	(3.44)	27	12.2	(6.82)	-0.6	(5.31)
End[1]	82	11.2	(13.42)	1.4	(11.28)	80	9.8	(4.29)	0.5	(3.08)	80	11.1	(5.36)	-0.0	(3.16)
CALCIUM															
Bsln	86	2.3	(0.09)			82	2.3	(0.11)			84	2.3	(0.10)		
Wk 2	84	2.3	(0.09)	-0.0	(0.10)	80	2.3	(0.12)	-0.0	(0.10)	78	2.3	(0.11)	-0.0	(0.11)
Wk 4	82	2.3	(0.09)	-0.0	(0.09)	72	2.3	(0.10)	-0.0	(0.08)	72	2.3	(0.10)	-0.0	(0.10)
Wk 6	75	2.3	(0.09)	-0.0	(0.10)	64	2.3	(0.10)	-0.0	(0.08)	67	2.3	(0.09)	-0.0	(0.10)
Wk 8	73	2.3	(0.09)	-0.0	(0.09)	60	2.3	(0.12)	-0.0	(0.09)	56	2.3	(0.12)	-0.0	(0.11)
Wk 12	67	2.3	(0.09)	-0.0	(0.08)	52	2.3	(0.10)	-0.0	(0.07)	50	2.3	(0.09)	-0.0	(0.09)
Wk 16	68	2.3	(0.10)	-0.0	(0.11)	42	2.3	(0.11)	-0.0	(0.08)	37	2.3	(0.11)	-0.0	(0.12)
Wk 20	66	2.3	(0.09)	-0.0	(0.09)	31	2.3	(0.10)	-0.0	(0.09)	31	2.3	(0.08)	-0.0	(0.09)
Wk 24	57	2.3	(0.09)	-0.1	(0.10)	27	2.3	(0.11)	-0.0	(0.12)	30	2.3	(0.10)	-0.1	(0.12)
Wk 26	57	2.3	(0.10)	-0.0	(0.10)	25	2.3	(0.10)	-0.0	(0.08)	27	2.3	(0.09)	-0.0	(0.10)
End[1]	84	2.3	(0.09)	-0.0	(0.10)	82	2.3	(0.10)	-0.0	(0.10)	80	2.3	(0.10)	-0.0	(0.11)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

	Placebo				Xanomeline Low				Xanomeline High			
			Change from Bsln				Change from Bsln				Change from Bsln	
Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
CHLORIDE									
Bsln	86	105.7 (3.19)		82	105.8 (3.25)		83	105.4 (3.33)	
Wk 2	84	106.0 (3.12)	0.3 (3.40)	80	105.6 (3.12)	-0.0 (3.44)	77	104.4 (3.49)	-0.8 (3.88)
Wk 4	82	105.6 (3.53)	-0.1 (4.24)	72	105.5 (2.88)	-0.3 (3.72)	72	105.0 (3.46)	-0.4 (3.94)
Wk 6	75	105.5 (3.14)	-0.1 (3.61)	64	106.3 (3.07)	0.6 (3.78)	67	105.3 (3.09)	-0.3 (3.47)
Wk 8	73	106.0 (3.34)	0.3 (3.52)	60	105.6 (3.01)	-0.2 (3.47)	56	105.2 (3.57)	-0.1 (3.71)
Wk 12	67	105.3 (2.93)	-0.3 (3.75)	52	105.7 (3.21)	-0.4 (3.63)	49	105.2 (2.40)	-0.1 (2.64)
Wk 16	68	105.5 (3.16)	-0.0 (3.57)	42	106.2 (2.93)	0.2 (3.17)	37	105.9 (2.66)	0.6 (2.54)
Wk 20	65	106.0 (3.68)	0.6 (4.13)	31	106.3 (2.75)	-0.1 (2.41)	31	105.4 (3.03)	-0.2 (3.69)
Wk 24	57	105.5 (3.14)	-0.1 (3.82)	27	105.3 (2.52)	-1.2 (2.95)	30	105.3 (3.21)	-0.1 (3.06)
Wk 26	57	106.2 (2.58)	0.8 (3.33)	25	105.7 (2.35)	-0.5 (2.72)	27	105.7 (3.44)	0.4 (2.92)
End[1]	84	105.6 (3.42)	-0.1 (3.86)	82	105.5 (3.37)	-0.1 (3.31)	80	105.0 (3.20)	-0.5 (3.17)
CHOLESTEROL									
Bsln	86	5.8 (1.07)		82	5.7 (1.00)		84	5.8 (1.02)	
Wk 2	84	5.6 (1.02)	-0.1 (0.54)	80	5.6 (0.92)	-0.1 (0.50)	78	5.6 (0.93)	-0.2 (0.53)
Wk 4	82	5.5 (0.94)	-0.2 (0.57)	72	5.5 (0.97)	-0.2 (0.49)	72	5.5 (1.00)	-0.3 (0.51)
Wk 6	75	5.6 (0.95)	-0.1 (0.67)	64	5.4 (0.95)	-0.2 (0.55)	67	5.5 (0.91)	-0.3 (0.64)
Wk 8	73	5.5 (1.02)	-0.2 (0.71)	60	5.5 (0.96)	-0.2 (0.49)	56	5.5 (0.94)	-0.3 (0.54)
Wk 12	67	5.5 (0.92)	-0.2 (0.57)	52	5.3 (0.90)	-0.3 (0.47)	50	5.4 (0.91)	-0.3 (0.63)
Wk 16	68	5.6 (0.98)	-0.1 (0.58)	42	5.3 (1.00)	-0.3 (0.48)	37	5.4 (0.94)	-0.2 (0.55)
Wk 20	66	5.5 (0.94)	-0.2 (0.68)	31	5.2 (0.86)	-0.4 (0.46)	31	5.3 (0.85)	-0.3 (0.49)
Wk 24	57	5.5 (1.01)	-0.3 (0.68)	27	5.4 (0.94)	-0.2 (0.65)	30	5.3 (0.89)	-0.3 (0.50)
Wk 26	57	5.5 (0.94)	-0.3 (0.62)	25	5.2 (0.76)	-0.4 (0.64)	27	5.4 (0.90)	-0.2 (0.81)
End[1]	84	5.5 (1.02)	-0.3 (0.76)	82	5.4 (0.96)	-0.3 (0.56)	80	5.4 (0.89)	-0.4 (0.60)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Population: Safety

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo				Xanomeline Low				Xanomeline High	
			Change from Bsln				Change from Bsln				Change from Bsln
Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)

CREATINE KINASE

Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
Bsln	86	86.9 (43.71)		82	100.6 (68.87)		84	104.0 (71.75)	
Wk 2	83	90.3 (66.11)	2.4 (57.72)	80	106.1 (83.92)	6.0 (84.97)	78	93.8 (53.19)	-12.0 (52.92)
Wk 4	79	96.9 (124.45)	8.3 (116.54)	72	93.2 (51.67)	-7.8 (55.54)	72	100.6 (58.39)	-4.8 (53.80)
Wk 6	73	88.0 (42.36)	-0.3 (40.55)	62	89.0 (44.29)	-13.7 (59.25)	66	123.5 (227.36)	17.8 (187.17)
Wk 8	72	93.8 (45.84)	1.2 (46.26)	60	90.0 (39.16)	-8.3 (61.09)	56	91.8 (52.25)	-9.3 (59.25)
Wk 12	67	101.8 (78.66)	8.9 (67.77)	51	94.7 (53.59)	-7.2 (65.59)	50	96.6 (60.55)	-2.8 (66.47)
Wk 16	68	104.9 (66.37)	12.7 (52.13)	42	97.5 (56.39)	-6.9 (72.02)	37	86.1 (47.70)	-1.6 (24.32)
Wk 20	65	93.8 (46.56)	1.0 (42.07)	30	111.6 (137.04)	21.5 (136.75)	31	97.5 (68.57)	6.0 (28.57)
Wk 24	57	127.4 (207.98)	32.6 (200.00)	26	83.6 (38.60)	0.8 (21.99)	30	90.9 (53.97)	-1.1 (23.40)
Wk 26	57	94.1 (51.03)	2.0 (46.93)	25	69.9 (23.70)	-15.0 (17.45)	27	93.0 (59.94)	1.4 (43.90)
End[1]	84	112.6 (173.34)	24.6 (165.91)	82	98.2 (61.12)	-1.9 (67.09)	80	95.1 (56.32)	-9.9 (60.94)

CREATININE

Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
Bsln	86	97.7 (17.78)		82	103.5 (20.01)		84	103.7 (19.37)	
Wk 2	84	99.0 (17.51)	1.4 (8.06)	80	106.2 (21.26)	2.3 (10.51)	78	106.3 (21.18)	2.8 (9.50)
Wk 4	82	98.6 (18.56)	1.1 (11.40)	72	105.1 (19.83)	2.0 (8.13)	72	105.8 (20.66)	2.6 (10.43)
Wk 6	75	101.7 (18.46)	3.3 (12.14)	64	104.4 (19.85)	1.7 (9.31)	67	105.8 (20.87)	3.2 (9.94)
Wk 8	73	99.1 (16.07)	-0.0 (9.88)	60	104.3 (21.27)	1.8 (7.54)	56	106.1 (22.24)	3.2 (9.14)
Wk 12	67	101.5 (16.53)	2.4 (9.68)	52	101.8 (17.72)	1.8 (7.99)	50	108.2 (20.48)	5.8 (10.95)
Wk 16	68	100.4 (16.43)	1.2 (10.57)	42	98.5 (16.63)	-1.3 (9.29)	37	102.5 (17.86)	2.2 (9.18)
Wk 20	66	100.3 (17.92)	1.3 (11.31)	31	97.2 (17.23)	-1.8 (8.17)	31	103.5 (19.66)	3.1 (11.76)
Wk 24	57	99.3 (15.85)	0.8 (11.37)	27	99.2 (16.14)	1.7 (7.08)	30	100.2 (19.61)	-0.6 (10.36)
Wk 26	57	100.0 (18.46)	2.0 (9.30)	25	99.7 (18.84)	2.9 (8.10)	27	101.8 (18.73)	0.3 (8.31)
End[1]	84	98.5 (16.13)	0.8 (10.77)	82	105.6 (19.79)	1.8 (8.60)	80	104.6 (20.50)	1.4 (10.38)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo				Xanomeline Low				Xanomeline High	
				Change from Bsln				Change from Bsln				Change from Bsln
Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)

GAMMA GLUTAMYL TRANSFERASE

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	86	24.9 (49.75)		82	22.2 (15.57)		84	22.8 (17.71)	
Wk 2	84	24.2 (47.03)	-0.8 (5.52)	80	22.6 (15.52)	0.2 (9.48)	78	23.7 (18.17)	0.6 (8.96)
Wk 4	82	24.5 (48.68)	-0.8 (5.69)	72	21.8 (13.82)	-1.1 (7.51)	72	23.3 (16.08)	0.1 (9.29)
Wk 6	75	19.9 (15.55)	0.3 (6.11)	64	21.9 (13.72)	-0.6 (6.88)	67	21.6 (13.48)	-0.5 (6.74)
Wk 8	73	20.6 (16.38)	0.1 (6.76)	60	23.6 (15.55)	1.1 (11.36)	56	26.8 (29.96)	4.0 (24.63)
Wk 12	67	21.4 (15.04)	0.5 (5.70)	52	21.9 (13.97)	-0.7 (8.80)	50	24.7 (21.26)	1.2 (8.19)
Wk 16	68	20.8 (13.00)	-0.1 (5.65)	42	22.8 (14.86)	-0.1 (6.38)	37	23.9 (17.79)	-1.3 (6.16)
Wk 20	66	20.4 (13.90)	-0.5 (5.42)	31	24.1 (17.52)	-0.4 (5.90)	31	22.2 (11.28)	-0.5 (5.98)
Wk 24	57	22.0 (16.68)	0.5 (10.90)	27	23.7 (14.75)	0.5 (7.28)	30	25.5 (22.64)	-0.9 (6.48)
Wk 26	57	21.4 (13.91)	-0.4 (7.08)	25	22.0 (15.31)	-1.0 (8.44)	27	23.4 (18.73)	-3.4 (7.97)
End[1]	84	25.7 (48.78)	0.7 (9.60)	82	22.4 (14.03)	0.3 (10.36)	80	22.3 (15.66)	-0.6 (9.81)

GLUCOSE

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	86	5.6 (2.14)		82	5.4 (0.94)		84	5.4 (1.34)	
Wk 2	83	5.6 (1.87)	-0.0 (1.37)	80	5.6 (1.75)	0.1 (1.50)	78	6.1 (2.92)	0.7 (2.06)
Wk 4	79	5.6 (1.87)	-0.0 (1.55)	70	5.4 (1.41)	-0.1 (1.09)	72	5.9 (1.84)	0.4 (1.25)
Wk 6	73	5.7 (2.22)	0.1 (1.37)	62	5.3 (1.34)	-0.1 (1.12)	66	6.0 (2.80)	0.5 (2.20)
Wk 8	72	5.5 (1.35)	-0.1 (2.09)	59	5.5 (1.76)	0.1 (1.34)	56	5.8 (2.15)	0.2 (1.68)
Wk 12	67	6.1 (1.97)	0.4 (1.97)	51	5.9 (3.18)	0.4 (2.78)	49	6.0 (2.28)	0.4 (1.64)
Wk 16	68	5.5 (1.42)	-0.2 (1.69)	42	5.3 (0.83)	-0.2 (0.89)	37	5.9 (2.30)	0.2 (1.74)
Wk 20	65	5.8 (1.50)	0.1 (2.08)	30	5.7 (1.73)	0.1 (1.39)	31	5.8 (1.61)	0.2 (1.47)
Wk 24	57	5.7 (1.83)	-0.1 (2.68)	26	5.7 (1.26)	0.2 (0.82)	30	6.0 (1.92)	0.5 (1.94)
Wk 26	57	5.8 (1.85)	-0.0 (1.60)	25	5.5 (1.72)	0.1 (1.35)	27	5.6 (1.01)	0.1 (1.66)
End[1]	84	5.6 (1.61)	0.0 (2.26)	82	5.4 (1.07)	-0.1 (1.03)	80	5.9 (2.15)	0.5 (1.62)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High			
				Change from Bsln					Change from Bsln					Change from Bsln	
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	
PHOSPHATE															
Bsln	86	1.2 (0.15)			81	1.2 (0.11)			83	1.2 (0.15)			
Wk 2	84	1.2 (0.15)	0.0 (0.16)	80	1.2 (0.15)	-0.0 (0.16)	78	1.2 (0.18)	0.0 (0.19)
Wk 4	82	1.1 (0.16)	-0.0 (0.17)	71	1.1 (0.14)	-0.0 (0.14)	72	1.2 (0.18)	-0.0 (0.16)
Wk 6	75	1.2 (0.15)	0.0 (0.17)	64	1.2 (0.17)	0.0 (0.17)	67	1.2 (0.15)	-0.0 (0.16)
Wk 8	73	1.1 (0.14)	0.0 (0.13)	60	1.1 (0.16)	-0.0 (0.16)	56	1.2 (0.16)	-0.0 (0.18)
Wk 12	67	1.2 (0.16)	0.0 (0.18)	52	1.1 (0.14)	-0.0 (0.18)	50	1.1 (0.15)	-0.0 (0.17)
Wk 16	68	1.1 (0.14)	-0.0 (0.15)	42	1.1 (0.17)	-0.0 (0.19)	37	1.2 (0.17)	0.0 (0.17)
Wk 20	65	1.2 (0.17)	0.0 (0.15)	31	1.1 (0.13)	0.0 (0.14)	31	1.2 (0.15)	-0.0 (0.16)
Wk 24	56	1.2 (0.15)	0.0 (0.16)	27	1.2 (0.19)	0.1 (0.19)	30	1.1 (0.17)	-0.0 (0.17)
Wk 26	57	1.2 (0.15)	0.0 (0.18)	25	1.1 (0.17)	0.0 (0.17)	27	1.2 (0.19)	0.0 (0.20)
End[1]	84	1.2 (0.17)	0.0 (0.18)	82	1.2 (0.17)	0.0 (0.18)	80	1.2 (0.16)	0.0 (0.17)
POTASSIUM															
Bsln	86	4.3 (0.43)			81	4.3 (0.34)			82	4.3 (0.41)			
Wk 2	84	4.2 (0.41)	-0.0 (0.37)	80	4.3 (0.41)	-0.0 (0.38)	77	4.3 (0.40)	-0.0 (0.46)
Wk 4	82	4.2 (0.37)	-0.1 (0.38)	71	4.3 (0.40)	-0.1 (0.36)	72	4.2 (0.37)	-0.1 (0.46)
Wk 6	75	4.3 (0.33)	0.0 (0.41)	64	4.3 (0.39)	-0.1 (0.41)	67	4.2 (0.32)	-0.1 (0.44)
Wk 8	73	4.2 (0.37)	-0.1 (0.43)	60	4.3 (0.39)	-0.0 (0.38)	56	4.2 (0.39)	-0.0 (0.50)
Wk 12	67	4.2 (0.41)	-0.0 (0.46)	52	4.2 (0.42)	-0.2 (0.40)	49	4.2 (0.26)	-0.1 (0.39)
Wk 16	68	4.2 (0.41)	-0.0 (0.46)	42	4.3 (0.33)	-0.1 (0.35)	37	4.3 (0.27)	0.0 (0.35)
Wk 20	64	4.3 (0.46)	0.0 (0.44)	31	4.3 (0.36)	-0.0 (0.44)	31	4.3 (0.37)	0.0 (0.40)
Wk 24	56	4.3 (0.44)	0.1 (0.44)	27	4.3 (0.41)	-0.0 (0.35)	30	4.2 (0.42)	-0.0 (0.50)
Wk 26	57	4.2 (0.38)	0.0 (0.34)	25	4.3 (0.40)	-0.0 (0.36)	27	4.3 (0.39)	0.0 (0.54)
End[1]	84	4.3 (0.43)	0.0 (0.41)	82	4.3 (0.43)	-0.1 (0.39)	80	4.2 (0.36)	-0.1 (0.47)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
Visit	N	Mean (SD)	Change from Bsln Mean (SD)		N	Mean (SD)	Change from Bsln Mean (SD)		N	Mean (SD)	Change from Bsln Mean (SD)	
PROTEIN														
Bsln	86	70.5 (4.72)			82	70.4 (4.29)			84	71.0 (4.24)		
Wk 2	84	69.2 (4.93)	-1.3 (4.53)		80	69.5 (4.48)	-0.9 (3.63)		78	69.5 (4.31)	-1.6 (3.91)	
Wk 4	82	69.0 (4.18)	-1.6 (3.93)		72	68.8 (4.30)	-1.5 (3.97)		72	69.8 (4.54)	-1.4 (3.90)	
Wk 6	75	69.6 (3.95)	-1.2 (4.01)		64	68.8 (4.33)	-1.3 (4.17)		67	70.2 (4.28)	-1.1 (4.10)	
Wk 8	73	70.5 (5.20)	-0.4 (4.35)		60	69.2 (3.95)	-0.9 (3.71)		56	70.6 (3.78)	-1.0 (3.57)	
Wk 12	67	70.0 (4.28)	-0.6 (3.86)		52	69.3 (4.98)	-0.8 (3.62)		50	70.4 (3.83)	-1.0 (4.11)	
Wk 16	68	71.2 (4.57)	0.4 (4.39)		42	69.3 (4.79)	-0.5 (4.27)		37	70.5 (4.93)	-1.0 (4.57)	
Wk 20	66	70.0 (4.92)	-1.1 (4.53)		31	68.7 (4.82)	-1.3 (3.88)		31	69.5 (4.15)	-1.8 (4.13)	
Wk 24	57	70.1 (4.33)	-0.8 (4.81)		27	70.9 (6.11)	0.7 (4.03)		30	70.7 (3.47)	-0.7 (3.83)	
Wk 26	57	70.4 (4.48)	-0.5 (4.56)		25	69.4 (5.29)	-1.1 (4.26)		27	69.4 (4.89)	-2.5 (4.01)	
End[1]	84	70.2 (4.26)	-0.3 (4.35)		82	70.1 (4.95)	-0.4 (3.97)		80	70.4 (3.91)	-0.7 (3.63)	
SODIUM														
Bsln	86	140.3 (2.74)			82	140.0 (2.61)			83	140.0 (3.11)		
Wk 2	84	140.4 (2.62)	-0.0 (3.35)		80	139.6 (2.47)	-0.3 (2.86)		77	139.1 (2.74)	-0.6 (2.87)	
Wk 4	82	139.9 (2.74)	-0.4 (3.58)		72	140.1 (2.40)	0.2 (3.16)		72	139.7 (2.75)	-0.3 (3.39)	
Wk 6	75	140.3 (2.58)	0.0 (3.08)		64	140.6 (2.69)	0.8 (3.25)		67	140.1 (2.61)	-0.2 (3.23)	
Wk 8	73	140.7 (2.48)	0.4 (3.33)		60	140.5 (2.58)	0.6 (3.33)		56	140.5 (3.15)	0.3 (3.79)	
Wk 12	67	140.4 (2.39)	0.2 (2.98)		52	141.1 (2.77)	1.1 (3.06)		49	140.2 (2.39)	-0.1 (2.79)	
Wk 16	68	141.1 (2.37)	0.9 (3.10)		42	141.0 (2.62)	1.2 (2.93)		37	141.6 (2.96)	1.4 (3.18)	
Wk 20	65	141.2 (2.53)	1.1 (3.01)		31	141.4 (2.53)	1.6 (3.42)		31	141.8 (3.87)	1.2 (3.61)	
Wk 24	57	141.7 (2.23)	1.6 (3.27)		27	141.5 (2.12)	1.2 (3.12)		30	141.6 (2.99)	1.0 (3.10)	
Wk 26	57	142.6 (2.25)	2.5 (2.90)		25	142.1 (2.08)	1.9 (3.13)		27	142.4 (3.07)	1.9 (3.43)	
End[1]	84	141.5 (2.74)	1.1 (3.51)		82	141.1 (2.65)	1.3 (3.09)		80	140.5 (3.22)	0.5 (3.50)	

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)		
URATE														
Bsln	86	285.0 (74.45)			82	300.7 (77.78)			84	302.2 (78.01)				
Wk 2	84	284.0 (68.72)	-1.8 (50.16)		80	305.8 (74.25)	1.0 (40.56)		78	301.7 (81.96)	-2.7 (33.85)			
Wk 4	82	285.6 (69.22)	-0.6 (35.59)		72	299.5 (79.44)	-3.7 (38.80)		72	291.4 (79.28)	-9.5 (42.17)			
Wk 6	75	288.0 (68.73)	-1.1 (38.24)		64	298.1 (74.46)	-6.2 (30.89)		67	291.6 (74.82)	-9.8 (34.48)			
Wk 8	73	285.6 (65.63)	-5.1 (36.28)		60	290.9 (71.15)	-15.6 (30.49)		56	291.6 (76.76)	-11.2 (35.13)			
Wk 12	67	291.1 (70.07)	3.2 (40.20)		52	290.3 (63.20)	-11.5 (31.83)		50	294.2 (78.84)	-9.0 (36.29)			
Wk 16	68	285.8 (68.72)	-3.6 (41.33)		42	288.8 (58.78)	-12.9 (39.98)		37	284.1 (80.47)	-19.9 (36.13)			
Wk 20	66	301.9 (73.43)	12.1 (40.18)		31	279.7 (58.71)	-16.5 (44.34)		31	295.1 (85.89)	-9.6 (43.81)			
Wk 24	57	293.5 (73.47)	4.6 (42.98)		27	274.9 (57.72)	-19.2 (31.26)		30	288.5 (88.37)	-19.4 (50.03)			
Wk 26	57	291.9 (74.43)	5.1 (44.39)		25	279.3 (60.01)	-13.6 (39.12)		27	301.1 (86.31)	-12.6 (47.68)			
End[1]	84	290.5 (73.86)	4.7 (46.43)		82	298.3 (80.54)	-3.1 (37.11)		80	292.4 (80.83)	-10.5 (42.35)			
UREA NITROGEN														
Bsln	86	5.5 (1.39)			82	6.4 (1.97)			84	5.8 (1.88)				
Wk 2	84	5.8 (1.51)	0.3 (1.17)		80	6.6 (1.82)	0.3 (1.53)		78	6.0 (2.06)	0.3 (1.36)			
Wk 4	82	5.9 (1.47)	0.3 (1.11)		72	6.4 (1.63)	0.0 (1.37)		72	5.9 (1.87)	0.3 (1.30)			
Wk 6	75	6.1 (1.42)	0.5 (1.16)		64	6.4 (1.76)	-0.1 (1.32)		67	6.0 (2.06)	0.3 (1.43)			
Wk 8	73	5.6 (1.58)	-0.0 (1.22)		60	6.3 (1.92)	-0.0 (0.95)		56	5.9 (1.93)	0.1 (1.25)			
Wk 12	67	5.9 (1.61)	0.2 (1.24)		52	6.2 (1.49)	-0.0 (1.45)		50	5.9 (1.76)	0.1 (1.50)			
Wk 16	68	5.8 (1.60)	0.2 (1.28)		42	6.0 (1.62)	-0.2 (1.25)		37	5.7 (1.92)	0.2 (1.29)			
Wk 20	66	5.8 (1.53)	0.1 (1.28)		31	5.6 (1.57)	-0.6 (1.39)		31	5.9 (2.25)	0.2 (1.50)			
Wk 24	57	5.9 (1.32)	0.3 (1.24)		27	6.0 (2.07)	-0.0 (1.37)		30	5.3 (1.92)	-0.3 (1.37)			
Wk 26	57	6.1 (1.62)	0.4 (1.36)		25	5.7 (1.93)	-0.3 (1.14)		27	5.9 (2.47)	0.3 (1.40)			
End[1]	84	5.9 (1.38)	0.3 (1.20)		82	6.6 (1.95)	0.2 (1.37)		80	5.7 (1.97)	-0.0 (1.57)			

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)		

HEMATOLOGY

BASOPHILS

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	85	0.1 (0.04)		81	0.1 (0.03)		81	0.1 (0.02)	
Wk 2	83	0.0 (0.02)	-0.0 (0.03)	80	0.1 (0.03)	-0.0 (0.03)	80	0.0 (0.03)	-0.0 (0.02)
Wk 4	79	0.0 (0.02)	-0.0 (0.03)	71	0.0 (0.03)	-0.0 (0.03)	71	0.0 (0.02)	-0.0 (0.02)
Wk 6	73	0.0 (0.03)	-0.0 (0.03)	62	0.0 (0.03)	-0.0 (0.03)	64	0.1 (0.03)	0.0 (0.03)
Wk 8	72	0.0 (0.02)	-0.0 (0.03)	59	0.1 (0.02)	-0.0 (0.04)	56	0.1 (0.03)	0.0 (0.02)
Wk 12	66	0.0 (0.02)	-0.0 (0.04)	50	0.0 (0.02)	-0.0 (0.03)	50	0.1 (0.03)	-0.0 (0.02)
Wk 16	68	0.0 (0.03)	-0.0 (0.04)	42	0.0 (0.02)	-0.0 (0.03)	37	0.1 (0.03)	-0.0 (0.02)
Wk 20	65	0.0 (0.03)	-0.0 (0.03)	30	0.0 (0.02)	-0.0 (0.03)	31	0.0 (0.02)	-0.0 (0.03)
Wk 24	58	0.0 (0.03)	-0.0 (0.03)	25	0.0 (0.03)	-0.0 (0.02)	30	0.1 (0.02)	-0.0 (0.02)
Wk 26	57	0.0 (0.02)	-0.0 (0.03)	25	0.0 (0.03)	-0.0 (0.02)	27	0.1 (0.03)	-0.0 (0.03)
End[1]	84	0.0 (0.03)	-0.0 (0.03)	82	0.0 (0.03)	-0.0 (0.03)	81	0.1 (0.02)	-0.0 (0.02)

EOSINOPHILS

Visit	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)	N	Mean (SD)	Change Mean (SD)
Bsln	85	0.1 (0.12)		81	0.1 (0.12)		81	0.1 (0.10)	
Wk 2	83	0.1 (0.10)	-0.0 (0.09)	80	0.2 (0.17)	0.0 (0.14)	80	0.1 (0.11)	-0.0 (0.07)
Wk 4	79	0.1 (0.13)	-0.0 (0.09)	71	0.2 (0.14)	0.0 (0.11)	71	0.2 (0.15)	0.0 (0.13)
Wk 6	73	0.1 (0.13)	-0.0 (0.11)	62	0.2 (0.21)	0.1 (0.16)	64	0.2 (0.28)	0.1 (0.25)
Wk 8	72	0.1 (0.10)	-0.0 (0.10)	59	0.3 (0.26)	0.2 (0.23)	56	0.2 (0.25)	0.1 (0.19)
Wk 12	66	0.1 (0.09)	-0.0 (0.11)	50	0.3 (0.21)	0.1 (0.19)	50	0.2 (0.17)	0.1 (0.14)
Wk 16	68	0.1 (0.08)	-0.0 (0.10)	42	0.2 (0.16)	0.1 (0.13)	37	0.2 (0.21)	0.1 (0.17)
Wk 20	65	0.1 (0.08)	-0.0 (0.10)	30	0.2 (0.19)	0.1 (0.16)	31	0.1 (0.11)	0.0 (0.12)
Wk 24	58	0.1 (0.08)	-0.0 (0.09)	25	0.2 (0.14)	0.0 (0.12)	30	0.2 (0.15)	0.0 (0.13)

[1] *Last observed value while on treatment (prior to or at Week 24)*
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas *21:05 Monday, June 26, 2006*

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

| | | Placebo | | | | | Xanomeline Low | | | | | Xanomeline High | | | |
| | | | | Change from Bsln | | | | | | Change from Bsln | | | | | | Change from Bsln | |
Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Wk 26	57	0.1 (	0.10)	-0.0 (	0.11)	25	0.2 (	0.15)	0.0 (	0.13)	27	0.1 (	0.10)	0.0 (	0.09)
End[1]	84	0.1 (	0.08)	-0.0 (	0.10)	82	0.2 (	0.17)	0.0 (	0.14)	81	0.2 (	0.20)	0.1 (	0.18)

ERY. MEAN CORPUSCULAR HB CONCENTRATION

Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Bsln	85	20.6 (	0.87)			80	20.2 (	0.98)			80	20.5 (	0.87)		
Wk 2	83	20.3 (	0.77)	-0.3 (	1.00)	80	20.3 (	0.85)	0.0 (	1.04)	80	20.4 (	0.74)	-0.0 (	0.98)
Wk 4	77	20.2 (	0.78)	-0.4 (	1.01)	69	20.2 (	0.72)	-0.0 (	0.94)	70	20.5 (	0.71)	-0.1 (	0.90)
Wk 6	72	20.5 (	0.77)	-0.2 (	0.98)	60	20.1 (	0.84)	-0.2 (	0.99)	65	20.4 (	0.89)	-0.2 (	1.00)
Wk 8	71	20.3 (	0.68)	-0.2 (	0.85)	56	20.2 (	0.83)	-0.0 (	0.92)	56	20.5 (	0.76)	-0.1 (	0.93)
Wk 12	65	20.3 (	0.74)	-0.3 (	0.96)	49	20.3 (	0.68)	-0.0 (	0.99)	50	20.5 (	0.76)	-0.1 (	1.03)
Wk 16	68	20.2 (	0.75)	-0.4 (	1.02)	42	20.0 (	0.82)	-0.2 (	1.02)	37	20.4 (	0.83)	-0.2 (	1.11)
Wk 20	64	20.3 (	0.80)	-0.3 (	0.94)	30	20.0 (	0.85)	-0.4 (	0.91)	31	20.3 (	0.88)	-0.3 (	1.22)
Wk 24	58	20.1 (	0.89)	-0.5 (	1.01)	25	20.3 (	0.91)	-0.3 (	0.95)	30	20.4 (	0.85)	-0.3 (	1.29)
Wk 26	56	20.3 (	0.99)	-0.4 (	1.16)	25	19.9 (	0.94)	-0.6 (	1.09)	27	20.2 (	0.92)	-0.6 (	1.12)
End[1]	83	20.2 (	0.85)	-0.4 (	0.99)	82	20.2 (	0.81)	-0.0 (	0.98)	81	20.4 (	0.78)	-0.1 (	1.08)

ERY. MEAN CORPUSCULAR HEMOGLOBIN

Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
Bsln	85	1.9 (	0.12)			81	1.9 (	0.09)			81	1.9 (	0.13)		
Wk 2	83	1.9 (	0.11)	-0.0 (	0.07)	80	1.9 (	0.09)	0.0 (	0.07)	80	1.9 (	0.13)	-0.0 (	0.07)
Wk 4	79	1.9 (	0.12)	-0.0 (	0.07)	71	1.9 (	0.09)	0.0 (	0.07)	71	1.9 (	0.13)	-0.0 (	0.06)
Wk 6	73	1.9 (	0.13)	0.0 (	0.08)	62	1.9 (	0.08)	0.0 (	0.05)	65	1.9 (	0.13)	-0.0 (	0.08)
Wk 8	72	1.9 (	0.12)	0.0 (	0.06)	59	1.9 (	0.09)	0.0 (	0.06)	56	1.9 (	0.10)	-0.0 (	0.07)
Wk 12	66	1.9 (	0.12)	0.0 (	0.06)	50	1.9 (	0.09)	0.0 (	0.05)	50	1.9 (	0.09)	-0.0 (	0.07)
Wk 16	68	1.9 (	0.12)	-0.0 (	0.05)	42	1.9 (	0.10)	-0.0 (	0.07)	37	1.9 (	0.11)	-0.0 (	0.08)
Wk 20	65	1.9 (	0.11)	-0.0 (	0.06)	30	1.9 (	0.08)	0.0 (	0.06)	31	1.9 (	0.12)	-0.0 (	0.08)
Wk 24	58	1.9 (	0.12)	-0.0 (	0.06)	25	1.9 (	0.09)	-0.0 (	0.06)	30	1.9 (	0.13)	-0.0 (	0.09)
Wk 26	57	1.9 (	0.12)	-0.0 (	0.07)	25	1.9 (	0.08)	-0.0 (	0.08)	27	1.9 (	0.12)	-0.0 (	0.08)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)	N	Mean	(SD)	Mean	(SD)
End[1]	84	1.9 (	0.12)	-0.0 (	0.07)	82	1.9 (	0.09)	0.0 (	0.06)	81	1.9 (	0.13)	0.0 (	0.07)
ERY. MEAN CORPUSCULAR VOLUME															
Bsln	85	92.9 (	5.69)			80	94.6 (	4.90)			80	93.3 (	5.91)		
Wk 2	83	94.1 (	5.31)	1.2 (	3.93)	80	94.6 (	4.12)	0.2 (	3.57)	80	93.4 (	5.93)	0.2 (	3.91)
Wk 4	77	94.6 (	5.87)	1.7 (	3.47)	69	95.1 (	4.22)	0.6 (	3.69)	70	93.0 (	5.52)	0.0 (	3.69)
Wk 6	72	94.2 (	6.21)	1.3 (	3.79)	60	95.2 (	4.51)	0.7 (	3.68)	65	94.0 (	6.61)	0.6 (	3.99)
Wk 8	71	94.3 (	5.51)	1.5 (	3.27)	56	94.9 (	3.97)	0.6 (	3.35)	56	94.4 (	4.77)	0.4 (	4.03)
Wk 12	65	94.2 (	5.66)	1.6 (	3.81)	49	95.1 (	4.17)	0.9 (	3.91)	50	94.9 (	4.90)	0.8 (	4.20)
Wk 16	68	94.1 (	6.01)	1.7 (	4.07)	42	95.8 (	5.17)	1.2 (	4.18)	37	94.7 (	6.27)	0.6 (	5.05)
Wk 20	64	93.3 (	5.58)	1.3 (	4.14)	30	95.4 (	5.43)	2.0 (	3.29)	31	95.1 (	5.91)	0.9 (	5.12)
Wk 24	58	93.9 (	5.90)	1.6 (	3.85)	25	94.3 (	3.85)	0.8 (	3.94)	30	95.0 (	5.99)	0.7 (	4.97)
Wk 26	56	93.9 (	6.40)	1.7 (	4.48)	25	95.8 (	4.33)	2.6 (	3.70)	27	95.4 (	6.19)	1.2 (	3.93)
End[1]	83	94.4 (	5.93)	1.4 (	4.07)	82	95.0 (	3.98)	0.6 (	3.83)	81	93.8 (	6.14)	0.7 (	4.40)
ERYTHROCYTES															
Bsln	85	4.5 (	0.45)			81	4.5 (	0.42)			81	4.7 (	0.47)		
Wk 2	83	4.4 (	0.40)	-0.1 (	0.22)	80	4.4 (	0.43)	-0.1 (	0.27)	80	4.6 (	0.47)	-0.1 (	0.22)
Wk 4	79	4.4 (	0.45)	-0.1 (	0.25)	71	4.4 (	0.38)	-0.2 (	0.30)	71	4.5 (	0.49)	-0.1 (	0.25)
Wk 6	73	4.4 (	0.37)	-0.1 (	0.24)	62	4.3 (	0.38)	-0.2 (	0.27)	65	4.5 (	0.50)	-0.1 (	0.24)
Wk 8	72	4.4 (	0.41)	-0.1 (	0.26)	59	4.4 (	0.34)	-0.2 (	0.24)	56	4.5 (	0.45)	-0.1 (	0.19)
Wk 12	66	4.4 (	0.44)	-0.1 (	0.26)	50	4.3 (	0.32)	-0.2 (	0.20)	50	4.6 (	0.47)	-0.1 (	0.27)
Wk 16	68	4.5 (	0.41)	-0.0 (	0.27)	42	4.3 (	0.36)	-0.1 (	0.24)	37	4.6 (	0.44)	-0.2 (	0.26)
Wk 20	65	4.5 (	0.41)	-0.1 (	0.30)	30	4.3 (	0.32)	-0.1 (	0.21)	31	4.5 (	0.50)	-0.2 (	0.30)
Wk 24	58	4.4 (	0.45)	-0.1 (	0.23)	25	4.4 (	0.38)	-0.1 (	0.19)	30	4.6 (	0.58)	-0.1 (	0.24)
Wk 26	57	4.4 (	0.42)	-0.0 (	0.25)	25	4.4 (	0.35)	-0.1 (	0.20)	27	4.5 (	0.47)	-0.2 (	0.27)
End[1]	84	4.4 (	0.43)	-0.1 (	0.27)	82	4.4 (	0.38)	-0.2 (	0.25)	81	4.6 (	0.49)	-0.1 (	0.22)

[1] Last observed value while on treatment (prior to or at Week 24)
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   *21:05 Monday, June 26, 2006*

Table 14-6.01

Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)		
HEMATOCRIT														
Bsln	85	0.4 (0.04)			80	0.4 (0.04)			80	0.4 (0.04)				
Wk 2	83	0.4 (0.04)	-0.0 (0.03)		80	0.4 (0.04)	-0.0 (0.03)		80	0.4 (0.04)	-0.0 (0.03)			
Wk 4	77	0.4 (0.04)	-0.0 (0.03)		69	0.4 (0.04)	-0.0 (0.03)		70	0.4 (0.04)	-0.0 (0.03)			
Wk 6	72	0.4 (0.04)	-0.0 (0.03)		60	0.4 (0.04)	-0.0 (0.03)		65	0.4 (0.04)	-0.0 (0.03)			
Wk 8	71	0.4 (0.04)	-0.0 (0.03)		56	0.4 (0.03)	-0.0 (0.02)		56	0.4 (0.03)	-0.0 (0.03)			
Wk 12	65	0.4 (0.04)	-0.0 (0.03)		49	0.4 (0.03)	-0.0 (0.02)		50	0.4 (0.04)	-0.0 (0.03)			
Wk 16	68	0.4 (0.04)	0.0 (0.03)		42	0.4 (0.03)	-0.0 (0.03)		37	0.4 (0.03)	-0.0 (0.04)			
Wk 20	64	0.4 (0.04)	-0.0 (0.03)		30	0.4 (0.03)	-0.0 (0.02)		31	0.4 (0.04)	-0.0 (0.04)			
Wk 24	58	0.4 (0.04)	0.0 (0.03)		25	0.4 (0.04)	-0.0 (0.02)		30	0.4 (0.04)	-0.0 (0.04)			
Wk 26	56	0.4 (0.04)	0.0 (0.03)		25	0.4 (0.04)	-0.0 (0.03)		27	0.4 (0.04)	-0.0 (0.03)			
End[1]	83	0.4 (0.04)	-0.0 (0.03)		82	0.4 (0.04)	-0.0 (0.03)		81	0.4 (0.04)	-0.0 (0.03)			
HEMOGLOBIN														
Bsln	85	8.6 (0.83)			81	8.6 (0.77)			81	8.9 (0.78)				
Wk 2	83	8.4 (0.76)	-0.2 (0.42)		80	8.4 (0.76)	-0.2 (0.46)		80	8.7 (0.83)	-0.2 (0.42)			
Wk 4	79	8.4 (0.82)	-0.2 (0.44)		71	8.4 (0.78)	-0.3 (0.50)		71	8.6 (0.78)	-0.2 (0.45)			
Wk 6	73	8.4 (0.77)	-0.2 (0.44)		62	8.3 (0.76)	-0.3 (0.46)		65	8.6 (0.75)	-0.3 (0.44)			
Wk 8	72	8.5 (0.76)	-0.2 (0.46)		59	8.3 (0.71)	-0.3 (0.39)		56	8.7 (0.73)	-0.3 (0.39)			
Wk 12	66	8.4 (0.83)	-0.2 (0.42)		50	8.3 (0.69)	-0.3 (0.34)		50	8.8 (0.79)	-0.3 (0.42)			
Wk 16	68	8.5 (0.73)	-0.1 (0.46)		42	8.3 (0.69)	-0.2 (0.42)		37	8.7 (0.70)	-0.3 (0.47)			
Wk 20	65	8.4 (0.80)	-0.2 (0.51)		30	8.2 (0.63)	-0.2 (0.46)		31	8.7 (0.79)	-0.4 (0.46)			
Wk 24	58	8.3 (0.82)	-0.2 (0.40)		25	8.4 (0.69)	-0.2 (0.36)		30	8.9 (0.85)	-0.3 (0.36)			
Wk 26	57	8.4 (0.80)	-0.2 (0.47)		25	8.3 (0.67)	-0.3 (0.39)		27	8.7 (0.74)	-0.5 (0.39)			
End[1]	84	8.4 (0.78)	-0.2 (0.44)		82	8.4 (0.69)	-0.2 (0.44)		81	8.7 (0.79)	-0.2 (0.36)			

[1] Last observed value while on treatment (prior to or at Week 24)

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_lb_cont.sas   21:05 Monday, June 26, 2006

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

		Placebo					Xanomeline Low					Xanomeline High		
				Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)	N	Mean (SD)		Mean (SD)
LEUKOCYTES												
Bsln	85	6.9 (1.76)			81	6.6 (1.95)			81	6.5 (1.54)		
Wk 2	83	6.5 (1.55)	-0.4 (1.40)	80	6.9 (1.99)	0.2 (1.37)	80	6.5 (1.59)	-0.1 (1.18)
Wk 4	79	6.4 (1.63)	-0.4 (1.17)	71	6.8 (2.12)	0.1 (1.53)	71	6.6 (1.42)	0.1 (1.21)
Wk 6	73	6.5 (1.57)	-0.4 (1.36)	62	6.9 (1.99)	0.1 (1.14)	65	7.0 (1.84)	0.4 (1.65)
Wk 8	72	6.5 (1.70)	-0.3 (1.28)	59	7.1 (1.88)	0.3 (1.26)	56	6.9 (1.95)	0.4 (1.64)
Wk 12	66	6.3 (1.28)	-0.5 (1.09)	50	6.8 (2.03)	0.2 (0.97)	50	6.6 (1.51)	-0.0 (1.21)
Wk 16	68	6.4 (1.50)	-0.5 (1.29)	42	6.6 (2.11)	0.2 (1.44)	37	6.8 (1.72)	-0.1 (1.37)
Wk 20	65	6.5 (1.77)	-0.5 (1.40)	30	6.5 (1.94)	0.1 (1.24)	31	6.6 (1.67)	-0.2 (1.21)
Wk 24	58	6.7 (1.77)	-0.2 (1.37)	25	6.3 (1.84)	0.0 (1.16)	30	6.7 (1.80)	-0.1 (1.16)
Wk 26	57	6.4 (1.47)	-0.4 (1.24)	25	6.1 (1.93)	-0.3 (1.15)	27	6.7 (1.78)	-0.2 (1.42)
End[1]	84	6.6 (1.80)	-0.2 (1.32)	82	6.8 (2.17)	0.1 (1.35)	81	6.7 (1.76)	0.2 (1.37)
LYMPHOCYTES												
Bsln	85	1.8 (0.57)			81	1.8 (0.57)			81	1.7 (0.52)		
Wk 2	83	1.7 (0.50)	-0.1 (0.37)	80	1.8 (0.66)	0.0 (0.45)	80	1.7 (0.50)	0.0 (0.38)
Wk 4	79	1.7 (0.56)	-0.0 (0.38)	71	1.8 (0.67)	0.0 (0.49)	71	1.7 (0.50)	-0.0 (0.44)
Wk 6	73	1.8 (0.58)	-0.0 (0.41)	62	1.9 (0.64)	0.1 (0.47)	64	1.7 (0.48)	-0.0 (0.44)
Wk 8	72	1.8 (0.67)	-0.0 (0.44)	59	1.9 (0.65)	0.1 (0.45)	56	1.7 (0.50)	-0.0 (0.36)
Wk 12	66	1.7 (0.58)	-0.1 (0.42)	50	1.8 (0.58)	-0.1 (0.45)	50	1.6 (0.47)	-0.0 (0.37)
Wk 16	68	1.7 (0.58)	-0.1 (0.42)	42	1.8 (0.63)	-0.1 (0.34)	37	1.7 (0.62)	0.0 (0.41)
Wk 20	65	1.7 (0.50)	-0.1 (0.45)	30	1.7 (0.59)	-0.1 (0.50)	31	1.7 (0.59)	-0.0 (0.36)
Wk 24	58	1.8 (0.65)	-0.0 (0.48)	25	1.8 (0.56)	-0.1 (0.37)	30	1.7 (0.56)	-0.0 (0.37)
Wk 26	57	1.8 (0.59)	-0.0 (0.43)	25	1.7 (0.62)	-0.1 (0.39)	27	1.8 (0.61)	0.1 (0.50)
End[1]	84	1.8 (0.59)	-0.0 (0.46)	82	1.8 (0.62)	-0.0 (0.46)	81	1.6 (0.54)	-0.0 (0.38)

[1] Last observed value while on treatment (prior to or at Week 24)

Table 14-6.01
Summary Statistics for Continuous Laboratory Values

	Placebo				Xanomeline Low				Xanomeline High			
			Change from Bsln					Change from Bsln					Change from Bsln
Visit	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
MONOCYTES									
Bsln	85	0.4 (0.15)		81	0.5 (0.16)		81	0.4 (0.12)	
Wk 2	83	0.4 (0.15)	-0.0 (0.14)	80	0.5 (0.16)	0.0 (0.13)	80	0.4 (0.15)	0.0 (0.12)
Wk 4	79	0.4 (0.12)	0.0 (0.11)	71	0.5 (0.17)	-0.0 (0.15)	71	0.4 (0.13)	0.0 (0.13)
Wk 6	73	0.4 (0.15)	-0.0 (0.13)	62	0.5 (0.19)	0.0 (0.16)	64	0.5 (0.15)	0.0 (0.13)
Wk 8	72	0.4 (0.14)	0.0 (0.14)	59	0.5 (0.14)	0.0 (0.14)	56	0.5 (0.15)	0.0 (0.14)
Wk 12	66	0.4 (0.13)	0.0 (0.13)	50	0.5 (0.15)	0.0 (0.12)	50	0.4 (0.15)	-0.0 (0.11)
Wk 16	68	0.5 (0.15)	0.0 (0.17)	42	0.5 (0.16)	0.0 (0.12)	37	0.5 (0.16)	0.0 (0.14)
Wk 20	65	0.5 (0.16)	0.0 (0.15)	30	0.5 (0.13)	0.0 (0.13)	31	0.5 (0.17)	0.0 (0.18)
Wk 24	58	0.5 (0.17)	0.0 (0.17)	25	0.5 (0.19)	0.0 (0.11)	30	0.5 (0.18)	-0.0 (0.12)
Wk 26	57	0.4 (0.14)	0.0 (0.14)	25	0.4 (0.17)	-0.0 (0.12)	27	0.5 (0.14)	-0.0 (0.13)
End[1]	84	0.5 (0.17)	0.0 (0.17)	82	0.5 (0.17)	0.0 (0.13)	81	0.5 (0.15)	0.0 (0.12)
PLATELET									
Bsln	84	250.3 (65.52)		79	233.8 (58.58)		81	227.7 (54.74)	
Wk 2	83	246.2 (57.55)	-4.4 (36.21)	78	247.4 (59.37)	9.1 (46.36)	80	238.2 (59.77)	8.4 (31.55)
Wk 4	78	243.8 (54.30)	-7.4 (40.04)	70	239.2 (57.80)	5.7 (39.75)	70	238.3 (49.60)	9.8 (29.21)
Wk 6	73	250.8 (58.97)	-3.3 (36.82)	62	238.3 (55.74)	3.5 (43.39)	63	239.1 (56.79)	9.2 (37.82)
Wk 8	72	246.0 (66.61)	-6.2 (42.35)	59	245.4 (60.21)	5.1 (46.18)	55	236.9 (70.88)	11.0 (48.13)
Wk 12	65	241.9 (53.71)	-12.8 (42.62)	50	238.8 (49.49)	1.9 (24.69)	49	236.1 (53.03)	9.1 (34.47)
Wk 16	68	241.8 (55.65)	-13.7 (43.45)	41	244.5 (57.60)	2.8 (32.93)	37	230.9 (58.00)	5.3 (25.87)
Wk 20	65	248.4 (60.70)	-8.4 (30.42)	30	240.7 (64.07)	7.3 (42.65)	30	235.1 (65.46)	2.3 (22.80)
Wk 24	57	238.8 (51.89)	-11.3 (35.06)	24	249.7 (63.44)	1.8 (33.48)	29	238.3 (67.53)	4.5 (26.74)
Wk 26	56	247.6 (60.11)	-2.7 (41.73)	25	241.3 (57.16)	-1.9 (38.84)	27	237.4 (67.14)	0.3 (26.99)
End[1]	84	241.5 (59.49)	-8.5 (35.55)	82	236.7 (63.56)	1.1 (36.31)	81	233.8 (60.79)	4.1 (35.89)

[1] Last observed value while on treatment (prior to or at Week 24)

Table 14-6.02
Frequency of Normal and Abnormal (Beyond Normal Range) Laboratory Values During Treatment

| | Placebo (N=86) | | | Xan. Low (N=84) | | | Xan. High (N=84) | | | p-val [1] |
	Low	Normal	High	Low	Normal	High	Low	Normal	High	
CHEMISTRY										

ALBUMIN	16(19%)	65(77%)	3(4%)	15(18%)	66(80%)	1(1%)	5(6%)	74(93%)	1(1%)	0.042
ALKALINE PHOSPHATASE	4(5%)	72(86%)	8(10%)	2(2%)	74(90%)	6(7%)	3(4%)	73(91%)	4(5%)	0.776
ALANINE AMINOTRANSFERASE	1(1%)	74(88%)	9(11%)	5(6%)	68(83%)	9(11%)	0	70(88%)	10(13%)	0.185
ASPARTATE AMINOTRANSFERASE	0	74(88%)	10(12%)	0	72(88%)	10(12%)	0	72(90%)	8(10%)	0.907
BILIRUBIN	0	78(93%)	6(7%)	0	79(98%)	2(2%)	0	75(94%)	5(6%)	0.402
UREA NITROGEN	0	75(89%)	9(11%)	0	60(73%)	22(27%)	0	68(85%)	12(15%)	0.023
CALCIUM	5(6%)	78(93%)	1(1%)	7(9%)	72(88%)	3(4%)	7(9%)	71(89%)	2(3%)	0.789
CHOLESTEROL	5(6%)	73(87%)	6(7%)	6(7%)	72(88%)	4(5%)	6(8%)	70(88%)	4(5%)	0.962
CREATINE KINASE	1(1%)	66(79%)	17(20%)	1(1%)	68(83%)	13(16%)	0	67(84%)	13(16%)	0.816
CHLORIDE	0	74(88%)	10(12%)	0	74(90%)	8(10%)	0	78(98%)	2(3%)	0.058
CREATININE	0	80(95%)	4(5%)	0	76(93%)	6(7%)	0	73(91%)	7(9%)	0.572
GAMMA GLUTAMYL TRANSFERASE	4(5%)	73(87%)	7(8%)	4(5%)	69(84%)	9(11%)	1(1%)	71(89%)	8(10%)	0.689
GLUCOSE	0	82(98%)	2(2%)	0	81(99%)	1(1%)	0	77(96%)	3(4%)	0.534
POTASSIUM	3(4%)	80(95%)	1(1%)	3(4%)	79(96%)	0	2(3%)	78(98%)	0	1.000
SODIUM	4(5%)	75(89%)	5(6%)	3(4%)	74(90%)	5(6%)	7(9%)	62(78%)	11(14%)	0.177
PHOSPHATE	1(1%)	83(99%)	0	0	80(98%)	2(2%)	1(1%)	78(98%)	1(1%)	0.518
PROTEIN	1(1%)	76(90%)	7(8%)	2(2%)	75(91%)	5(6%)	1(1%)	77(96%)	2(3%)	0.536
URATE	3(4%)	77(92%)	4(5%)	1(1%)	75(91%)	6(7%)	4(5%)	69(86%)	7(9%)	0.564
HEMATOLOGY										

Note: Percentages are based on the number of subjects with non-missing assessments (i.e., the total of the subjects in the low, normal, and high categories) within each treatment group.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labnormfreq.sas   21:05 Monday, June 26, 2006

Table 14-6.02

Frequency of Normal and Abnormal (Beyond Normal Range) Laboratory Values During Treatment

	Placebo (N=86)			Xan. Low (N=84)			Xan. High (N=84)			p-val [1]
	Low	Normal	High	Low	Normal	High	Low	Normal	High	
BASOPHILS	0	84(100%)	0	0	82(100%)	0	0	81(100%)	0	
EOSINOPHILS	0	84(100%)	0	0	71(87%)	11(13%)	0	74(91%)	7(9%)	0.001
HEMATOCRIT	5(6%)	74(89%)	4(5%)	9(11%)	72(88%)	1(1%)	1(1%)	78(96%)	2(2%)	0.052
HEMOGLOBIN	14(17%)	68(81%)	2(2%)	10(12%)	72(88%)	0	5(6%)	73(90%)	3(4%)	0.093
LYMPHOCYTES	6(7%)	73(87%)	5(6%)	4(5%)	69(84%)	9(11%)	4(5%)	76(94%)	1(1%)	0.103
ERY. MEAN CORPUSCULAR HEMOGLOBIN	0	81(96%)	3(4%)	0	81(99%)	1(1%)	1(1%)	75(93%)	5(6%)	0.186
ERY. MEAN CORPUSCULAR HB CONCENTRATION	15(18%)	68(82%)	0	17(21%)	65(79%)	0	9(11%)	72(89%)	0	0.231
ERY. MEAN CORPUSCULAR VOLUME	1(1%)	53(64%)	29(35%)	0	64(78%)	18(22%)	1(1%)	64(79%)	16(20%)	0.077
MONOCYTES	2(2%)	80(95%)	2(2%)	1(1%)	77(94%)	4(5%)	0	79(98%)	2(2%)	0.626
PLATELET	0	81(96%)	3(4%)	2(2%)	77(94%)	3(4%)	2(2%)	77(95%)	2(2%)	0.681
ERYTHROCYTES	13(15%)	71(85%)	0	18(22%)	64(78%)	0	11(14%)	68(84%)	2(2%)	0.238
LEUKOCYTES	7(8%)	73(87%)	4(5%)	6(7%)	68(83%)	8(10%)	4(5%)	74(91%)	3(4%)	0.462

Note: Percentages are based on the number of subjects with non-missing assessments (i.e., the total of the subjects in the low, normal, and high categories) within each treatment group.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labnormfreq.sas   21:05 Monday, June 26, 2006

Table 14-6.03
Frequency of Normal and Abnormal (Clinically Significant Change from Previous Visit) Laboratory Values
During Treatment

	Placebo (N=86)			Xan. Low (N=84)			Xan. High (N=84)			p-val [1]
	Low	Normal	High	Low	Normal	High	Low	Normal	High	
CHEMISTRY										

ALBUMIN	10(12%)	71(85%)	3(4%)	6(7%)	72(88%)	4(5%)	5(6%)	66(83%)	9(11%)	0.235
ALKALINE PHOSPHATASE	1(1%)	78(93%)	5(6%)	0	79(98%)	2(2%)	0	77(96%)	3(4%)	0.599
ALANINE AMINOTRANSFERASE	4(5%)	75(89%)	5(6%)	6(7%)	69(84%)	7(9%)	7(9%)	68(85%)	5(6%)	0.820
ASPARTATE AMINOTRANSFERASE	2(2%)	73(87%)	9(11%)	8(10%)	71(87%)	3(4%)	3(4%)	75(94%)	2(3%)	0.045
BILIRUBIN	0	79(94%)	5(6%)	1(1%)	79(98%)	1(1%)	2(3%)	75(94%)	3(4%)	0.296
UREA NITROGEN	0	83(99%)	1(1%)	1(1%)	79(96%)	2(2%)	1(1%)	78(98%)	1(1%)	0.796
CALCIUM	6(7%)	76(90%)	2(2%)	4(5%)	76(93%)	2(2%)	0	77(96%)	3(4%)	0.140
CHOLESTEROL	1(1%)	81(96%)	2(2%)	0	82(100%)	0	1(1%)	79(99%)	0	0.500
CREATINE KINASE	8(10%)	64(76%)	12(14%)	6(7%)	71(87%)	5(6%)	7(9%)	65(81%)	8(10%)	0.474
CHLORIDE	3(4%)	78(93%)	3(4%)	0	80(98%)	2(2%)	2(3%)	77(96%)	1(1%)	0.496
CREATININE	0	82(98%)	2(2%)	0	81(99%)	1(1%)	0	80(100%)	0	0.775
GAMMA GLUTAMYL TRANSFERASE	1(1%)	81(96%)	2(2%)	4(5%)	72(88%)	6(7%)	2(3%)	74(93%)	4(5%)	0.378
GLUCOSE	1(1%)	81(96%)	2(2%)	1(1%)	81(99%)	0	3(4%)	74(93%)	3(4%)	0.317
POTASSIUM	2(2%)	82(98%)	0	2(2%)	78(96%)	1(1%)	3(4%)	74(93%)	3(4%)	0.464
SODIUM	10(12%)	60(71%)	14(17%)	7(9%)	62(76%)	13(16%)	12(15%)	58(73%)	10(13%)	0.728
PHOSPHATE	1(1%)	82(98%)	1(1%)	0	79(98%)	2(2%)	2(3%)	76(95%)	2(3%)	0.661
PROTEIN	5(6%)	73(87%)	6(7%)	1(1%)	80(98%)	1(1%)	5(6%)	74(93%)	1(1%)	0.062
URATE	2(2%)	81(96%)	1(1%)	0	82(100%)	0	0	80(100%)	0	0.331

Note: Percentages are based on the number of subjects with non-missing assessments (i.e., the total of the subjects in the low, normal, and high categories) within each treatment group.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labnormfreq.sas   21:05 Monday, June 26, 2006

Population: Safety

Table 14-6.03
Frequency of Normal and Abnormal (Clinically Significant Change from Previous Visit) Laboratory Values
During Treatment

	Placebo (N=86)			Xan. Low (N=84)			Xan. High (N=84)			p-val [1]
	Low	**Normal**	**High**	**Low**	**Normal**	**High**	**Low**	**Normal**	**High**	
HEMATOLOGY										

BASOPHILS	1(1%)	82(98%)	1(1%)	2(2%)	80(98%)	0	1(1%)	79(99%)	0	0.948
EOSINOPHILS	4(5%)	80(95%)	0	3(4%)	70(85%)	9(11%)	4(5%)	68(85%)	8(10%)	0.010
HEMATOCRIT	2(2%)	79(95%)	2(2%)	4(5%)	77(95%)	0	1(1%)	76(95%)	3(4%)	0.351
HEMOGLOBIN	0	84(100%)	0	2(2%)	80(98%)	0	0	80(100%)	0	0.215
LYMPHOCYTES	4(5%)	76(90%)	4(5%)	2(2%)	79(96%)	1(1%)	2(3%)	77(96%)	1(1%)	0.498
ERY. MEAN CORPUSCULAR HEMOGLOBIN	1(1%)	83(99%)	0	0	81(99%)	1(1%)	0	80(100%)	0	0.884
ERY. MEAN CORPUSCULAR HB CONCENTRATION	1(1%)	82(99%)	0	0	80(99%)	1(1%)	0	80(100%)	0	0.885
ERY. MEAN CORPUSCULAR VOLUME	0	80(96%)	3(4%)	2(2%)	78(96%)	1(1%)	1(1%)	75(94%)	4(5%)	0.396
MONOCYTES	5(6%)	74(88%)	5(6%)	1(1%)	80(98%)	1(1%)	1(1%)	78(98%)	1(1%)	0.081
PLATELET	0	84(100%)	0	1(1%)	80(98%)	1(1%)	0	79(99%)	1(1%)	0.546
ERYTHROCYTES	0	83(99%)	1(1%)	1(1%)	81(99%)	0	0	80(100%)	0	0.884
LEUKOCYTES	4(5%)	78(93%)	2(2%)	2(2%)	77(94%)	3(4%)	3(4%)	74(93%)	3(4%)	0.934

Note: Percentages are based on the number of subjects with non-missing assessments (i.e., the total of the subjects in the low, normal, and high categories) within each treatment group.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labnormfreq.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
CHEMISTRY								

ALANINE AMINOTRANSFERASE	2	n	81	2	77	1	78	0
		Normal	81(100%)	0	77(100%)	0	78(100%)	0
		High	0	2(100%)	0	1(100%)	0	0
	4	n	77	2	69	1	72	0
		Normal	77(100%)	1(50%)	69(100%)	0	72(100%)	0
		High	0	1(50%)	0	1(100%)	0	0
	6	n	72	1	59	1	66	0
		Normal	71(99%)	1(100%)	59(100%)	0	66(100%)	0
		High	1(1%)	0	0	1(100%)	0	0
	8	n	71	1	57	1	56	0
		Normal	71(100%)	0	57(100%)	0	54(96%)	0
		High	0	1(100%)	0	1(100%)	2(4%)	0
	12	n	66	1	49	1	50	0
		Normal	65(98%)	1(100%)	48(98%)	1(100%)	49(98%)	0
		High	1(2%)	0	1(2%)	0	1(2%)	0
	16	n	67	1	40	0	37	0
		Normal	67(100%)	1(100%)	40(100%)	0	37(100%)	0
	20	n	64	1	29	0	31	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Population: Safety

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	64(100%)	1(100%)	29(100%)	0	31(100%)	0
	24	n	56	1	25	0	30	0
		Normal	55(98%)	1(100%)	25(100%)	0	30(100%)	0
		High	1(2%)	0	0	0	0	0
	26	n	56	1	24	0	27	0
		Normal	56(100%)	1(100%)	23(96%)	0	27(100%)	0
		High	0	0	1(4%)	0	0	0
ALBUMIN	2	n	83	0	78	0	78	0
		Normal	83(100%)	0	78(100%)	0	78(100%)	0
	4	n	79	0	70	0	72	0
		Normal	79(100%)	0	70(100%)	0	72(100%)	0
	6	n	73	0	60	0	66	0
		Normal	73(100%)	0	60(100%)	0	66(100%)	0
	8	n	72	0	58	0	56	0
		Normal	72(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	20	n	65	0	29	0	31	0
		Normal	65(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	25	0	30	0
		Normal	57(100%)	0	25(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0
ALKALINE PHOSPHATASE	2	n	82	2	78	0	77	1
		Normal	82(100%)	0	78(100%)	0	77(100%)	0
		High	0	2(100%)	0	0	0	1(100%)
	4	n	80	2	69	0	71	1
		Normal	80(100%)	0	69(100%)	0	71(100%)	0
		High	0	2(100%)	0	0	0	1(100%)
	6	n	75	0	62	0	66	1
		Normal	75(100%)	0	62(100%)	0	66(100%)	0
		High	0	0	0	0	0	1(100%)
	8	n	72	1	58	0	55	1
		Normal	72(100%)	0	57(98%)	0	55(100%)	0
		High	0	1(100%)	1(2%)	0	0	1(100%)
	12	n	66	1	50	0	49	1

NOTES: Only subjects with baseline results are included in the summary.

There were no subjects with abnormal low values at baseline.

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas　　　　　*21:05 Monday, June 26, 2006*

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	66(100%)	0	50(100%)	0	49(100%)	0
		High	0	1(100%)	0	0	0	1(100%)
	16	n	67	1	40	0	36	1
		Normal	67(100%)	0	40(100%)	0	36(100%)	0
		High	0	1(100%)	0	0	0	1(100%)
	20	n	64	1	30	0	30	1
		Normal	63(98%)	0	30(100%)	0	30(100%)	0
		High	1(2%)	1(100%)	0	0	0	1(100%)
	24	n	55	1	26	0	30	0
		Normal	54(98%)	0	26(100%)	0	30(100%)	0
		High	1(2%)	1(100%)	0	0	0	0
	26	n	56	1	24	0	27	0
		Normal	55(98%)	0	24(100%)	0	27(100%)	0
		High	1(2%)	1(100%)	0	0	0	0
ASPARTATE AMINOTRANSFERASE	2	n	81	2	78	0	78	0
		Normal	80(99%)	1(50%)	77(99%)	0	78(100%)	0
		High	1(1%)	1(50%)	1(1%)	0	0	0
	4	n	77	2	69	1	72	0
		Normal	76(99%)	1(50%)	69(100%)	1(100%)	72(100%)	0
		High	1(1%)	1(50%)	0	0	0	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

		Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
6	n	72	1	60	0	66	0
	Normal	71(99%)	1(100%)	60(100%)	0	65(98%)	0
	High	1(1%)	0	0	0	1(2%)	0
8	n	71	1	58	0	56	0
	Normal	70(99%)	1(100%)	58(100%)	0	55(98%)	0
	High	1(1%)	0	0	0	1(2%)	0
12	n	66	1	50	0	50	0
	Normal	65(98%)	1(100%)	49(98%)	0	50(100%)	0
	High	1(2%)	0	1(2%)	0	0	0
16	n	67	1	40	0	37	0
	Normal	67(100%)	1(100%)	39(98%)	0	37(100%)	0
	High	0	0	1(3%)	0	0	0
20	n	64	1	29	0	31	0
	Normal	64(100%)	1(100%)	29(100%)	0	31(100%)	0
24	n	56	1	25	0	30	0
	Normal	54(96%)	1(100%)	24(96%)	0	30(100%)	0
	High	2(4%)	0	1(4%)	0	0	0
26	n	56	1	24	0	27	0
	Normal	55(98%)	1(100%)	23(96%)	0	27(100%)	0
	High	1(2%)	0	1(4%)	0	0	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
BILIRUBIN	2	n	83	0	78	0	77	1
		Normal	82(99%)	0	78(100%)	0	77(100%)	1(100%)
		High	1(1%)	0	0	0	0	0
	4	n	79	0	70	0	71	1
		Normal	78(99%)	0	70(100%)	0	71(100%)	0
		High	1(1%)	0	0	0	0	1(100%)
	6	n	73	0	60	0	65	1
		Normal	73(100%)	0	60(100%)	0	65(100%)	1(100%)
	8	n	72	0	58	0	55	1
		Normal	72(100%)	0	58(100%)	0	55(100%)	1(100%)
	12	n	67	0	50	0	49	1
		Normal	67(100%)	0	50(100%)	0	48(98%)	1(100%)
		High	0	0	0	0	1(2%)	0
	16	n	68	0	40	0	36	1
		Normal	68(100%)	0	40(100%)	0	36(100%)	1(100%)
	20	n	65	0	29	0	30	1
		Normal	65(100%)	0	29(100%)	0	29(97%)	1(100%)
		High	0	0	0	0	1(3%)	0
	24	n	57	0	25	0	29	1

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | Shift | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
	Week	to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	57(100%)	0	25(100%)	0	29(100%)	1(100%)
	26	n	57	0	24	0	26	1
		Normal	57(100%)	0	23(96%)	0	26(100%)	1(100%)
		High	0	0	1(4%)	0	0	0
CALCIUM	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	70	0	72	0
		Normal	82(100%)	0	70(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	66	0	30	0	31	0
		Normal	66(100%)	0	30(100%)	0	31(100%)	0

NOTES: Only subjects with baseline results are included in the summary.

There were no subjects with abnormal low values at baseline.

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86) Normal at Baseline	High at Baseline	Xan. Low (N=84) Normal at Baseline	High at Baseline	Xan. High (N=84) Normal at Baseline	High at Baseline
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0
CHLORIDE	2	n	84	0	78	0	76	0
		Normal	84(100%)	0	78(100%)	0	76(100%)	0
	4	n	82	0	70	0	71	0
		Normal	82(100%)	0	70(100%)	0	71(100%)	0
	6	n	75	0	62	0	66	0
		Normal	75(100%)	0	62(100%)	0	66(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	49	0
		Normal	67(100%)	0	50(100%)	0	49(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	65	0	30	0	31	0
		Normal	65(100%)	0	30(100%)	0	31(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0
CHOLESTEROL	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	70	0	72	0
		Normal	82(100%)	0	70(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	66	0	30	0	31	0
		Normal	66(100%)	0	30(100%)	0	31(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86) Normal at Baseline	Placebo (N=86) High at Baseline	Xan. Low (N=84) Normal at Baseline	Xan. Low (N=84) High at Baseline	Xan. High (N=84) Normal at Baseline	Xan. High (N=84) High at Baseline
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0
CREATINE KINASE	2	n	83	0	77	1	75	3
		Normal	81(98%)	0	74(96%)	1(100%)	74(99%)	3(100%)
		High	2(2%)	0	3(4%)	0	1(1%)	0
	4	n	79	0	69	1	69	3
		Normal	78(99%)	0	68(99%)	1(100%)	68(99%)	3(100%)
		High	1(1%)	0	1(1%)	0	1(1%)	0
	6	n	73	0	59	1	63	3
		Normal	73(100%)	0	58(98%)	1(100%)	61(97%)	2(67%)
		High	0	0	1(2%)	0	2(3%)	1(33%)
	8	n	72	0	57	1	54	2
		Normal	71(99%)	0	57(100%)	1(100%)	53(98%)	2(100%)
		High	1(1%)	0	0	0	1(2%)	0
	12	n	67	0	49	1	48	2
		Normal	65(97%)	0	48(98%)	1(100%)	47(98%)	1(50%)
		High	2(3%)	0	1(2%)	0	1(2%)	1(50%)
	16	n	68	0	39	1	36	1

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	66(97%)	0	39(100%)	1(100%)	36(100%)	1(100%)
		High	2(3%)	0	0	0	0	0
	20	n	65	0	29	0	30	1
		Normal	65(100%)	0	27(93%)	0	29(97%)	1(100%)
		High	0	0	2(7%)	0	1(3%)	0
	24	n	57	0	25	0	29	1
		Normal	55(96%)	0	25(100%)	0	29(100%)	1(100%)
		High	2(4%)	0	0	0	0	0
	26	n	57	0	24	0	26	1
		Normal	57(100%)	0	24(100%)	0	25(96%)	1(100%)
		High	0	0	0	0	1(4%)	0
CREATININE	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	70	0	72	0
		Normal	82(100%)	0	70(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0

NOTES: Only subjects with baseline results are included in the summary.

There were no subjects with abnormal low values at baseline.

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | Week | Shift to | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	66	0	30	0	31	0
		Normal	66(100%)	0	30(100%)	0	31(100%)	0
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0
GAMMA GLUTAMYL TRANSFERASE	2	n	82	2	76	2	76	2
		Normal	82(100%)	1(50%)	75(99%)	1(50%)	75(99%)	1(50%)
		High	0	1(50%)	1(1%)	1(50%)	1(1%)	1(50%)
	4	n	80	2	68	2	70	2
		Normal	80(100%)	1(50%)	68(100%)	1(50%)	70(100%)	1(50%)
		High	0	1(50%)	0	1(50%)	0	1(50%)
	6	n	74	1	61	1	66	1
		Normal	74(100%)	0	61(100%)	1(100%)	66(100%)	0
		High	0	1(100%)	0	0	0	1(100%)

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

		Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
8	n	72	1	57	1	55	1
	Normal	72(100%)	0	56(98%)	1(100%)	54(98%)	0
	High	0	1(100%)	1(2%)	0	1(2%)	1(100%)
12	n	66	1	49	1	49	1
	Normal	66(100%)	0	49(100%)	1(100%)	49(100%)	0
	High	0	1(100%)	0	0	0	1(100%)
16	n	67	1	39	1	36	1
	Normal	67(100%)	1(100%)	39(100%)	1(100%)	36(100%)	0
	High	0	0	0	0	0	1(100%)
20	n	65	1	29	1	31	0
	Normal	65(100%)	0	29(100%)	0	31(100%)	0
	High	0	1(100%)	0	1(100%)	0	0
24	n	56	1	26	0	29	1
	Normal	54(96%)	1(100%)	25(96%)	0	29(100%)	0
	High	2(4%)	0	1(4%)	0	0	1(100%)
26	n	56	1	24	0	26	1
	Normal	55(98%)	1(100%)	23(96%)	0	26(100%)	0
	High	1(2%)	0	1(4%)	0	0	1(100%)
GLUCOSE 2	n	82	1	78	0	78	0
	Normal	82(100%)	1(100%)	78(100%)	0	77(99%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   *21:05 Monday, June 26, 2006*

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | Shift | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
Week	to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	High	0	0	0	0	1(1%)	0
4	n	78	1	69	0	72	0
	Normal	78(100%)	1(100%)	69(100%)	0	72(100%)	0
6	n	72	1	60	0	66	0
	Normal	72(100%)	1(100%)	60(100%)	0	65(98%)	0
	High	0	0	0	0	1(2%)	0
8	n	71	1	57	0	56	0
	Normal	71(100%)	1(100%)	57(100%)	0	56(100%)	0
12	n	66	1	50	0	49	0
	Normal	66(100%)	1(100%)	49(98%)	0	49(100%)	0
	High	0	0	1(2%)	0	0	0
16	n	67	1	40	0	37	0
	Normal	67(100%)	1(100%)	40(100%)	0	37(100%)	0
20	n	64	1	29	0	31	0
	Normal	64(100%)	1(100%)	29(100%)	0	31(100%)	0
24	n	56	1	25	0	30	0
	Normal	56(100%)	1(100%)	25(100%)	0	30(100%)	0
26	n	56	1	24	0	27	0
	Normal	56(100%)	1(100%)	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86) Normal at Baseline	High at Baseline	Xan. Low (N=84) Normal at Baseline	High at Baseline	Xan. High (N=84) Normal at Baseline	High at Baseline
PHOSPHATE	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	68	0	72	0
		Normal	82(100%)	0	68(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	65	0	30	0	31	0
		Normal	65(100%)	0	30(100%)	0	31(100%)	0
	24	n	56	0	26	0	30	0
		Normal	56(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
POTASSIUM	2	n	84	0	78	0	76	0
		Normal	84(100%)	0	78(100%)	0	76(100%)	0
	4	n	82	0	68	0	71	0
		Normal	82(100%)	0	68(100%)	0	71(100%)	0
	6	n	75	0	62	0	66	0
		Normal	75(100%)	0	62(100%)	0	66(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	49	0
		Normal	67(100%)	0	50(100%)	0	49(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	64	0	30	0	31	0
		Normal	64(100%)	0	30(100%)	0	31(100%)	0
	24	n	56	0	26	0	30	0
		Normal	56(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
PROTEIN	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	70	0	72	0
		Normal	82(100%)	0	70(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	66	0	30	0	31	0
		Normal	66(100%)	0	30(100%)	0	31(100%)	0
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
SODIUM	2	n	84	0	78	0	76	0
		Normal	84(100%)	0	78(100%)	0	76(100%)	0
	4	n	82	0	70	0	71	0
		Normal	82(100%)	0	70(100%)	0	71(100%)	0
	6	n	75	0	62	0	66	0
		Normal	75(100%)	0	62(100%)	0	66(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	49	0
		Normal	67(100%)	0	50(100%)	0	49(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	65	0	30	0	31	0
		Normal	65(100%)	0	30(100%)	0	31(100%)	0
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
URATE	2	n	84	0	78	0	78	0
		Normal	84(100%)	0	78(100%)	0	78(100%)	0
	4	n	82	0	70	0	72	0
		Normal	82(100%)	0	70(100%)	0	72(100%)	0
	6	n	75	0	62	0	67	0
		Normal	75(100%)	0	62(100%)	0	67(100%)	0
	8	n	73	0	58	0	56	0
		Normal	73(100%)	0	58(100%)	0	56(100%)	0
	12	n	67	0	50	0	50	0
		Normal	67(100%)	0	50(100%)	0	50(100%)	0
	16	n	68	0	40	0	37	0
		Normal	68(100%)	0	40(100%)	0	37(100%)	0
	20	n	66	0	30	0	31	0
		Normal	66(100%)	0	30(100%)	0	31(100%)	0
	24	n	57	0	26	0	30	0
		Normal	57(100%)	0	26(100%)	0	30(100%)	0
	26	n	57	0	24	0	27	0
		Normal	57(100%)	0	24(100%)	0	27(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
| | | Shift | Normal at | High at | Normal at | High at | Normal at | High at |
	Week	to	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
UREA NITROGEN	2	n	84	0	76	2	78	0
		Normal	84(100%)	0	76(100%)	2(100%)	77(99%)	0
		High	0	0	0	0	1(1%)	0
	4	n	82	0	68	2	72	0
		Normal	82(100%)	0	68(100%)	2(100%)	72(100%)	0
	6	n	75	0	60	2	67	0
		Normal	75(100%)	0	60(100%)	2(100%)	67(100%)	0
	8	n	73	0	56	2	56	0
		Normal	73(100%)	0	56(100%)	2(100%)	56(100%)	0
	12	n	67	0	49	1	50	0
		Normal	67(100%)	0	49(100%)	1(100%)	50(100%)	0
	16	n	68	0	39	1	37	0
		Normal	68(100%)	0	39(100%)	1(100%)	37(100%)	0
	20	n	66	0	29	1	31	0
		Normal	66(100%)	0	29(100%)	1(100%)	31(100%)	0
	24	n	57	0	25	1	30	0
		Normal	57(100%)	0	25(100%)	1(100%)	30(100%)	0
	26	n	57	0	23	1	27	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

		Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	Normal	57(100%)	0	23(100%)	1(100%)	26(96%)	0
	High	0	0	0	0	1(4%)	0

HEMATOLOGY

BASOPHILS							
2	n	82	0	77	0	77	0
	Normal	82(100%)	0	77(100%)	0	77(100%)	0
4	n	78	0	69	0	69	0
	Normal	78(100%)	0	69(100%)	0	69(100%)	0
6	n	72	0	59	0	62	0
	Normal	72(100%)	0	59(100%)	0	62(100%)	0
8	n	71	0	56	0	55	0
	Normal	71(100%)	0	56(100%)	0	55(100%)	0
12	n	65	0	48	0	49	0
	Normal	65(100%)	0	48(100%)	0	49(100%)	0
16	n	67	0	39	0	36	0
	Normal	67(100%)	0	39(100%)	0	36(100%)	0
20	n	64	0	29	0	31	0
	Normal	64(100%)	0	29(100%)	0	31(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   *21:05 Monday, June 26, 2006*

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
EOSINOPHILS	2	n	82	0	76	1	77	0
		Normal	82(100%)	0	74(97%)	1(100%)	77(100%)	0
		High	0	0	2(3%)	0	0	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	68(99%)	0
		High	0	0	0	0	1(1%)	0
	6	n	72	0	59	0	62	0
		Normal	72(100%)	0	59(100%)	0	58(94%)	0
		High	0	0	0	0	4(6%)	0
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	53(95%)	0	52(95%)	0
		High	0	0	3(5%)	0	3(5%)	0
	12	n	65	0	48	0	49	0
		Normal	65(100%)	0	46(96%)	0	49(100%)	0
		High	0	0	2(4%)	0	0	0
	16	n	67	0	39	0	36	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
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Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	67(100%)	0	39(100%)	0	35(97%)	0
		High	0	0	0	0	1(3%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
ERY. MEAN CORPUSCULAR HB CONCENTRATION	2	n	82	0	76	0	76	0
		Normal	82(100%)	0	76(100%)	0	76(100%)	0
	4	n	76	0	67	0	67	0
		Normal	76(100%)	0	67(100%)	0	67(100%)	0
	6	n	71	0	57	0	63	0
		Normal	71(100%)	0	57(100%)	0	63(100%)	0
	8	n	70	0	53	0	55	0
		Normal	70(100%)	0	53(100%)	0	55(100%)	0
	12	n	64	0	47	0	49	0
		Normal	64(100%)	0	47(100%)	0	49(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
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Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	63	0	29	0	31	0
		Normal	63(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	55	0	24	0	26	0
		Normal	55(100%)	0	24(100%)	0	26(100%)	0
ERY. MEAN CORPUSCULAR HEMOGLOBIN	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	63	0
		Normal	72(100%)	0	59(100%)	0	63(100%)	0
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	56(100%)	0	55(100%)	0
	12	n	65	0	48	0	49	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
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Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
		Normal	65(100%)	0	48(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
ERY. MEAN CORPUSCULAR VOLUME	2	n	82	0	76	0	76	0
		Normal	82(100%)	0	76(100%)	0	76(100%)	0
	4	n	76	0	67	0	67	0
		Normal	76(100%)	0	67(100%)	0	67(100%)	0
	6	n	71	0	57	0	63	0
		Normal	71(100%)	0	57(100%)	0	63(100%)	0
	8	n	70	0	53	0	55	0
		Normal	70(100%)	0	53(100%)	0	55(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
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Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	12	n	64	0	47	0	49	0
		Normal	64(100%)	0	47(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	63	0	29	0	31	0
		Normal	63(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	55	0	24	0	26	0
		Normal	55(100%)	0	24(100%)	0	26(100%)	0
ERYTHROCYTES	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	63	0
		Normal	72(100%)	0	59(100%)	0	63(100%)	0
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	56(100%)	0	55(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86) Normal at Baseline	High at Baseline	Xan. Low (N=84) Normal at Baseline	High at Baseline	Xan. High (N=84) Normal at Baseline	High at Baseline
	12	n	65	0	48	0	49	0
		Normal	65(100%)	0	48(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
HEMATOCRIT	2	n	82	0	76	0	76	0
		Normal	82(100%)	0	76(100%)	0	76(100%)	0
	4	n	76	0	67	0	67	0
		Normal	76(100%)	0	67(100%)	0	67(100%)	0
	6	n	71	0	57	0	63	0
		Normal	71(100%)	0	57(100%)	0	63(100%)	0
	8	n	70	0	53	0	55	0
		Normal	70(100%)	0	53(100%)	0	55(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)	
			Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	12	n	64	0	47	0	49	0
		Normal	64(100%)	0	47(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	63	0	29	0	31	0
		Normal	63(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	55	0	24	0	26	0
		Normal	55(100%)	0	24(100%)	0	26(100%)	0
HEMOGLOBIN	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	63	0
		Normal	72(100%)	0	59(100%)	0	63(100%)	0
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	56(100%)	0	55(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
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Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
| | | | | | | | | |
	Week	Shift to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
	12	n	65	0	48	0	49	0
		Normal	65(100%)	0	48(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
LEUKOCYTES	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	63	0
		Normal	72(100%)	0	59(100%)	0	63(100%)	0
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	56(100%)	0	55(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | | | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
| | | | Normal at | High at | Normal at | High at | Normal at | High at |
	Week	Shift to	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
	12	n	65	0	48	0	49	0
		Normal	65(100%)	0	48(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
LYMPHOCYTES	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	62	0
		Normal	72(100%)	0	59(100%)	0	62(100%)	0
	8	n	71	0	56	0	55	0
		Normal	70(99%)	0	56(100%)	0	55(100%)	0
		High	1(1%)	0	0	0	0	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

	Week	Shift to	Placebo (N=86) Normal at Baseline	High at Baseline	Xan. Low (N=84) Normal at Baseline	High at Baseline	Xan. High (N=84) Normal at Baseline	High at Baseline
	12	n	65	0	48	0	49	0
		Normal	64(98%)	0	48(100%)	0	49(100%)	0
		High	1(2%)	0	0	0	0	0
	16	n	67	0	39	0	36	0
		Normal	67(100%)	0	39(100%)	0	36(100%)	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
MONOCYTES	2	n	82	0	77	0	77	0
		Normal	82(100%)	0	77(100%)	0	77(100%)	0
	4	n	78	0	69	0	69	0
		Normal	78(100%)	0	69(100%)	0	69(100%)	0
	6	n	72	0	59	0	62	0
		Normal	71(99%)	0	59(100%)	0	62(100%)	0
		Low	1(1%)	0	0	0	0	0

NOTES: Only subjects with baseline results are included in the summary.

There were no subjects with abnormal low values at baseline.

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Population: Safety

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

		Shift to	Placebo (N=86) Normal at Baseline	High at Baseline	Xan. Low (N=84) Normal at Baseline	High at Baseline	Xan. High (N=84) Normal at Baseline	High at Baseline
	8	n	71	0	56	0	55	0
		Normal	71(100%)	0	56(100%)	0	55(100%)	0
	12	n	65	0	48	0	49	0
		Normal	65(100%)	0	48(100%)	0	49(100%)	0
	16	n	67	0	39	0	36	0
		Normal	66(99%)	0	39(100%)	0	36(100%)	0
		Low	1(1%)	0	0	0	0	0
	20	n	64	0	29	0	31	0
		Normal	64(100%)	0	29(100%)	0	31(100%)	0
	24	n	57	0	24	0	29	0
		Normal	57(100%)	0	24(100%)	0	29(100%)	0
	26	n	56	0	24	0	26	0
		Normal	56(100%)	0	24(100%)	0	26(100%)	0
PLATELET	2	n	82	0	74	0	77	0
		Normal	82(100%)	0	74(100%)	0	77(100%)	0
	4	n	77	0	67	0	68	0
		Normal	77(100%)	0	67(100%)	0	68(100%)	0
	6	n	72	0	57	0	61	0
		Normal	72(100%)	0	57(100%)	0	61(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.04
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

| | Shift | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | |
Week	to	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline
8	n	71	0	55	0	54	0
	Normal	71(100%)	0	55(100%)	0	54(100%)	0
12	n	64	0	47	0	48	0
	Normal	64(100%)	0	47(100%)	0	48(100%)	0
16	n	67	0	37	0	36	0
	Normal	67(100%)	0	37(100%)	0	36(100%)	0
20	n	64	0	28	0	30	0
	Normal	64(100%)	0	28(100%)	0	30(100%)	0
24	n	56	0	22	0	28	0
	Normal	56(100%)	0	22(100%)	0	28(100%)	0
26	n	55	0	23	0	26	0
	Normal	55(100%)	0	23(100%)	0	26(100%)	0

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshiftweek.sas   21:05 Monday, June 26, 2006

Table 14-6.05
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

| | Shift [1] | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | | p-value [2] |
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
CHEMISTRY								

ALANINE AMINOTRANSFERASE	n	82	2	79	1	80	0	0.828
	Normal	80(98%)	0	78(99%)	0	78(98%)	0	
	High	2(2%)	2(100%)	1(1%)	1(100%)	2(3%)	0	
ALBUMIN	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	
ALKALINE PHOSPHATASE	n	82	2	79	0	79	1	0.611
	Normal	81(99%)	0	78(99%)	0	79(100%)	0	
	High	1(1%)	2(100%)	1(1%)	0	0	1(100%)	
ASPARTATE AMINOTRANSFERASE	n	82	2	79	1	80	0	0.770
	Normal	79(96%)	1(50%)	77(97%)	1(100%)	78(98%)	0	
	High	3(4%)	1(50%)	2(3%)	0	2(3%)	0	
BILIRUBIN	n	84	0	80	0	79	1	0.353
	Normal	83(99%)	0	80(100%)	0	77(97%)	0	

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.05
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

	Shift [1]	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)		p-value [2]
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
	High	1(1%)	0	0	0	2(3%)	1(100%)	
CALCIUM	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	
CHLORIDE	n	84	0	80	0	79	0	
	Normal	84(100%)	0	80(100%)	0	79(100%)	0	
CHOLESTEROL	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	
CREATINE KINASE	n	84	0	79	1	77	3	0.811
	Normal	77(92%)	0	74(94%)	1(100%)	72(94%)	1(33%)	
	High	7(8%)	0	5(6%)	0	5(6%)	2(67%)	
CREATININE	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	
GAMMA GLUTAMYL TRANSFERASE	n	82	2	78	2	78	2	0.898
	Normal	80(98%)	0	75(96%)	1(50%)	76(97%)	1(50%)	

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.05
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

	Shift [1]	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)		p-value [2]
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
	High	2(2%)	2(100%)	3(4%)	1(50%)	2(3%)	1(50%)	
GLUCOSE	n	83	1	80	0	80	0	0.354
	Normal	83(100%)	1(100%)	79(99%)	0	78(98%)	0	
	High	0	0	1(1%)	0	2(3%)	0	
PHOSPHATE	n	84	0	79	0	80	0	
	Normal	84(100%)	0	79(100%)	0	80(100%)	0	
POTASSIUM	n	84	0	79	0	79	0	
	Normal	84(100%)	0	79(100%)	0	79(100%)	0	
PROTEIN	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	
SODIUM	n	84	0	80	0	79	0	
	Normal	84(100%)	0	80(100%)	0	79(100%)	0	
URATE	n	84	0	80	0	80	0	
	Normal	84(100%)	0	80(100%)	0	80(100%)	0	

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.05

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

| | Shift [1] | Placebo (N=86) | | Xan. Low (N=84) | | Xan. High (N=84) | | p-value [2] |
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
UREA NITROGEN	n	84	0	78	2	80	0	0.363
	Normal	84(100%)	0	78(100%)	2(100%)	79(99%)	0	
	High	0	0	0	0	1(1%)	0	
HEMATOLOGY								

BASOPHILS	n	83	0	79	0	78	0	
	Normal	83(100%)	0	79(100%)	0	78(100%)	0	
EOSINOPHILS	n	83	0	78	1	78	0	0.044
	Normal	83(100%)	0	73(94%)	1(100%)	72(92%)	0	
	High	0	0	5(6%)	0	6(8%)	0	
ERY. MEAN CORPUSCULAR HB CONCENTRATION	n	82	0	78	0	77	0	
	Normal	82(100%)	0	78(100%)	0	77(100%)	0	
ERY. MEAN CORPUSCULAR HEMOGLOBIN	n	83	0	79	0	78	0	
	Normal	83(100%)	0	79(100%)	0	78(100%)	0	

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.05

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

	Shift [1]	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)		p-value [2]
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
ERY. MEAN CORPUSCULAR VOLUME	n	82	0	78	0	77	0	
	Normal	82(100%)	0	78(100%)	0	77(100%)	0	
ERYTHROCYTES	n	83	0	79	0	78	0	
	Normal	83(100%)	0	79(100%)	0	78(100%)	0	
HEMATOCRIT	n	82	0	78	0	77	0	
	Normal	82(100%)	0	78(100%)	0	77(100%)	0	
HEMOGLOBIN	n	83	0	79	0	78	0	
	Normal	83(100%)	0	79(100%)	0	78(100%)	0	
LEUKOCYTES	n	83	0	79	0	78	0	
	Normal	83(100%)	0	79(100%)	0	78(100%)	0	
LYMPHOCYTES	n	83	0	79	0	78	0	0.388
	Normal	82(99%)	0	79(100%)	0	78(100%)	0	
	High	1(1%)	0	0	0	0	0	

NOTES: Only subjects with baseline results are included in the summary.
There were no subjects with abnormal low values at baseline.
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.05
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

	Shift [1]	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)		p-value [2]
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
MONOCYTES	n	83	0	79	0	78	0	0.150
	Normal	81(98%)	0	79(100%)	0	78(100%)	0	
	Low	2(2%)	0	0	0	0	0	
PLATELET	n	83	0	77	0	78	0	
	Normal	83(100%)	0	77(100%)	0	78(100%)	0	

NOTES: Only subjects with baseline results are included in the summary.

There were no subjects with abnormal low values at baseline.

[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).

[2] CMH test for general association, controlling for status at baseline.

Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_labshift.sas   21:05 Monday, June 26, 2006

Table 14-6.06
Shifts of Hy's Law Values During Treatment

	Shift [1]	Placebo (N=86)		Xan. Low (N=84)		Xan. High (N=84)		p-value [2]
		Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	Normal at Baseline	High at Baseline	
Transaminase 1.5 x ULN	n	82	2	80	2	80	0	0.392
	Normal	79(96%)	0	79(99%)	1(50%)	77(96%)	0	
	High	3(4%)	2(100%)	1(1%)	1(50%)	3(4%)	0	
Total Bili 1.5 x ULN and								
Transaminase 1.5 x ULN	n	84	0	82	0	80	0	0.381
	Normal	83(99%)	0	82(100%)	0	80(100%)	0	
	High	1(1%)	0	0	0	0	0	

NOTES: Only subjects with baseline results are included in the summary.
The single subject with elevated transaminase and elevated bilirubin also had elevated alk phos (>3xULN).
[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rt_hyslaw.sas   21:03 Monday, June 26, 2006

Table 14-7.01
Summary of Vital Signs at Baseline and End of Treatment

				Planned Relative						
Measure	Position	Treatment	N	Time	n	Mean	SD	Median	Min.	Max.
Systolic Blood Pressure(mmHg)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Baseline	85	138.6	16.75	140.0	90.0	180.0
				Week 24	59	135.8	17.30	131.0	100.0	180.0
				End of Trt.	84	136.7	18.30	134.0	100.0	180.0
		Xan.Low	84	Baseline	84	138.8	16.55	138.0	100.0	178.0
				Week 24	27	134.1	16.74	136.0	100.0	173.0
				End of Trt.	84	135.7	17.17	134.0	100.0	190.0
		Xan.High	84	Baseline	84	140.1	17.82	141.0	100.0	188.0
				Week 24	30	132.2	18.18	130.0	101.0	178.0
				End of Trt.	82	134.0	17.86	130.0	101.0	178.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Baseline	85	135.3	17.89	134.0	90.0	180.0
				Week 24	59	133.5	19.23	130.0	90.0	199.0
				End of Trt.	84	133.9	18.68	130.5	90.0	199.0
		Xan.Low	84	Baseline	84	135.6	18.04	136.0	100.0	186.0
				Week 24	27	131.0	17.82	130.0	92.0	168.0
				End of Trt.	84	132.8	17.53	130.0	92.0	180.0
		Xan.High	84	Baseline	84	137.3	19.71	138.0	100.0	194.0
				Week 24	30	130.4	20.83	128.0	96.0	198.0
				End of Trt.	82	130.4	20.37	128.0	90.0	198.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Baseline	85	136.5	18.77	136.0	80.0	184.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).

Table 14-7.01
Summary of Vital Signs at Baseline and End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
				Week 24	59	134.8	17.35	131.0	100.0	190.0
				End of Trt.	84	134.1	18.01	130.0	90.0	190.0
		Xan.Low	84	Baseline	84	136.4	18.11	134.5	104.0	182.0
				Week 24	27	131.0	17.92	130.0	100.0	168.0
				End of Trt.	83	133.1	17.80	130.0	98.0	200.0
		Xan.High	84	Baseline	84	138.8	18.75	138.0	100.0	186.0
				Week 24	30	129.2	16.95	126.0	90.0	172.0
				End of Trt.	81	130.4	17.77	130.0	88.0	184.0
Diastolic Blood Pressure(mmHg)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Baseline	85	75.7	11.09	76.0	40.0	99.0
				Week 24	59	72.9	11.32	74.0	44.0	109.0
				End of Trt.	84	74.5	11.11	76.0	44.0	109.0
		Xan.Low	84	Baseline	84	76.3	9.77	76.0	57.0	100.0
				Week 24	27	76.1	9.14	76.0	60.0	90.0
				End of Trt.	84	74.3	8.88	74.0	45.0	90.0
		Xan.High	84	Baseline	84	77.2	9.80	78.0	51.0	98.0
				Week 24	30	73.9	9.23	74.0	60.0	92.0
				End of Trt.	82	74.1	9.27	74.0	56.0	94.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Baseline	85	77.9	10.63	78.0	51.0	104.0
				Week 24	59	74.2	12.89	74.0	45.0	117.0
				End of Trt.	84	74.9	12.16	76.0	45.0	117.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).
Source: C:\cdisc_pilot\PROGRAMS\DRAFT\TFLs\rtvs.sas   21:06 Monday, June 26, 2006

Table 14-7.01
Summary of Vital Signs at Baseline and End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
		Xan.Low	84	Baseline	84	76.2	10.14	78.0	54.0	98.0
				Week 24	27	76.3	10.28	78.0	60.0	98.0
				End of Trt.	84	75.0	9.34	75.0	51.0	98.0
		Xan.High	84	Baseline	84	78.1	10.77	78.0	56.0	108.0
				Week 24	30	74.9	11.00	76.0	50.0	97.0
				End of Trt.	82	75.9	11.77	76.5	48.0	112.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Baseline	85	77.7	11.00	78.0	46.0	110.0
				Week 24	59	74.3	11.38	74.0	51.0	110.0
				End of Trt.	84	75.0	11.19	74.5	51.0	110.0
		Xan.Low	84	Baseline	84	76.6	10.93	76.0	48.0	108.0
				Week 24	27	76.2	10.18	76.0	57.0	98.0
				End of Trt.	83	74.9	9.66	74.0	57.0	102.0
		Xan.High	84	Baseline	84	79.6	10.19	80.0	51.0	104.0
				Week 24	30	76.0	10.63	78.5	50.0	98.0
				End of Trt.	81	76.8	11.71	78.0	50.0	118.0
Pulse(bpm)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Baseline	85	70.4	10.46	70.0	51.0	100.0
				Week 24	59	69.1	9.46	68.0	50.0	92.0
				End of Trt.	84	69.3	9.42	68.5	50.0	92.0
		Xan.Low	84	Baseline	84	68.8	9.52	68.0	50.0	88.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).

Table 14-7.01
Summary of Vital Signs at Baseline and End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
				Week 24	27	68.1	9.28	68.0	52.0	90.0
				End of Trt.	84	67.8	10.55	68.0	48.0	100.0
		Xan.High	84	Baseline	84	70.1	9.27	68.0	52.0	98.0
				Week 24	30	69.3	11.88	68.0	47.0	96.0
				End of Trt.	82	68.1	11.27	68.0	47.0	100.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Baseline	85	75.5	12.68	76.0	56.0	133.0
				Week 24	59	72.8	8.98	74.0	52.0	88.0
				End of Trt.	84	73.5	9.09	74.0	52.0	96.0
		Xan.Low	84	Baseline	84	73.5	10.59	72.0	53.0	100.0
				Week 24	27	72.1	9.53	74.0	52.0	88.0
				End of Trt.	84	73.0	10.84	73.0	51.0	104.0
		Xan.High	84	Baseline	84	75.0	10.89	72.0	56.0	104.0
				Week 24	30	73.4	11.93	72.0	54.0	98.0
				End of Trt.	82	72.6	11.11	71.0	52.0	100.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Baseline	85	74.6	11.94	74.0	54.0	134.0
				Week 24	59	72.8	8.73	74.0	56.0	88.0
				End of Trt.	84	73.4	9.08	74.0	56.0	98.0
		Xan.Low	84	Baseline	84	72.3	10.99	70.0	51.0	104.0
				Week 24	27	70.7	10.78	72.0	52.0	96.0
				End of Trt.	83	71.6	10.42	72.0	52.0	97.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).

Table 14-7.01
Summary of Vital Signs at Baseline and End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
		Xan.High	84	Baseline	84	74.0	10.76	72.0	52.0	100.0
				Week 24	30	72.4	11.92	71.5	54.0	96.0
				End of Trt.	81	71.8	10.76	70.0	54.0	106.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).
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Table 14-7.02
Summary of Vital Signs Change from Baseline at End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic Blood Pressure(mmHg)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Week 24	58	-2.1	14.73	-4.0	-28.0	50.0
				End of Trt.	83	-2.0	16.76	-4.0	-32.0	50.0
		Xan.Low	84	Week 24	27	-0.3	17.19	2.0	-48.0	30.0
				End of Trt.	84	-3.1	16.57	-2.0	-48.0	34.0
		Xan.High	84	Week 24	30	-5.6	17.18	-7.0	-36.0	26.0
				End of Trt.	82	-5.8	14.48	-8.0	-36.0	29.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Week 24	58	-1.7	16.87	0.0	-32.0	40.0
				End of Trt.	83	-1.6	17.76	0.0	-46.0	48.0
		Xan.Low	84	Week 24	27	-0.1	17.73	-1.0	-30.0	48.0
				End of Trt.	84	-2.8	17.40	-1.5	-52.0	48.0
		Xan.High	84	Week 24	30	-6.3	19.49	-9.0	-36.0	42.0
				End of Trt.	82	-6.7	16.98	-8.0	-44.0	42.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Week 24	58	-1.0	15.80	-3.5	-36.0	38.0
				End of Trt.	83	-2.5	16.61	-4.0	-40.0	48.0
		Xan.Low	84	Week 24	27	-0.1	16.20	0.0	-30.0	30.0
				End of Trt.	83	-3.5	16.51	-4.0	-52.0	60.0
		Xan.High	84	Week 24	30	-9.0	16.88	-8.0	-40.0	30.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).
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Table 14-7.02
Summary of Vital Signs Change from Baseline at End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
				End of Trt.	81	-8.3	15.21	-8.0	-40.0	30.0
Diastolic Blood Pressure(mmHg)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Week 24	58	-0.8	10.82	-0.5	-18.0	41.0
				End of Trt.	83	-1.0	10.99	0.0	-34.0	41.0
		Xan.Low	84	Week 24	27	-0.9	7.71	-2.0	-20.0	16.0
				End of Trt.	84	-2.0	8.80	-2.0	-30.0	18.0
		Xan.High	84	Week 24	30	-2.2	9.20	-1.0	-20.0	21.0
				End of Trt.	82	-3.1	8.79	-4.0	-24.0	21.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Week 24	58	-2.3	10.08	-4.0	-23.0	24.0
				End of Trt.	83	-2.8	10.17	-2.0	-34.0	24.0
		Xan.Low	84	Week 24	27	1.0	7.30	2.0	-20.0	18.0
				End of Trt.	84	-1.2	8.93	0.0	-30.0	20.0
		Xan.High	84	Week 24	30	-2.3	10.85	-7.0	-18.0	22.0
				End of Trt.	82	-2.1	12.10	-2.0	-34.0	28.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Week 24	58	-2.3	9.56	-3.5	-22.0	20.0
				End of Trt.	83	-2.7	9.36	-2.0	-30.0	20.0
		Xan.Low	84	Week 24	27	-1.6	8.29	0.0	-20.0	10.0
				End of Trt.	83	-1.8	9.69	-1.0	-24.0	38.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).
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Population: Safety

Table 14-7.02
Summary of Vital Signs Change from Baseline at End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
		Xan.High	84	Week 24	30	-2.1	9.77	-3.5	-20.0	16.0
				End of Trt.	81	-2.6	10.81	-2.0	-40.0	27.0
Pulse(bpm)	AFTER LYING DOWN FOR 5 MINUTES	Placebo	86	Week 24	58	-0.3	8.77	-1.0	-24.0	24.0
				End of Trt.	83	-0.9	8.69	-1.0	-24.0	24.0
		Xan.Low	84	Week 24	27	-1.6	10.53	0.0	-24.0	25.0
				End of Trt.	84	-1.0	11.12	-0.5	-24.0	32.0
		Xan.High	84	Week 24	30	-2.0	11.16	-2.0	-34.0	20.0
				End of Trt.	82	-1.7	8.95	-2.0	-34.0	20.0
	AFTER STANDING FOR 1 MINUTE	Placebo	86	Week 24	58	-1.7	11.72	0.5	-53.0	18.0
				End of Trt.	83	-1.8	11.05	-1.0	-53.0	20.0
		Xan.Low	84	Week 24	27	-1.3	9.05	0.0	-20.0	12.0
				End of Trt.	84	-0.5	11.69	0.0	-24.0	34.0
		Xan.High	84	Week 24	30	-1.8	13.41	-3.0	-36.0	20.0
				End of Trt.	82	-2.1	10.43	-1.5	-36.0	22.0
	AFTER STANDING FOR 3 MINUTES	Placebo	86	Week 24	58	-1.5	10.47	0.0	-46.0	14.0
				End of Trt.	83	-1.0	9.89	0.0	-46.0	18.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).

Table 14-7.02
Summary of Vital Signs Change from Baseline at End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
		Xan.Low	84	Week 24	27	-2.1	8.77	-2.0	-20.0	16.0
				End of Trt.	83	-0.7	10.73	-1.0	-22.0	29.0
		Xan.High	84	Week 24	30	-2.7	11.12	-2.0	-40.0	14.0
				End of Trt.	81	-1.9	9.49	-1.0	-40.0	20.0

End of treatment is the last on-treatment assessment of the specified vital sign (on or before the Week 24 visit).
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Table 14-7.03
Summary of Weight Change from Baseline at End of Treatment

| | | | Planned Relative | | | | | | |
Measure	Treatment	N	Time	n	Mean	SD	Median	Min.	Max.
Weight(kg)	Placebo	86	Baseline	86	62.8	12.77	60.6	34.0	86.2
			Week 24	59	63.2	12.58	63.5	34.0	86.6
			End of Trt.	84	63.3	12.66	64.0	34.0	86.6
	Xan.Low	84	Baseline	83	67.3	14.13	64.9	45.4	106.1
			Week 24	27	67.4	14.07	62.6	45.5	106.1
			End of Trt.	84	66.7	14.32	65.9	41.7	106.1
	Xan.High	84	Baseline	84	70.0	14.65	69.2	41.7	108.0
			Week 24	30	71.1	15.82	68.7	49.9	105.7
			End of Trt.	81	69.7	14.00	70.3	42.2	105.7
Weight Change from Baseline	Placebo	86	Week 24	59	0.1	2.30	0.0	-4.5	8.2
			End of Trt.	84	0.2	2.05	0.0	-4.5	8.2
	Xan.Low	84	Week 24	27	-0.3	2.04	0.0	-5.4	3.2
			End of Trt.	83	-0.4	2.41	0.0	-14.5	5.9
	Xan.High	84	Week 24	30	1.0	6.47	-0.2	-4.5	33.3
			End of Trt.	81	0.1	4.19	-0.4	-5.5	33.3

End of treatment is the last on-treatment assessment of weight (on or before the Week 24 visit).
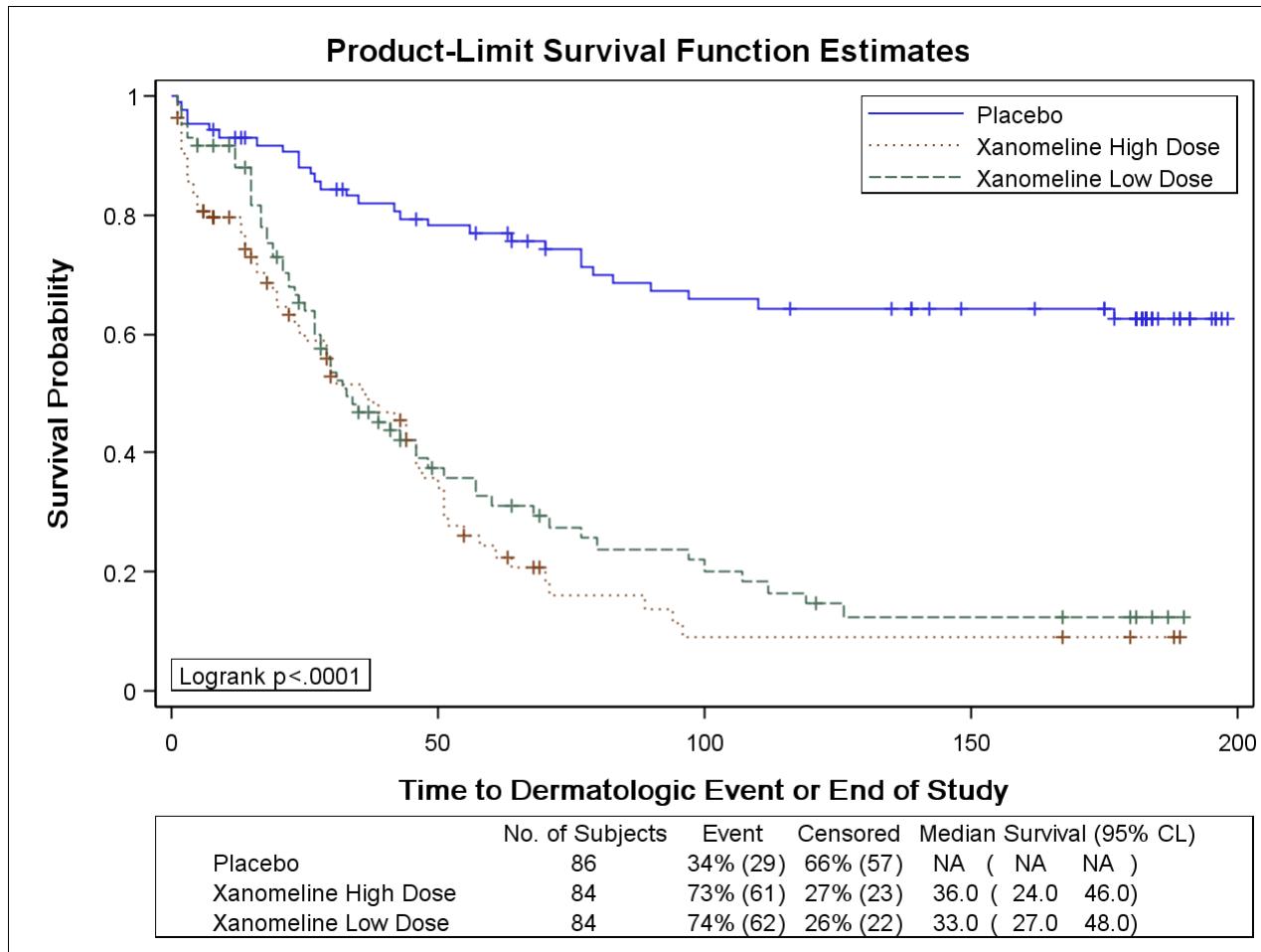
Table 14-7.04
Summary of Concomitant Medications (Number of Subjects)

Therapeutic class, n (%)	Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)
Patients receiving at least one concomitant medication	77 (90%)	74 (88%)	78 (93%)
ALIMENTARY TRACT AND METABOLISM	12 (14%)	11 (13%)	9 (11%)
CALCIUM	7 (8%)	6 (7%)	3 (4%)
ALGELDRATE	2 (2%)	0	2 (2%)
LOPERAMIDE HYDROCHLORIDE	1 (1%)	1 (1%)	1 (1%)
METFORMIN HYDROCHLORIDE	1 (1%)	1 (1%)	0
NIZATIDINE	1 (1%)	1 (1%)	4 (5%)
CALCIUM CARBONATE	0	0	1 (1%)
CIMETIDINE	0	1 (1%)	0
SIMETICONE	0	2 (2%)	0
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	1 (1%)	0	1 (1%)
LEUPRORELIN ACETATE	1 (1%)	0	1 (1%)
BLOOD AND BLOOD FORMING ORGANS	0	1 (1%)	0
FERROUS SULFATE	0	1 (1%)	0
CARDIOVASCULAR SYSTEM	12 (14%)	12 (14%)	7 (8%)
AMLODIPINE	8 (9%)	1 (1%)	2 (2%)
FUROSEMIDE	2 (2%)	2 (2%)	1 (1%)
NIFEDIPINE	2 (2%)	0	0
DOXAZOSIN MESILATE	1 (1%)	2 (2%)	1 (1%)
DIGOXIN	0	3 (4%)	2 (2%)
DILTIAZEM HYDROCHLORIDE	0	0	1 (1%)
FELODIPINE	0	1 (1%)	0
FLUVASTATIN	0	2 (2%)	0
LOSARTAN POTASSIUM	0	2 (2%)	0
DERMATOLOGICALS	0	0	1 (1%)

Table 14-7.04
Summary of Concomitant Medications (Number of Subjects)

Therapeutic class, n (%)	Placebo (N=86)	Xanomeline Low Dose (N=84)	Xanomeline High Dose (N=84)
CLOBETASOL PROPIONATE	0	0	1 (1%)
GENITO URINARY SYSTEM AND SEX HORMONES	6 (7%)	10 (12%)	5 (6%)
ESTROGENS CONJUGATED	6 (7%)	10 (12%)	5 (6%)
NERVOUS SYSTEM	23 (27%)	14 (17%)	8 (10%)
ACETYLSALICYLIC ACID	21 (24%)	11 (13%)	6 (7%)
ALPRAZOLAM	1 (1%)	0	0
DONEPEZIL HYDROCHLORIDE	1 (1%)	2 (2%)	2 (2%)
SUMATRIPTAN	1 (1%)	0	0
HALOPERIDOL	0	1 (1%)	0
PAROXETINE HYDROCHLORIDE	0	1 (1%)	0
RESPIRATORY SYSTEM	4 (5%)	1 (1%)	4 (5%)
SALBUTAMOL SULFATE	2 (2%)	1 (1%)	0
GUAIFENESIN	1 (1%)	0	0
IPRATROPIUM BROMIDE	1 (1%)	0	0
NAPROXEN SODIUM	1 (1%)	0	3 (4%)
BUDESONIDE	0	0	1 (1%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	2 (2%)	13 (15%)	8 (10%)
HYDROCORTISONE	2 (2%)	13 (15%)	8 (10%)
UNCODED	74 (86%)	70 (83%)	77 (92%)
UNCODED	74 (86%)	70 (83%)	77 (92%)

Figure 14-1
Time to Dermatologic Event by Treatment Group

Product-Limit Survival Function Estimates

	No. of Subjects	Event	Censored	Median Survival (95% CL)
Placebo	86	34% (29)	66% (57)	NA (NA NA)
Xanomeline High Dose	84	73% (61)	27% (23)	36.0 (24.0 46.0)
Xanomeline Low Dose	84	74% (62)	26% (22)	33.0 (27.0 48.0)

Note: Dermatologic events were identified as adverse events associated with skin conditions such as rash,
pruritus, dermatitis. A full list of adverse event terms is presented in the final study report.
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15.   REFERENCES

Due to the nature of this CDISC Pilot Project, references are not included in this study report.

16.   APPENDICES

Appendix 1.   Protocol and Amendments

Xanomeline (LY246708)

Protocol H2Q-MC-LZZT(c)

Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

Table of Contents

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List of Attachments

Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

1. Introduction

The M_1 muscarinic-cholinergic receptor is 1 of 5 characterized muscarinic-cholinergic receptor subtypes (Fisher and Barak 1994). M_1 receptors in the cerebral cortex and hippocampus are, for the most part, preserved in Alzheimer's disease (AD), while the presynaptic neurons projecting to these receptors from the nucleus basalis of Meynert degenerate (Bierer et al. 1995). The presynaptic loss of cholinergic neurons has been correlated to the antimortum cognitive impairment in AD patients, prompting speculation that replacement therapy with cholinomimetics will alleviate the cognitive dysfunction of the disorder (Fisher and Barak 1994).

Xanomeline is a novel M_1 agonist which has shown high affinity for the M_1 receptor subtype (in transfected cells), and substantially less or no affinity for other muscarinic subtypes. Positron emission tomography (PET) studies of ^{11}C-labeled xanomeline in cynomolgus monkeys have suggested that the compound crosses the blood-brain barrier and preferentially binds the striatum and neocortex.

Clinical development of an oral formulation of xanomeline for the indication of mild and moderate AD was initiated approximately 4 years ago. A large-scale study of safety and efficacy provided evidence that an oral dosing regimen of 75 mg three times daily (TID) may be associated with enhanced cognition and improved clinical global impression, relative to placebo. As well, a dramatic reduction in psychosis, agitation, and other problematic behaviors, which often complicate the course of the disease, was documented. However, the discontinuation rate associated with this oral dosing regimen was 58.6%, and alternative clinical strategies have been sought to improve tolerance for the compound.

To that end, development of a Transdermal Therapeutic System (TTS) has been initiated. Relative to the oral formulation, the transdermal formulation eliminates high concentrations of xanomeline in the gastrointestinal (GI) tract and presystemic (first-pass) metabolism. Three transdermal delivery systems, hereafter referred to as the xanomeline TTS Formulation A, xanomeline TTS Formulation B, and xanomeline TTS formulation E have been manufactured by Lohman Therapy Systems GmbH of Andernach Germany. TTS Formulation A is 27 mg xanomeline freebase in a 25-cm^2 matrix. TTS Formulation B is 57.6 mg xanomeline freebase in a 40-cm^2 matrix. Formulation E has been produced in 2 patch sizes: 1) 54 mg xanomeline freebase with 0.06 mg Vitamin E USP in a 50-cm^2 matrix and 2) 27 mg xanomeline freebase with 0.03 mg Vitamin E USP in a 25-cm^2 matrix. For a detailed description of the composition of

these formulations please refer to Part II, Section 14 of the Xanomeline (LY246708) Clinical Investigator's Brochure. For characterization of the safety, tolerance, and pharmacokinetics of xanomeline TTS Formulations A, B, and E, please refer to Part II, Sections 7, 8, and 10 of the Xanomeline (LY246708) Clinical Investigator's Brochure. Formulation E will be studied in this protocol, H2Q-MC-LZZT(c).

2. Objectives

2.1. Primary Objectives

The primary objectives of this study are

- To determine if there is a statistically significant relationship (overall Type 1 error rate, $\alpha=.05$) between the change in both ADAS-Cog (see Attachment LZZT.2) and CIBIC+ (see Attachment LZZT.3) scores, and drug dose (0, 50 cm^2 [54 mg], and 75 cm^2 [81 mg]).

- To document the safety profile of the xanomeline TTS.

2.2. Secondary Objectives

The secondary objectives of this study are

- To assess the dose-dependent improvement in behavior. Improved scores on the Revised Neuropsychiatric Inventory (NPI-X) will indicate improvement in these areas (see Attachment LZZT.4).

- To assess the dose-dependent improvements in activities of daily living. Improved scores on the Disability Assessment for Dementia (DAD) will indicate improvement in these areas (see Attachment LZZT.5).

- To assess the dose-dependent improvements in an extended assessment of cognition that integrates attention/concentration tasks. The Alzheimer's Disease Assessment Scale-14 item Cognitive Subscale, hereafter referred to as ADAS-Cog (14), will be used for this assessment (see Attachment LZZT.2).

- To assess the treatment response as a function of Apo E genotype.

3. Investigational Plan

3.1. Summary of Study Design

Patients with probable mild to moderate AD will be studied in a randomized, double-blind, parallel (3 arm), placebo-controlled trial of 26 weeks duration. The study will be conducted on an outpatient basis. Approximately 300 patients will be enrolled (see Schedule of Events for Protocol H2Q-MC-LZZT(c), Attachment LZZT.1).

Following informed consent, patients will be screened at Visit 1. At screening, patients will undergo complete neuropsychiatric assessment, psychometric testing, and general medical assessment (including medical history, pre-existing conditions, physical examination). In addition, vital signs, temperature, medication history, electrocardiogram (ECG), chest x-ray, and safety laboratories will be obtained. During the screening visit, patients will wear a placebo TTS to determine willingness and ability to comply with transdermal administration procedures. If patients have not had central nervous system (CNS) imaging in the previous 12 months, a computed tomography (CT) or magnetic resonance imaging (MRI) scan will be obtained. If patients are insulin dependent diabetics, a hemoglobin A_{1c} will be obtained. Screening exams and procedures may be performed after Visit 1; however, their results must be completed and available prior to randomization. The screening process should occur within 2 weeks of randomization (Visit 3 of the study).

Patients who meet enrollment criteria from Visit 1 will proceed to Visit 2 at which time they will undergo a 24-hour Ambulatory ECG. At Visit 3 the Ambulatory ECG will be removed and patients will be randomized to 1 of 3 treatment arms. The treatment arms will include a placebo arm, a low-dose xanomeline arm (50 cm² TTS Formulation E, 54 mg xanomeline), and a high-dose xanomeline arm (75 cm² TTS Formulation E, 81 mg xanomeline). All patients receiving xanomeline will be started at 50 cm² TTS Formulation E. For the first 8 weeks of treatment, patients will be assessed at clinic visits every 2 weeks and, thereafter, at clinic visits every 4 weeks. Patients who discontinue prior to Visit 12 (Week 24) will be brought back for full efficacy assessments at or near to 24 weeks, whenever possible.

A Data Safety Monitoring Board (DSMB), chaired by an external cardiologist, will meet after 75, 150, 225, and 300 patients have completed 1 month of treatment. The DSMB will review cardiovascular findings to decide if discontinuation of the study or any treatment arm is appropriate, if additional cardiovascular monitoring is required, if further cardiovascular monitoring is unnecessary, or if adjustment of dose within a treatment arm (or arms) is appropriate (see Section 3.9.4).

At Visits 3, 8, 10, and 12, efficacy instruments (ADAS-Cog, CIBIC+, and DAD) will be administered. NPI-X will be administered at 2-week intervals either at clinic visits or via a telephone interview. Vital signs, temperature, and an assessment of adverse events will

be obtained at all clinic visits. An electrocardiogram (ECG), and chemistry/hematology safety labs will be obtained at Visits 4, 5, 7, 8, 9, 10, 11, 12, and 13. Urinalysis will be done at Visits 4, 9, and 12. Use of concomitant medications will be collected at Visits 3, 4, 5, 7, 8, 9, 10, 11, 12, and 13. Plasma levels of xanomeline and metabolites will be obtained at Visits 3, 4, 5, 7, 9, and 11. At Visits 3, 4, 5, 7, 8, 9, 10, 11, and 12, medications will be dispensed to the patients.

Visits 1 through 13 should be scheduled relative to Visit 3 (Week 0 - randomization). Visits 4, 5, 7, 8, and 13 should occur within 3 days of their scheduled date. Visits 9, 10, 11, and 12 should occur within 4 days of their scheduled date. At Visit 13 patients will be given the option to enter the open-label extension phase (see Section 3.10.3. Study Extensions).
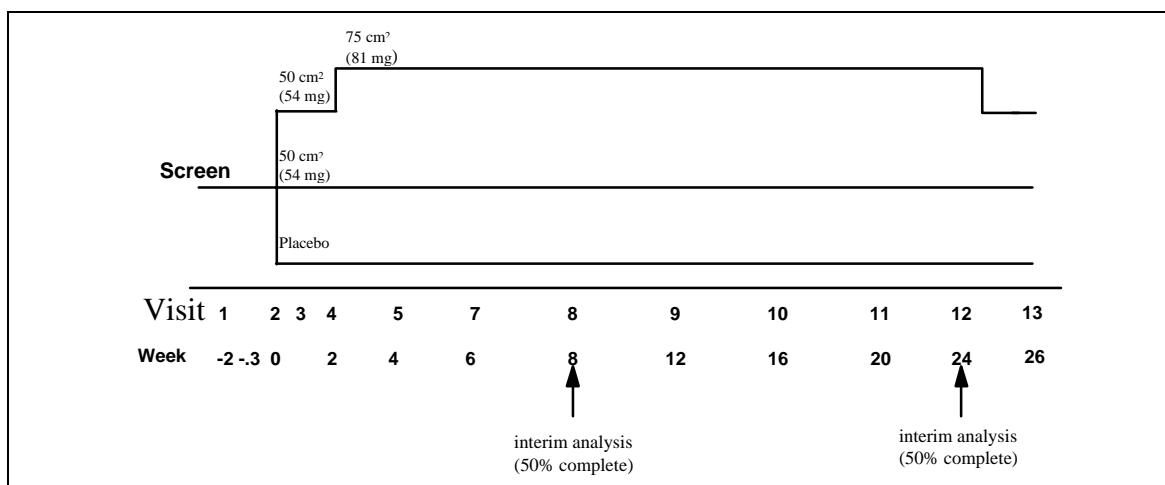

Figure LZZT.1.   Illustration of study design for Protocol H2Q-MC-LZZT(c).

3.2. Discussion of Design and Control

Previous studies of the oral formulation have shown that xanomeline tartrate may improve behavior and cognition. Effects on behavior are manifest within 2 to 4 weeks of initiation of treatment. The same studies have shown that 8 to 12 weeks are required to demonstrate effects on cognition and clinical global assessment. This study is intended to determine the acute and chronic effects of the TTS formulation in AD; for that reason, the study is of 26 weeks duration. Dosage specification has been made on the basis of tolerance to the xanomeline TTS in a clinical pharmacology study (H2Q-EW-LKAA), and target plasma levels as determined in studies of the oral formulation of xanomeline (H2Q-MC-LZZA).

The parallel dosing regimen maximizes the ability to make direct comparisons between the treatment groups. The use of placebo allows for a blinded, thus minimally biased, study. The placebo treatment group is a comparator group for efficacy and safety assessment.

Two interim analyses are planned for this study. The first interim analysis will occur when 50% of the patients have completed Visit 8 (8 weeks). If required, the second interim analysis will occur when 50% of the patients have completed Visit 12 (24 weeks). (See Section 4.6, Interim Analyses.)

3.3. Investigator Information

The name, title, and institution of the investigator(s) is/are listed on the Investigator/Contacts cover pages provided with this protocol. If the investigator is changed after the study has been approved by an ethical review board, or a regulatory agency, or by Lilly, this addition will not be considered a change to the protocol. However, the Investigator/Contacts cover pages will be updated to provide this information.

3.3.1. Final Report Signature

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The investigator who will serve as the final report coordinating investigator will be an individual that is involved with the design and analysis of the study. This final report coordinating investigator will be named by the sponsor of the study.

3.4. Study Population

3.4.1. Entry Procedures

An Ethical Review Board (ERB) approved informed consent will be signed by the patient (and/or legal representative) and caregiver after the nature of the study is explained.

3.4.2. Criteria for Enrollment

For Lilly studies, the following definitions are used:

Screen   Screening is the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

In this study, **screening** will include asking the candidate preliminary questions (such as age and general health status) and conducting invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). Patients will sign the consent at

their screening visit, thereby consenting to undergo the screening procedures and to participate in the study if they qualify.

To **enter** Patients **entered** into the study are those from whom informed consent for the study has been obtained. Adverse events will be reported for each patient who has **entered** the study, even if the patient is never assigned to a treatment group (**enrolled**).

To **enroll** Patients who are **enrolled** in the study are those who have been assigned to a treatment group. Patients who are **entered** into the study but fail to meet criteria specified in the protocol for treatment assignment will not be **enrolled** in the study.

At Visit 1, patients who meet the enrollment criteria of Mini-Mental State Examination (MMSE) score of 10 to 23 (Attachment LZZT.6), Hachinski Ischemia Score ≤4 (Attachment LZZT.8), a physical exam, safety labs, ECG, and urinalysis, will proceed to Visit 2 and Visit 3. At Visit 3, patients whose CNS imaging and other pending labs from Visit 1 satisfy the inclusion criteria (Section 3.4.2.1) will be enrolled in the study. Approximately 300 patients with a diagnosis of probable mild to moderate AD will be enrolled in the study.

3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** the following criteria:

[1] Males and postmenopausal females at least 50 years of age.

[2] Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Attachment LZZT.7).

[3] MMSE score of 10 to 23.

[4] Hachinski Ischemic Scale score of ≤4 (Attachment LZZT.8).

[5] CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year.

The following findings are incompatible with AD:

a) Large vessel strokes

1) Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory.

2) Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts.

The above are exclusionary. Exceptions are made for small areas of cortical asymmetry which may represent a small cortical stroke or a focal area of atrophy provided there is no abnormal signal intensity in the immediately underlying parenchyma. Only one such questionable area allowed per scan, and size is restricted to ≤1cm in frontal/parietal/temporal cortices and ≤2 cm in occipital cortex.

b) Small vessel ischemia

1) Lacunar infarct is defined as an area of abnormal intensity seen on CT scan or on both T1 and T2 weighted MRI images in the basal ganglia, thalamus or deep white matter which is ≤1 cm in maximal diameter. A maximum of one lacune is allowed per scan.

2) Leukoariosis or leukoencephalopathy is regarded as an abnormality seen on T2 but not T1 weighted MRIs, or on CT. This is accepted if mild or moderate in extent, meaning involvement of less than 25% of cortical white matter.

c) Miscellaneous

1) Benign small extra-axial tumors (ie, meningiomas) are accepted if they do not contact or indent the brain parenchyma.

2) Small extra-axial arachnoid cysts are accepted if they do not indent or deform the brain parenchyma.

[6] Investigator has obtained informed consent signed by the patient (and/or legal representative) and by the caregiver.

[7] Geographic proximity to investigator's site that allows adequate follow-up.

[8] A reliable caregiver who is in frequent or daily contact with the patient and who will accompany the patient to the office and/or be available by telephone at designated times, will monitor administration of prescribed medications, and will be responsible for the overall care of the patient at home. The caregiver and the patient must be able to communicate in English and willing to comply with 26 weeks of transdermal therapy.

3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

[9] Persons who have previously completed or withdrawn from this study or any other study investigating xanomeline TTS or the oral formulation of xanomeline.

[10] Use of any investigational agent or approved Alzheimer's therapeutic medication within 30 days prior to enrollment into the study.

[11] Serious illness which required hospitalization within 3 months of screening.

[12] Diagnosis of serious neurological conditions, including

a) Stroke or vascular dementia documented by clinical history and/or radiographic findings interpretable by the investigator as indicative of these disorders

b) Seizure disorder other than simple childhood febrile seizures

c) Severe head trauma resulting in protracted loss of consciousness within the last 5 years, or multiple episodes of head trauma

d) Parkinson's disease

e) Multiple sclerosis

f) Amyotrophic lateral sclerosis

g) Myasthenia gravis.

[13] Episode of depression meeting DSM-IV criteria within 3 months of screening.

[14] A history within the last 5 years of the following:

a) Schizophrenia

b) Bipolar Disease

c) Ethanol or psychoactive drug abuse or dependence.

[15] A history of syncope within the last 5 years.

[16b] Evidence from ECG recording at screening of any of the following conditions :

a) Left bundle branch block

b) Bradycardia ≤50 beats per minute

c) Sinus pauses >2 seconds

d) Second or third degree heart block unless treated with a pacemaker

e) Wolff-Parkinson-White syndrome

f) Sustained supraventricular tachyarrhythmia including SVT≥10 sec, atrial fibrillation, atrial flutter.

g) Ventricular tachycardia at a rate of ≥120 beats per minute lasting ≥10 seconds.

[17] A history within the last 5 years of a serious cardiovascular disorder, including

    a) Clinically significant arrhythmia

    b) Symptomatic sick sinus syndrome not treated with a pacemaker

    c) Congestive heart failure refractory to treatment

    d) Angina except angina controlled with PRN nitroglycerin

    e) Resting heart rate <50 or >100 beats per minute, on physical exam

    f) Uncontrolled hypertension.

[18] A history within the last 5 years of a serious gastrointestinal disorder, including

    a) Chronic peptic/duodenal/gastric/esophageal ulcer that are untreated or refractory to treatment

    b) Symptomatic diverticular disease

    c) Inflammatory bowel disease

    d) Pancreatitis

    e) Hepatitis

    f) Cirrhosis of the liver.

[19] A history within the last 5 years of a serious endocrine disorder, including

    a) Uncontrolled Insulin Dependent Diabetes Mellitus (IDDM)

    b) Diabetic ketoacidosis

    c) Untreated hyperthyroidism

    d) Untreated hypothyroidism

    e) Other untreated endocrinological disorder

[20] A history within the last 5 years of a serious respiratory disorder, including

    a) Asthma with bronchospasm refractory to treatment

b) Decompensated chronic obstructive pulmonary disease.

[21] A history within the last 5 years of a serious genitourinary disorder, including

a) Renal failure

b) Uncontrolled urinary retention.

[22] A history within the last 5 years of a serious rheumatologic disorder, including

a) Lupus

b) Temporal arteritis

c) Severe rheumatoid arthritis.

[23] A known history of human immunodeficiency virus (HIV) within the last 5 years.

[24] A history within the last 5 years of a serious infectious disease including

a) Neurosyphilis

b) Meningitis

c) Encephalitis.

[25] A history within the last 5 years of a primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with a normal PSA postresection.

[26] Visual, hearing, or communication disabilities impairing the ability to participate in the study; (for example, inability to speak or understand English, illiteracy).

[27b] Laboratory test values exceeding the Lilly Reference Range III for the patient's age in any of the following analytes: $\uparrow$ creatinine, $\uparrow$ total bilirubin, $\uparrow$ SGOT, $\uparrow$ SGPT, $\uparrow$ alkaline phosphatase, $\uparrow$ GGT, $\uparrow\downarrow$ hemoglobin, $\uparrow\downarrow$ white blood cell count, $\uparrow\downarrow$ platelet count, $\uparrow\downarrow$ serum sodium, potassium, or calcium.

If values exceed these laboratory reference ranges, clinical significance will be judged by the monitoring physicians. If the monitoring physician determines that the deviation from the reference range is not clinically significant, the patient may be included in the study. This decision will be documented.

[28b] Central laboratory test values below reference range for folate, and Vitamin B_{12}, and outside reference range for thyroid function tests.

a) Folate reference range 2.0 to 25.0 ng/mL. Patients will be allowed to enroll if their folate levels are above the upper end of the range if patients are taking vitamin supplements.

b) Vitamin B_{12} reference range 130 to 900 pg/mL. Patients will be allowed to enroll if their B_{12} levels are above the upper reference range if patients are taking oral vitamin supplements.

c) Thyroid functions

  i) Thyroid Uptake reference range 25 to 38%. Patients will be allowed to enroll with results of 23 to 51% provided the remainder of the thyroid profile is normal and there are no clinical signs or symptoms of thyroid abnormality.

  ii) TSH reference range 0.32 to 5.0. Patients will be allowed to enroll with results of 0.03 to 6.2 if patients are taking stable doses of exogenous thyroid supplements, with normal free thyroid index, and show no clinical signs or symptoms of thyroid abnormality.

  iii) Total T4 reference range 4.5 to 12.5. Patients will be allowed to enroll with results of 4.1 to 13.4 if patients are taking stable doses of exogenous thyroid hormone, with normal free thyroid index, and show no clinical signs or symptoms of thyroid abnormality.

  iv) Free Thyroid Index reference range 1.1 to 4.6.

[29b] Positive syphilis screening.

Positive syphilis screening. As determined by positive RPR followed up by confirmatory FTA-Abs. Confirmed patients are excluded unless there is a documented medical history of an alternative disease (for example, yaws) which caused the lab abnormality.

[30b] Glycosylated hemoglobin (A1C). Required only on patients with known diabetes mellitus or random blood sugar >200 on screening labs. Patients will be excluded if levels are >9.5%

[31b] Treatment with the following medications within the specified washout periods prior to enrollment and during the study:

a) Anticonvulsants including but not limited to

Depakote® (valproic acid)	2 weeks
Dilantin® (phenytoin)	2 weeks
Felbatol® (felbamate)	1 month
Klonopin® (clonazepam)	2 weeks
Lamictal® (lamotrigine)	2 weeks
Mysoline® (primidone)	1 month
Neurontin® (gabapentin)	2 weeks
Phenobarbitol	1 month
Tegretol® (carbamazepine)	2 weeks

b) Alpha receptor blockers including but not limited to

Aldomet® (methyldopa)	2 weeks
Cardura® (doxazosin)	2 weeks
Catapres® (clonidine)	2 weeks
Hytrin® (terazosin)	2 weeks
Minipress® (prazosin)	2 weeks
Tenex® (guanfacine)	2 weeks
Wytensin® (guanabenz)	2 weeks

The use of low doses (2 mg daily) of either Hytrin® or Cardura® for relief of urinary retention for patients with prostatic hypertrophy will be considered on a case-by-case basis provided blood pressure is stable and the medication has not had demonstrable effect on dementia symptoms in the opinion of the treating physician. Contact CRO medical monitor.

c) Calcium channel blockers that are CNS active including but not limited to

Calan®, Isoptin®, Verelan® (verapamil)	2 weeks
Cardizem® (diltiazem)	2 weeks
Nimotop® (nimodipine)	2 weeks
Adalat®, Procardia XL® (nifedipine)	2 weeks

Cardene® (nicardipine), Norvasc®, (amlodipine), and DynaCirc® (isradipine) will be allowed during the study. If a patient is taking an excluded calcium channel blocker and is changed to an equivalent dose of an allowed calcium channel blocker, enrollment may proceed in as little as 24 hours though 1 week is preferred when possible.

d) Beta blockers including but not limited to

Betapace® (sotalol)	2 weeks
Inderal® (propranolol)	2 weeks
Lopressor®, Toprol XL® (metoprolol)	2 weeks
Corgard® (nadolol)	2 weeks
Sectral® (acebutolol)	2 weeks
Tenormin® (atenolol)	2 weeks
Visken® (pindolol)	2 weeks

Beta blocker eye drops for glaucoma will be considered on a case-by-case basis. Call medical monitor.

e) Beta sympathomimetics (unless inhaled) including but not limited to

Alupent® tablets (metaproterenol)	2 weeks
Brethine® tablets (terbutaline)	2 weeks
Dopamine	2 weeks
Proventil Repetabs®, Ventolin® tablets (albuterol tablets)	2 weeks

f) Parasympathomimetics (cholinergics) (unless opthalmic) including but not limited to

Antilirium® (physostigmine)	1 month
Aricept® (donepezil)	1 month
Cognex® (tacrine)	1 month
Mestinon® (pyridostigmine)	1 week
Reglan® (metoclopramide)	2 weeks
Urecholine®, Duvoid (bethanechol)	2 weeks

Cholinergic eye drops for treatment of glaucoma will be allowed during the study on a case-by-case basis. Please contact the CRO medical monitor.

g) Muscle relaxants-centrally active including but not limited to

Equanil® (meprobamate)	2 weeks
Flexeril® (cyclobenzaprine)	2 weeks
Lioresal® (baclofen)	2 weeks
Norflex® (orphenadrine)	2 weeks
Parafon Forte® (chlorzoxazone)	2 weeks
Robaxin® (methocarbamol)	2 weeks
Skelaxin® (metaxalone)	2 weeks
Soma® (carisoprodol)	2 weeks

h) Monamine oxidase inhibitors (MAOI) including but not limited to

Eldepryl®(selegiline)	1 month
Nardil® (phenelzine)	1 month
Parnate® (tranylcypromine)	1 month

i) Parasympatholytics including but not limited to

Antivert®, Bonine®, Dramamine II® (meclizine)	3 days
Artane® (trihexyphenidyl)	2 weeks
Bellergal-S® (alkaloids of belladonna and ergotamine)	2 weeks
Bentyl® (dicyclomine)	3 days
Cogentin® (benztropine)	2 weeks
Cystospaz®, Levsin®, Levsinex® (hyoscyamine)	2 weeks
Ditropan® (oxybutynin)	2 weeks
Donnatal®, Hyosophen® (atropine, scopolamine, hyoscyamine and phenobarbitol)	1 month
Dramamine® (dimenhydrinate)	3 days
Lomotil®, Lonox® (atropine, diphenoxylate)	2 weeks
Pro-Banthine® (propantheline)	2 weeks
Robinul® (glycopyrrolate)	3 days
Tigan® (trimethobenzamide)	3 days
Transderm-Scop® (scopolamine)	2 weeks
Urispas® (flavoxate)	2 weeks

j) Antidepressants including but not limited to

Anafranil® (clomipramine)	1 month
Asendin® (amoxapine)	1 month
Desyrel® (trazodone)	1 month
Effexor® (venlafaxine)	1 month
Elavil® (amitriptyline)	1 month
Ludiomil® (maprotiline)	1 month
Norpramin® (desipramine)	1 month
Pamelor®, Aventyl® (nortriptyline)	1 month
Paxil® (paroxetine)	1 month
Prozac® (fluoxetine)	1 month
Remeron® (mirtazapine)	1 month
Serzone® (nefazodone)	1 month
Sinequan® (doxepin)	1 month
Tofranil® (imipramine)	1 month
Vivactil® (protriptyline)	1 month
Wellbutrin® (bupropion)	1 month
Zoloft® (sertraline)	1 month

k) Systemic corticosteroids including but not limited to

Cortisone	2 weeks
Decadron® (dexamethasone)	2 weeks
Depo-Medrol® (methylprednisolone)	1 month
Prednisone	2 weeks

l) Xanthine derivatives including but not limited to

Aminophylline	2 weeks
Fioricet®, Esgic®, Phrenilin Forte® (caffeine, butalbital)	3 days
Theo-Dur® (theophylline)	2 weeks
Wigraine®, Cafergot® (caffeine, ergotamine)	3 days

m) Histamine (H_2) antagonists including but not limited to

Axid® (nizatidine)	1 week
Pepcid® (famotidine)	1 week
Tagamet® (cimetidine)	1 week
Zantac® (ranitidine)	1 week

If an H_2 antagonist is needed by the patient, Axid® will be allowed on a case-by-case basis. Please consult CRO medical monitor.

n) Narcotic Analgesics including but not limited to

Darvocet-N 100®, (propoxyphene)	1 week
Demerol® (meperidine)	1 week
Dilaudid® (hydromorphone)	1 week
Duragesic® (fentanyl)	1 week
MS Contin®, Roxanol®, Oramorph® (morphine)	1 week
Percocet®, Roxicet® (oxycodone with acetaminophen)	3 days
Percodan®, Roxiprin	1 week
Stadol® (butorphanol)	1 week
Talacen® (pentazocine)	1 week
Tylenol #2®, #3®, #4® (codeine and acetaminophen)	3 days
Tylox®, Roxilox® (oxycodone)	3 days
Vicodin®, Lorcet® (hydrocodone)	1 week

Percocet (oxycodone with acetaminophen) and Tylenol® with codeine #2, #3, #4 (acetaminophen + codeine) ARE allowed in the month prior to enrollment, but are not permitted in the 3 days prior to enrollment.

o) Neuroleptics (antipsychotics) including but not limited to

Clozaril® (clozapine)	2 weeks
Haldol® (haloperidol)	2 weeks
Loxitane® (loxapine)	2 weeks
Mellaril® (thioridazine)	2 weeks
Moban® (molindone)	2 weeks
Navane® (thiothixene)	2 weeks
Orap® (pimozide)	2 weeks
Prolixin® (fluphenazine)	1 month
Risperdal® (risperidone)	2 weeks
Stelazine® (trifluoperazine)	2 weeks
Thorazine® (chlorpromazine)	2 weeks
Trilafon® (perphenazine)	2 weeks
Serentil® (mesoridazine)	2 weeks

The use of neuroleptics on a daily basis must be discontinued 2 to 4 weeks prior to enrollment. The use of neuroleptics on an as-needed basis is allowable during the screening period, but the last dose must be at least 7 days prior to enrollment.

p) Antianxiety agents including but not limited to

Atarax® (hydroxyzine)	2 weeks
BuSpar® (buspirone)	2 weeks
Librium® (chlordiazepoxide)	2 weeks
Serax® (oxazepam)	2 weeks
Tranxene® (clorazepate)	2 weeks
Valium® (diazepam)	2 weeks
Vistaril® (hydroxyzine pamoate)	2 weeks
Xanax® (alprazolam)	2 weeks

Ativan® (lorazepam) should be discontinued on a daily basis 2 weeks prior to enrollment. It may be used on an as-needed basis during the screening period, but is not permitted in the 24 hours prior to enrollment.

q) Hypnotics/Sedatives including but not limited to

Ambien® (zolpidem)	3 days
Dalmane® (flurazepam)	3 days
Doral® (quazepam)	3 days
Halcion® (triazolam)	3 days
Nembutal®	2 weeks
ProSom® (estazolam)	3 days
Restoril® (temazepam)	3 days
Seconal®	2 weeks

Chloral Hydrate is allowed on an as-needed basis during screening, but is not permitted in the 24 hours prior to enrollment.

r) Histamine (H$_1$) antagonists including but not limited to

Actifed®, Actifed Plus® (triprolidine)	3 days
Benadryl®, Unisom®, Tylenol P.M.® (diphenhydramine)	3 days
Compazine® (prochlorperazine)	3 days
Contac®, Coricidin D®, Sinutab®, Novahistine®, Alka Seltzer Plus®, Naldecon®, Sudafed Plus®, Tylenol Cold®, Tylenol Cold and Flu® (chlorpheniramine)	3 days
Dimetapp® (brompheniramine)	3 days
Drixoral® (dexbrompheniramine)	3 days
Hismanal® (astemizole)	1 week
Phenergan® (promethazine)	3 days
Seldane® (terfenadine)	1 week
Tavist® (clemastine fumarate)	3 days
Zyrtec® (cetrizine)	1 week

Allegra® (fexofenadine hydrochloride) or Claritin® (loratadine) may be taken on as-needed basis during screening but must be discontinued within 24 hours of enrollment.

s) Stimulants including but not limited to

Cylert® (pemoline)	1 month
Ritalin® (methylphenidate)	1 month

t) Antiarrhythmics including but not limited to the following
Adenocard® (adenosine)
Cordarone® (amiodarone)
Ethmozine® (moricizine)
Mexitil® (mexiletine)
Norpace® (disopyramide)
Procan® (procainamide)
Quinaglute® (quinidine)
Rythmol® (propafenone)
Tambocor® (flecainide)
Tonocard® (tocainide)

Requirement of these drugs for control of cardiac arrhythmia indicates that the patient should be excluded from the study. If discontinuation of an antiarrhythmic is considered, please discuss case with CRO medical monitor.

u) Miscellaneous drugs including but not limited to

Coenzyme Q	2 weeks
Eskalith®, Lithobid® (lithium)	2 weeks
Ginkgo biloba	1 week
Lecithin	1 week
Lupron	2 weeks
Tamoxifen	1 month

v) Estrogen supplements are permitted during the study, but dosage must be stable for at least 3 months prior to enrollment.

3.4.2.3. Violation of Criteria for Enrollment

The criteria for enrollment must be followed explicitly. If there is inadvertent enrollment of individuals who do not meet enrollment criteria, these individuals should be discontinued from the study. Such individuals can remain in the study only if there are ethical reasons to have them continue. In these cases, the investigator must obtain approval from the Lilly research physician for the study participant to continue in the study (even if the study is being conducted through a contract research organization).

3.4.3. Disease Diagnostic Criteria

Probable AD will be defined clinically by NINCDS/ADRDA guidelines as follows:

- Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines.

- Mild to moderate severity of AD will be defined by the Mini-Mental State Exam as follows:

  - Mini-Mental State Examination (MMSE) score of 10 to 23.

- The absence of other causes of dementia will be performed by clinical opinion and by the following:

  - Hachinski Ischemic Scale score of ≤ 4.

- CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year (see Section 3.4.2.1).

3.4.4. Sample Size

Approximately 100 patients will be randomized to each of the 3 treatment groups. Previous experience with the oral formulation of xanomeline suggests that this sample size has 90% power to detect a 3.0 mean treatment difference in ADAS-Cog (p<.05, two-sided), based on a standard deviation of 6.5. Furthermore, this sample size has 80% power to detect a 0.36 mean treatment difference in CIBIC+ (p<.05, two-sided), based on a standard deviation of 0.9.

3.5. Patient Assignment

Commencing at Visit 1, all patients will be assigned an identification number. This identification number and the patient's three initials must appear on all patient-related documents submitted to Lilly.

When qualified for enrollment at Visit 3 the patient will be randomized to 1 of 3 treatment arms.

3.6. Dosage and Administration

3.6.1. Materials and Supplies

Primary Study Material:	Xanomeline	TTS (adhesive patches)	50 cm^2, 54 mg* 25 cm^2, 27 mg*
Comparator Material:	Placebo	TTS	Identical in appearance to primary study material

*All doses are measured in terms of the xanomeline base.

Patches should be stored at controlled room temperature, and all used patches must be handled and disposed of as biohazardous waste.

For a detailed description of the composition of these formulations please refer to Part II, Section 14 of the Xanomeline (LY246708) Clinical Investigator's Brochure.

3.6.2. TTS Administration Procedures

To test acute tolerance of transdermal formulation, patients will have a TTS (placebo) administered at the start of Visit 1, and removed at the conclusion of Visit 1. The patient's and caregiver's willingness to comply with 26 weeks of transdermal therapy should be elicited, and those patients/caregivers unwilling to comply should be excluded.

Upon enrollment at Visit 3, and on the morning of each subsequent day of therapy , xanomeline or placebo will be administered with the application of 2 adhesive patches, one 50 cm^2 in area, the other 25 cm^2 in area. Each morning, prior to the application of the patches, hydrocortisone cream (1%) should be applied to the skin at the intended site of administration, rubbed in, and allowed to penetrate for approximately 30 minutes. Thereafter, excess cream should be wiped away and the patches applied.

The patches are to be worn continuously throughout the day, for a period of approximately 12 to 14 hours, and removed in the evening. After removal of the patches, hydrocortisone cream (1%) should be applied locally to the site of administration.

Patches should be applied to a dry, intact, non-hairy area. Applying the patch to a shaved area is not recommended. The application site of the patches should be rotated according to the following schedule:

Day	Patch Location
Sunday	right or left upper arm
Monday	right or left upper back
Tuesday	right or left lower back (above belt line)
Wednesday	right or left buttocks
Thursday	right or left mid-axillary region
Friday	right or left upper thigh
Saturday	right or left upper chest

Patients and caregivers are free to select either the left or right site within the constraints of the rotation schedule noted above. Patches should be applied at approximately the same time each day. For patients who habitually bathe in the morning, the patient should bathe prior to application of new patches. Every effort should be taken to allow for morning administration of the patches. Exceptions allowing administration of TTS patches at night instead of in the morning will be made on a case-by-case basis by the CRO medical monitor. In the event that some adhesive remains on the patient's skin and cannot be removed with normal bathing, a special solution will be provided to remove the adhesive.

Following randomization at Visit 3, patients will be instructed to call the site if they have difficulty with application or wearing of patches. In the event that a patch becomes detached, a new patch of the same size should be applied (at earliest convenience) to an area of the dermis adjacent to the detachment site, and the rotation schedule should be resumed the following morning. If needed, the edges of the patch may be secured with a special adhesive tape that will be provided. If daily doses are reduced, improperly administered, or if a patch becomes detached and requires application of a new patch on three or more days in any 30-day period, the CRO research physician will be notified.

If the daily dose is reduced or improperly administered in the 24 hours prior to any scheduled clinic visit, the visit should be rescheduled (except for early termination and retrieval visits).

Patients must be instructed to return all used and unused study drug to the investigator at each visit for proper disposal and CT reconciliation by the investigator.

3.7. Blinding

The study will be double-blind. To further preserve the blinding of the study, only a minimum number of Lilly and CRO personnel will see the randomization table and codes before the study is complete.

Emergency codes generated by a computer drug-labeling system will be available to the investigator. These codes, which reveal the patients treatment group, may be opened during the study only if the choice of follow-up treatment depends on the patient's therapy assignment.

The investigator should make every effort to contact the clinical research physician prior to unblinding a patient's therapy assignment. If a patient's therapy assignment is unblinded, Lilly must be notified immediately by telephone. After the study, the investigator must return all sealed and any opened codes.

3.8. Concomitant Therapy

Intermittent use of chloral hydrate, zolpidem, or lorazepam is permitted during this clinical trial as indicated for agitation or sleep. If medication is required for agitation for a period exceeding 1 week, a review of the patient's status should be made in consultation with the CRO research physician. Caregivers and patients should be reminded that these medications should not be taken within 24 hours of a clinic visit (including the enrollment visit), and administration of efficacy measures should be deferred if the patient has been treated with these medications within the previous 24 hours.

If an antihistamine is required during the study, Claritin® (loratadine) or Allegra® (fexofenadine hydrochloride) are the preferred agents, but should not be taken within 24 hours of a clinic visit. Intermittent use (per package insert) of antitussives (containing antihistamines or codeine) and select narcotic analgesics (acetaminophen with oxycodone, acetaminophen with codeine) are permitted during the trial. Caregivers and patients should be reminded that antihistamines and narcotics should not be taken within 3 days of a clinic efficacy visit (including enrollment visit). If an H_2 blocker is required during the study, Axid® (nizatidine) will be permitted on a case-by-case basis by the CRO medical monitor. For prostatic hypertrophy, small doses (2 mg per day) of Hytrin® (terazosin) or Cardura® (doxazosin) will be permitted on a case-by-case basis. Please consult the medical monitor. The calcium channel blockers Cardene® (nicardipine),

Norvasc® (amlodipine), and DynaCirc® (isradipine) are allowed during the study. If a patient has been treated with any medication within disallowed time periods prior to the clinic visit, efficacy measures should be deferred.

Other classes of medications not stated in Exclusion Criteria, Section 3.4.2.2, will be permitted. Patients who require treatment with an excluded medication (Section 3.4.2.2) will be discontinued from the study following consultation with the CRO research physician.

3.9. Efficacy, Pharmacokinetic, and Safety Evaluations

3.9.1. Efficacy

See Schedule of Events, Attachment LZZT.1 for the times of the study at which efficacy data will be collected.

3.9.1.1. Efficacy Measures

The following measures will be performed in the course of the study. At Visits 3, 8, 10, and 12, ADAS-Cog, CIBIC+, and DAD will be administered. NPI-X will be administered at 2-week intervals either at clinic visits or via a telephone interview. Efficacy measures will also be collected at early termination visits, and at the retrieval visit. The neuropsychological assessment should be performed first; other protocol requirements, such as labs and the physical, should follow.

a) **Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog):** ADAS-Cog is an established measure of cognitive function in Alzheimer's Disease. This scale has been incorporated into this study by permission of Dr. Richard C. Mohs and the American Journal of Psychiatry and was adapted from an article entitled, "The Alzheimer's Disease Assessment Scale (ADAS)," which was published in the American Journal of Psychiatry, Volume No.141, pages 1356-1364, November, 1984, Copyright 1984.

The ADAS-Cog (11) and the ADAS-Cog (14): The ADAS-Cog (11) is a standard 11-item instrument used to assess word recall, naming objects, commands, constructional praxis, ideational praxis, orientation, word recognition tasks, spoken language ability, comprehension, word finding difficulty, and recall of test instructions. For the purposes of this study, three items (delayed word recall, attention/visual search task, and maze solution) have been added to the ADAS-Cog (11) to assess the patient's attention and concentration. The 14 item instrument will be referred to as the ADAS-Cog (14). At each efficacy visit, all 14 items will be assessed, and in subsequent data analyses, performance on the ADAS-Cog (14) and performance on the subset ADAS-Cog (11) will be considered.

b) **Video-referenced Clinician's Interview-Based Impression of Change (CIBIC+):** The CIBIC+ is an assessment of the global clinical status relative to baseline. The CIBIC+ used in this study is derived from the Clinical Global Impression of Change, an instrument in the public domain, developed by the National Institute on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator). The instrument employs semi-structured interviews with the patient and caregiver, to assess mental/cognitive state, behavior, and function. These domains are not individually scored, but rather are aggregated in the assignment of a global numeric score on a 1 to 7 scale (1 = marked improvement; 4 = no change; and 7 = marked worsening).

The clinician assessing CIBIC+ will have at least one year of experience with the instrument and will remain blinded to all other efficacy and safety measures.

c) **Revised Neuropsychiatric Inventory (NPI-X):** The NPI-X is an assessment of change in psychopathology in patients with dementia. The NPI-X is administered to the designated caregiver. This instrument has been revised from its original version (Cummings et al. 1994) and incorporated into this study with the permission of Dr. Jeffrey L. Cummings.

d) **Disability Assessment for Dementia (DAD):** The DAD is used to assess functional abilities of activities of daily living (ADL) in individuals with cognitive impairment. This scale has been revised and incorporated into this study by permission of Louise Gauthier, M.Sc., and Dr. Isabelle Gelinas. The DAD is administered to the designated caregiver.

For each instrument, each assessment is to be performed by the same trained health care professional. If circumstances preclude meeting this requirement, the situation is to be documented on the Clinical Report Form (CRF), and the CRO research physician is to be notified.

In addition to the efficacy measures noted above, a survey form will be used to collect information from the caregiver on TTS acceptability (Attachment LZZT.9).

3.9.1.2. Efficacy Criteria

Group mean changes from baseline in the primary efficacy parameters will serve as efficacy criteria. The ADAS-Cog (11) and the video-referenced CIBIC+ will serve as the primary efficacy instruments. Secondary efficacy instruments will include the DAD, the NPI-X, and the ADAS-Cog (14). The procedures and types of analyses to be done are outlined in Section 4.

The primary analysis of efficacy will include only the data obtained up to and including the visit of discontinuation of study drug. Furthermore, the primary analysis will not include efficacy data obtained at any visit where the study drug was not administered in the preceding three days. Analyses that include the retrieved dropouts are considered secondary.

3.9.2. Pharmacokinetics

Blood samples (7 mL) for the determination of xanomeline concentrations in plasma will be collected from each patient at Visits 3, 4, 5, 7, 9, and 11. The blood sample drawn at Visit 3 is a baseline sample. The remaining 5 clinic visits should be scheduled so that 1 blood sample is collected at any time during each of the following intervals: early AM visit (hold application of new patch until after blood sample is collected); 9AM to 11AM; 11AM to 1PM; 1PM to 3PM; and 3PM to 5PM. Collection of blood samples during each of these intervals should not occur in any particular order, nor should they occur in the same order for each patient. Every effort should be made to comply with the suggested sampling times. This blood-sampling schedule is based on a sparse sampling strategy where only a few samples will be collected from each patient. The most crucial aspect of the sampling design is to record the date and exact time the sample was drawn and to record the date and time of patch application on the day of the clinic visit and the previous 2 days.

If a patient is discontinued from the study prior to protocol completion, a pharmacokinetic blood sample should be drawn at the early discontinuation visit. The date and exact time the sample was drawn and the date of the last patch application should be recorded.

Immediately after collection, each sample will be centrifuged at approximately $177 \times G$ for 15 minutes. The plasma will be transferred into a polypropylene tube bearing the identical label as the blood collection tube. Samples will be capped and frozen at approximately $-20°C$. Care must be taken to insure that the samples remain frozen during transit.

The samples will be shipped on dry ice to Central Laboratory.

3.9.3. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting CRO to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. See Section 3.9.3.2.1.

Investigators must ensure that appropriate medical care is maintained throughout the study and after the trial (for example, to follow adverse events).

3.9.3.1. Safety Measures

Safety measures will be performed at designated times by recording adverse events, laboratory test results, vital signs (including supine/standing pulse and blood pressure readings) ECG monitoring, and Ambulatory ECGs (see Schedule of Events, Attachment LZZT.1).

3.9.3.2. Clinical Adverse Events

Lilly has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that are less stringent. For purposes of collecting and evaluating *all* information about Lilly drugs used in clinical trials, an adverse event is defined as any undesirable experience or an unanticipated benefit (see Section 3.9.3.2.1) that occurs after informed consent for the study has been obtained, without regard to treatment group assignment, even if no study medication has been taken. Lack of drug effect is not an adverse event in clinical trials, because the purpose of the clinical trial is to establish drug effect.

At the first visit, study site personnel will question the patient and will note the occurrence and nature of presenting condition(s) and of any preexisting condition(s). At subsequent visits, site personnel will again question the patient and will note any change in the presenting condition(s), any change in the preexisting condition(s), and/or the occurrence and nature of any adverse events.

3.9.3.2.1. Adverse Event Reporting Requirements

All adverse events must be reported to CRO via case report form.

Study site personnel must report to CRO immediately, by telephone, any **serious** adverse event (see Section 3.9.3.2.2 below), or if the investigator **unblinds** a patient's treatment group assignment because of an adverse event or for any other reason.

If a patient's dosage is reduced or if a patient is discontinued from the study because of any significant laboratory abnormality, inadequate response to treatment, or any other reason, the circumstances and data leading to any such dosage reduction or discontinuation must be reported and clearly documented by study site personnel on the clinical report form.

An event that may be considered an unanticipated benefit to the patient (for example, sleeping longer) should be reported to CRO as an adverse event on the clinical report form. "Unanticipated benefit" is a COSTART classification term. In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should enter the actual term such as "sleeping longer," and code "unanticipated benefit" in the clinical report form adverse event section.

Solicited adverse events from the skin rash questionnaire (see Section 3.9.3.4) should be reported on the questionnaire only and not also on the adverse event clinical report form

3.9.3.2.2. Serious Adverse Events

Study site personnel must report to CRO immediately, by telephone, any adverse event from this study that is alarming or that:

- Results in death

- Results in initial or prolonged inpatient hospitalization

- Is life-threatening

- Results in severe or permanent disability

- Results in cancer [(other than cancers diagnosed prior to enrollment in studies involving patients with cancer)]

- Results in a congenital anomaly

- Is a drug overdose

- Is significant for any other reason.

Definition of *overdose*: For a drug under clinical investigation, an overdose is any intentional or unintentional consumption of the drug (by any route) that exceeds the dose recommended in the Clinical Investigator's Brochure or in an investigational protocol, whichever dose is larger. For a marketed drug, a drug overdose is any intentional or unintentional consumption of the drug (by any route) that exceeds the dose listed in product labeling, even if the larger dose is prescribed by a physician.

3.9.3.3. Clinical Laboratory Tests

Table LZZT.1 lists the clinical laboratory tests that will be performed at Visit 1.

Table LZZT.1.   Laboratory Tests Performed at Admission (Visit 1)

Hematology:
  Hemoglobin
  Hematocrit
  Erythrocyte count (RBC)
  Mean cell volume (MCV)
  Mean cell hemoglobin (MCH)
  Mean cell hemoglobin concentration (MCHC)
  Leukocytes (WBC)
  Neutrophils, segmented
  Neutrophils, juvenile (bands)
  Lymphocytes
  Monocytes
  Eosinophils
  Basophils
  Platelet
  Cell morphology

Urinalysis:
  Color
  Specific gravity
  pH
  Protein
  Glucose
  Ketones
  Bilirubin
  Urobilinogen
  Blood
  Nitrite
  Microscopic examination of sediment

**Clinical Chemistry -
Serum Concentrations of:**
  Sodium
  Potassium
  Bicarbonate
  Chloride
  Total bilirubin
  Alkaline phosphatase (ALP)
  Gamma-glutamyl transferase (GGT)
  Alanine transaminase (ALT/SGPT)
  Aspartate transaminase (AST/SGOT)
  Blood urea nitrogen (BUN)
  Serum creatinine
  Uric acid
  Phosphorus
  Calcium
  Glucose, nonfasting
  Total protein
  Albumin
  Cholesterol
  Creatine kinase (CK)

Thyroid Function Test (Visit 1 only):
  Free thyroid index
  T_3 Uptake
  T_4
  Thyroid-stimulating hormone (TSH)

Other Tests (Visit 1 only):
  Folate
  Vitamin B_{12}
  Syphilis screening
  Hemoglobin A_{1C} (IDDM patients only)

Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented on by the investigator by marking CS (for clinically significant) or NCS (for not clinically significant) next to the values. Any clinically significant laboratory values that are outside a clinically acceptable range or differ importantly from a previous value should be further commented on in the clinical report form comments page.

Hematology, and clinical chemistry will also be performed at Visits 4, 5, 7, 8, 9, 10, 11, 12, and 13. Patients that experience a rash and/or eosinophilia may have additional hematology samples obtained as described in 3.9.3.4 (Other Safety Measures).

Urinalysis will also be performed at Visits 4, 9, and 12. The following criteria have been developed to monitor hepatic function.

- Patients with ALT/SGPT levels >120 IU will be retested weekly.

- Patients with ALT/SGPT values >400 IU, or alternatively, an elevated ALT/SGPT accompanied by GGT and/or ALP values >500 IU will be retested within 2 days. The sponsor's clinical research administrator or clinical research physician is to be notified. If the retest value does not decrease by at least 10%, the study drug will be discontinued; additional laboratory tests will be performed until levels return to normal. If the retest value does decrease by 10% or more, the study drug may be continued with monitoring at 3 day intervals until ALT/SGPT values decrease to <400 IU or GGT and/or ALP values decrease to <500 IU.

3.9.3.4. Other Safety Measures

Patients experiencing Rash and/or Eosinophilia

The administration of placebo and xanomeline TTS is associated with a rash and/or eosinophilia in some patients. The rash is characterized in the following ways:

- The rash is confined to sites of application.

- The rash may be associated with pruritus.

- In 5% of cases of rash observed in the Interim Analysis, blistering has been observed.

- The onset of rash may occur at any time during the course of the study.

- A moderate eosinophilia (0.6-1.5 x 10^3/microliter) is associated with rash and has been noted in approximately 10% of patients.

It does not appear that the rash constitutes a significant safety risk; however, it could affect the well-being of the patients. The following monitoring is specified:

Skin Rash Follow-up

For patients who exit the study or its extension with rash at the site(s) of application:

a) Approximately 2 weeks after the last visit, the study site personnel should contact the patient/caregiver by phone and complete the skin rash questionnaire. (Note: those patients with rash who have previously exited the study or its extension should be contacted at earliest convenience.)

b) If caregiver states unequivocally that skin problems have completely resolved, no further follow-up is needed.

c) If caregiver reports scarring and/or other problems, patient should return to clinic for a follow-up visit. The skin rash questionnaire should again be completed. If in the opinion of the investigator, further follow-up is required, contact the CRO medical monitor.

Completed skin rash questionnaires should be faxed to CRO.

Completion of the questionnaires will create a separate data set for solicited adverse events. In completing these forms please note the following:

1. Solicited events (events discovered as result of completion of follow-up questionnaires) should be reported on questionnaire page only.

2. Spontaneously reported adverse events (events presented by the patient without direct questioning of the event) should be reported as described in 3.9.3.2.1 (Adverse Event Reporting Requirements).

Serious adverse events should be handled and reported as described in 3.9.3.2.1 without regard to whether the event is solicited or spontaneously reported.

Eosinophilia Follow-up

1. For patients that are currently in the study with eosinophil counts greater than 0.6×10^3/microliter:

   - Repeat hematology at each visit until resolved in the opinion of the investigator.

2. For patients that are currently in the study with eosinophil counts greater than 1.5×10^3/microliter:

   - Obtain hematology profile every 2 weeks until resolved or explained by other causes in the opinion of the investigator.

   - Notify CRO medical monitor.

3. For patients with eosinophil counts greater than 0.6×10^3/microliter at exit from the study or its extension:

   - Obtain hematology profile approximately every 2 weeks until resolved or, in the opinion of the investigator, explained by other causes. (Note: patients with eosinophil counts greater than 0.6×10^3/microliter who have previously exited the study or its extension should return for hematology profile at earliest convenience.)

3.9.3.4.1   Vital Sign Determination

Patient should lie supine quietly for at least 5 minutes prior to vital signs measurement. Blood pressure should be measured in the dominant arm with a standardized mercury manometer according to the American Heart Association standard recommendations. Diastolic blood pressure will be measured as the point of disappearance of the Korotkoff

sounds (phase V). Heart rate will be measured by auscultation. Patient should then stand up. Blood pressure should again be measured in the dominant arm and heart rate should be measured after approximately 1 and 3 minutes.

An automated blood pressure cuff may be used in place of a mercury manometer if it is regularly (at least monthly) standardized against a mercury manometer.

3.9.3.4.2.Cardiovascular Safety Measures

Cardiovascular status will be assessed during the trial with the following measures:

- All patients will be screened by obtaining a 12-lead ECG, and will have repeat ECGs performed at Visits 4, 5, 7, 8, 9, 10, 11, 12, 13, and early termination (ET) (see Schedule of Events, Attachment LZZT.1).

- All patients will undergo a 24-hour Ambulatory ECG at Visit 2 (prior to the initiation of study medication). Although every effort will be made to obtain the entire 24-hour ambulatory ECG recording, this may not always be feasible because of patient behavior or technical difficulties. The minimal recording period for an ambulatory ECG to be considered interpretable will be 8 hours, of which at least 3 hours must be sleep.

- The incidence of syncope, defined as an observed loss of consciousness and muscle tone not attributable to transient ischemic attack or to seizure, will be closely monitored. Caregivers will be instructed to report any instance of syncopal episodes to the investigator within 24 hours. The investigator should immediately report such events to the CRO research physician. The CRO research physician will make a clinical assessment of each episode, and with the investigator determine if continuation of therapy is appropriate. These findings will be reported to the Lilly research physician immediately.

3.9.4. Safety Monitoring

The CRO research physician will monitor safety data throughout the course of the study.

Cardiovascular measures, including ECGs and 24-hour Ambulatory ECGs (see Section 3.9.3.4.2) will be monitored on an ongoing basis as follows:

- As noted in Section 3.9.3.4.2, all patients will be screened by obtaining a 12-lead ECG, and will have repeat ECGs performed at Visits 4, 5, 7, 8, 9, 10, 11, 12, 13, and early termination (ET) (see Schedule of Events for Protocol H2Q-MC-LZZT(c), Attachment LZZT.1). ECG data will be interpreted at the site and express mailed overnight to a central facility which will produce a report within 48 hours. The report will be forwarded to the investigator. At screening, the report of the central facility will be used to exclude patients according to criteria specified in Section 3.4.2.2. If, during the treatment phase of the study, review of ECG data (either at the site or at the central facility) reveals left bundle branch block, bradycardia ≤50 beats per minute, sinus pauses >2 seconds, second degree heart block, third degree heart block, Wolff-Parkinson-White syndrome, sustained supraventricular tachyarrhythmia, or ventricular tachycardia at a rate of ≥120 beats per minute lasting ≥10 seconds, the investigator, the Lilly research physician, the CRO research physician, and the cardiologist chairing the DSMB will be notified immediately, and discontinuation of the patient will be considered.

- As noted in Section 3.9.3.4.2, all patients will undergo a 24-hour Ambulatory ECG at Visit 2 (prior to the initiation of study medication). Ambulatory ECG data from Visit 2 will be express mailed overnight to a central facility which will produce a report within 24 hours. The report will be forwarded to the investigator. If a report documents sustained ventricular tachycardia with rate >120 beats per minute, third degree heart block, or sinus pauses of >6.0 seconds, the investigator, the Lilly research physician, the CRO research physician, and the cardiologist chairing the DSMB will be notified immediately, and the patient will be discontinued. If any report documents sinus pauses of >3.0 seconds or second degree heart block, the CRO research physician, and Lilly research physician, and cardiologist chairing the DSMB will be immediately notified and the record will be reviewed within 24 hours of notification by the cardiologist chairing the DSMB.

In addition to ongoing monitoring of cardiac measures, a comprehensive, periodic review of cardiovascular safety data will be conducted by the DSMB, which will be chaired by an external cardiologist with expertise in arrhythmias, their pharmacological bases, and their clinical implications. The membership of the board will also include two other external cardiologists, a cardiologist from Lilly, a statistician from Lilly, and the Lilly research physician. Only the three external cardiologists will be voting members.

After approximately 75 patients have completed 1 month of treatment, the DSMB will meet to decide:

- If discontinuation of the study or any treatment arm is appropriate

- If additional cardiovascular monitoring is required

- If further cardiovascular monitoring is unnecessary

- If adjustment of dose within a treatment arm (or arms) is appropriate.

If necessary, this analysis will be repeated after 150 patients have completed 1 month of treatment, after 225 patients have completed 1 month of treatment, and after 300 patients have completed 1 month of treatment. Primary consideration will be given to the frequency of pauses documented in Ambulatory ECG reports. The number of pauses greater than or equal to 2, 3, 4, 5, and 6 seconds will be tabulated. Primary analysis will focus on the number of pauses greater than or equal to 3 seconds.

In the event of a high incidence of patient discontinuation due to syncope, the following guideline may be employed by the DSMB in determining if discontinuation of any treatment arm is appropriate. If the frequency of syncope in a xanomeline treatment arm relative to the frequency of syncope in the placebo arm equals or exceeds the following numbers, then consideration will be given to discontinuing that treatment arm. The Type I error rate for this rule is approximately 0.032 if the incidence in each group is 0.04. The power of this rule is 0.708 if the incidence is 0.04 for placebo and 0.16 for xanomeline TTS.

Placebo	Xanomeline		Placebo	Xanomeline
0	6		6	15
1	7		7	16
2	9		8	17
3	11		9	18
4	12		10	20
5	13		X	2X (2-fold)

This rule has been used in other studies for monitoring spontaneous events with an incidence of less than 10%. This rule is constructed assuming a 2-group comparison with each group having a final sample size of 100. Unblinding which occurs during these analyses will be at the group level and will be documented.

The stopping rule based on Ambulatory ECG findings is as follows:

If the number of patients experiencing a pause of ≥6 seconds in a xanomeline treatment arm relative to the number of patients in the placebo arm equals or exceeds the numbers in the following table, then that treatment arm will be discontinued. The Type I error rate for this rule is approximately 0.044 if the incidence in each group is 0.01. The power of this rule is 0.500 if the incidence is 0.01 for placebo and 0.04 for xanomeline TTS.

Placebo	Xanomeline
0	3
1	5
2	6
3	7
4	8
x	2x

3.9.5. Appropriateness and Consistency of Measurements

The medications and efficacy measurements have been used in other studies in elderly subjects and patients.

3.10. Patient Disposition Criteria

3.10.1. Discontinuations

Participation in the study shall be terminated for any patient who is unable or unwilling to comply with the study protocol or who develops a serious adverse event.

In addition, patients may be discontinued for any of the following reasons:

- In the opinion of the investigator, a significant adverse event occurs or the safety of the patient is otherwise compromised.

- The patient requests to be withdrawn from the study.

- The physician in charge of the study or Lilly, for any reason stops the patient's participation in the study.

If a patient's participation terminates early, an early termination visit should be scheduled. Upon decision to discontinue a patient from the study, the patient's dose should be titrated down by instructing the patient to immediately remove the 25-cm^2 patch. Patients should be instructed to continue to apply a 50-cm^2 patch daily until the early termination visit, at which time the drug will be discontinued. Physical exam, vital signs, temperature, use of concomitant medications, chemistry/hematology/urinalysis labs, xanomeline plasma sample, TTS acceptability survey, efficacy measures, adverse events, and an ECG will be collected at the early termination visit.

In the event that a patient's participation or the study itself is terminated, the patient shall return all study drug(s) to the investigator.

3.10.1.1. Retrieval of Discontinuations

If possible, patients who have terminated early will be retrieved on the date which would have represented Visit 12 (Week 24). Vital signs, temperature, use of concomitant medications, adverse events, and efficacy measure assessment will be gathered at this visit. If the patient is not retrievable, this will be documented in the source record.

3.10.2. Qualifications for Analysis

All patients who are enrolled in the study will be included in the efficacy analysis and the safety analysis. Patients will not be excluded from the efficacy analysis for reasons such as non-compliance or ineligibility, except for the time period immediately preceding the efficacy assessment (see Section 3.9.1.2).

3.10.3. Study Extensions

Patients who successfully complete the study will be eligible for participation in an open-label extension phase, where every patient will be treated with active agent. The patients who elect to participate in the open-label extension phase will be titrated to their maximally titrated dose. This open-label extension phase will continue until the time the product becomes marketed and is available to the public or until the project is discontinued by the sponsor. Patients may terminate at any time at their request.

3.10.3.1. Compliance

Because patients enrolled in this study will be outpatients, the knowledge that patients have taken the medication as prescribed will be assured in the following ways:

a)   Investigators will attempt to select those patients and caregivers who have been judged to be compliant.

b)   Study medication including unused, partially used, and empty patch containers will be returned at each clinical visit so that the remaining medication can be counted by authorized investigator staff (nurse, pharmacist, or physician). The number of patches remaining will be recorded on the CRF.

c) Following randomization at Visit 3, patients will be instructed to call the site if they have difficulty with application or wearing of patches. If daily doses are reduced, improperly administered, or if a patch becomes detached and requires application of a new patch on three or more days in any 30-day period, the CRO research physician will be notified.

If the daily dose is reduced or improperly administered in the 24 hours prior to any scheduled clinic visit, the visit should be rescheduled (except for early termination and retrieval visits).

3.11. Quality Assurance

To ensure both the safety of participants in the study, and the collection of accurate, complete, and reliable data, Lilly or its representatives will perform the following activities:

- Provide instructional material to the study sites, as appropriate.

- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the clinical report forms, and study procedures.

- Make periodic visits to the study site.

- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.

- Review and evaluate clinical report form data and use standard computer edits to detect errors in data collection.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will do the following:

- Keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) and/or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

4.   Data Analysis Methods

4.1.   General Considerations

In general, all patients will be included in all analyses of efficacy if they have a baseline measurement and at least one postrandomization measurement. Refer to Section 3.9.1.2. for a discussion of which specific efficacy data will be included in the primary analysis.

In the event that the doses of xanomeline TTS are changed after the study starts, the analysis will be of three treatment groups (high dose, low dose, and placebo), even though patients within the high dose treatment group, for example, may not all be at exactly the same dose. Also, if the dose is changed midway through the study, the mean dose within each group will be used in the dose response analysis described in Section 4.3.3.

All analyses described below will be conducted using the most current production version of SAS® available at the time of analysis.

4.2.   Demographics and Patient Characteristics Measured at Baseline

All measures (for example, age, gender, origin) obtained at either Visits 1, 2, or 3, prior to randomization, will be summarized by treatment group and across all treatment groups. The groups will be compared by analysis of variance (ANOVA) for continuous variables and by Pearson's chi-square test for categorical variables. Note that because patients are randomized to 1 of the 3 treatment groups, any statistically significant treatment group differences are by definition a Type I error; however, the resulting p-values will be used as another descriptive statistic to help focus possible additional analyses (for example, analysis of covariance, subset analyses) on those factors that are most imbalanced (that is, that have the smallest p-values).

4.3.   Efficacy Analyses

4.3.1.   Efficacy Variables to be Analyzed

Efficacy measures are described in Section 3.9.1.1. As stated in Section 3.9.1.2, the primary outcome measures are the ADAS-Cog (11) and CIBIC+ instruments. Because both of these variables must reach statistical significance, an adjustment to the nominal p-values is necessary in order to maintain a .05 Type I error rate for this study. This adjustment is described in detail in Section 4.3.5.

The DAD will be analyzed with respect to the total score, as well as the subscores of initiation, planning and organization, and effective performance. This variable is considered a secondary variable in the US, but is a third primary variable in Europe.

The NPI-X is a secondary variable. The primary assessment of this instrument will be for the total score, not including the sleep, appetite, and euphoria domains. This total score is computed by taking the product of the frequency and severity scores and summing them up across the domains. Secondary variables derived from the NPI-X include evaluating each domain/behavior separately. Also, caregiver distress from the NPI-X will be analyzed.

ADAS-Cog (14) and each of the 14 individual components will also be analyzed. In addition, a subscore of the ADAS-Cog will be computed and analyzed, based on results from a previous large study of oral xanomeline. This subscore, referred to as ADAS-Cog (4), will be the sum of constructional praxis, orientation, spoken language ability, and word finding difficulty in spontaneous speech.

Any computed total score will be treated as missing if more than 30% of the items are missing or scored "not applicable". For example, when computing ADAS-Cog(11), if 4 or more items are missing, then the total score will not be computed. When one or more items are missing (but not more than 30%), the total score will be adjusted in order to maintain the full range of the scale. For example, ADAS-Cog(11) is a 0-70 scale. If the first item, Word Recall (ranges from 0 to 10), is missing, then the remaining 10 items of the ADAS-Cog(11) will be summed and multiplied by (70 / (70-10)), or 7/6. This computation will occur for all totals and subtotals of ADAS-Cog and NPI-X. DAD is a 40 item questionnaire where each question is scored as either "0" or "1". The DAD total score and component scores are reported as percentage of items that are scored "1". So if items of the DAD are "not applicable" or missing, the percentage will be computed for only those items that are scored. As an example, if two items are missing (leaving 38 that are scored), and there are 12 items scored as "1", the rest as "0", then the DAD score is 12/38=.316.

4.3.2. Times of Analyses

Baseline data will be collected at Visit 3.

The primary analysis of ADAS-Cog (11) and CIBIC+ will be the 24-week endpoint, which is defined for each patient and variable as the last measurement obtained postrandomization (prior to protocol defined reduction in dose).

Similar analyses at 24 weeks will be conducted for the secondary efficacy variables. Analysis of patients who complete the 24-week study will also be conducted for all efficacy variables; this is referred to as a "completer" analysis.

Additionally, each of the efficacy variables will be analyzed at each time point both as "actual cases," that is, analyzing the data collected at the various time points, and also as

a last-observation-carried-forward (LOCF). Note that the LOCF analysis at 24 weeks is the same as the endpoint analysis described previously.

Several additional analyses of NPI-X will be conducted. Data from this instrument will be collected every 2 weeks, and represent not the condition of the patient at that moment in time, but rather the worst condition of the patient in the time period since the most recent NPI-X administration. For this reason, the primary analysis of the NPI-X will be of the average of all postrandomization NPI-X subscores except for the one obtained at Week 2. In the event of early discontinuations, those scores that correspond to the interval between Weeks 2 to 24 will be averaged. The reason for excluding Week 2 data from this analysis is that patients could be confused about when a behavior actually stops after randomization; the data obtained at Week 2 could be somewhat "tainted." Also, by requiring 2 weeks of therapy prior to use of the NPI-X data, the treatment difference should be maximized by giving the drug 2 weeks to work, thereby increasing the statistical power. Secondary analyses of the NPI-X will include the average of all postrandomization weeks, including measures obtained at Weeks 2 and 26.

4.3.3. Statistical Methodology

The primary method to be used for the primary efficacy variables described in Sections 4.3.1 and 4.3.2 will be analysis of covariance (ANCOVA), except for CIBIC+ which is a score that reflects change from baseline, so there is no corresponding baseline CIBIC+ score. Effects in the ANCOVA model will be the corresponding baseline score, investigator, and treatment. CIBIC+ will be analyzed by analysis of variance (ANOVA), with effects in the model being investigator and treatment. Investigator-by-treatment interaction will be tested in a full model prior to conducting the primary ANCOVA or ANOVA (see description below).

Because 3 treatment groups are involved, the primary analysis will be the test for linear dose response in the ANCOVA and ANOVA models described in the preceding paragraph. The result is then a single p-value for each of ADAS-Cog and CIBIC+.

Analysis of the secondary efficacy variables will also be ANCOVA. Pairwise treatment comparisons of the adjusted means for all efficacy variables will be conducted using a LSMEANS statement within the GLM procedure.

Investigator-by-treatment interaction will be tested in a full ANCOVA or ANOVA model, which takes the models described above, and adds the interaction term to the model. Interaction will be tested at $\alpha = .10$ level. When the interaction is significant at this level, the data will be examined for each individual investigator to attempt to identify the source of the significant interaction. When the interaction is not significant, this term will be dropped from the model as described above, to test for investigator and treatment main effects. By doing so, all ANCOVA and ANOVA models will be able to validly test for treatment differences without weighting each investigator equally, which is what occurs when using Type III sums of squares (cell means model) with the interaction term

present in the model. This equal weighting of investigators can become a serious problem when sample sizes are dramatically different between investigators.

For all ANOVA and ANCOVA models, data collected from investigators who enrolled fewer than 3 patients in any one treatment group will be combined prior to analysis. If this combination still results in a treatment group having fewer than 3 patients in any one treatment group, then this group of patients will be combined with the next fewest-enrolling investigator. In the event that there is a tie for fewest-enrolling investigator, one of these will be chosen at random by a random-number generator.

The inherent assumption of normally distributed data will be evaluated by generating output for the residuals from the full ANCOVA and ANOVA models, which include the interaction term, and by testing for normality using the Shapiro-Wilk test from PROC UNIVARIATE. In the event that the data are predominantly nonnormally distributed, analyses will also be conducted on the ranked data. This rank transformation will be applied by ranking all the data for a particular variable, across all investigators and treatments, from lowest to highest. Integer ranks will be assigned starting at 1; mean ranks will be assigned when ties occur.

In addition, the NPI-X will be analyzed in a manner similar to typical analyses of adverse events. In this analysis, each behavior will be considered individually. This analysis is referred to as "treatment-emergent signs and symptoms" (TESS) analysis. For each behavior, the patients will be dichotomized into 1 of 2 groups: those who experienced the behavior for the first time postrandomization, or those who had the quotient between frequency and severity increase relative to the baseline period defines one group. All other patients are in the second group. Treatments will be compared for overall differences by Cochran-Mantel-Haentzel (CMH) test referred to in SAS® as "row mean scores differ," 2 degrees of freedom. The CMH correlation statistic (1 degree of freedom test), will test for increasing efficacy with increasing dose (trend test).

4.3.4. One-sided Justification

All comparisons between xanomeline and placebo with respect to efficacy variables should be one-sided. The justification for this follows.

The statistical hypothesis that is tested needs to be consistent with the ultimate data-based decision that is reached. When conducting placebo-controlled trials, it is imperative that the drug be demonstrated to be superior in efficacy to placebo, since equivalent or worse efficacy than placebo will preclude approvability. Consequently, a one-sided test for efficacy is required.

The null hypothesis is that the drug is equal or worse than placebo. The alternative hypothesis is that the drug has greater efficacy than placebo. A Type I error occurs only when it is concluded that a study drug is effective when in fact it is not. This can occur in only one tail of the distribution of the treatment difference. Further details of the

arguments for one-sided tests in placebo-controlled trials are available in statistical publications (Fisher 1991; Koch 1991; Overall 1991; and Peace 1991).

The argument for one-sided tests does not necessarily transfer to safety measures, in general, because one can accept a certain level of toxicity in the presence of strong efficacy. That is, safety is evaluated as part of a benefit/risk ratio.

Note that this justification is similar to that used by regulatory agencies worldwide that routinely require one-sided tests for toxicological oncogenicity studies. In that case, the interest is not in whether a drug seems to lessen the occurrence of cancer; the interest is in only one tail of the distribution, namely whether the drug causes cancer to a greater extent than the control.

Different regulatory agencies require different type I error rates. Treatment differences that are significant at the .025 α-level will be declared to be "statistically significant." When a computed p-value falls between .025 and .05, the differences will be described as "marginally statistically significant." This approach satisfies regulatory agencies who have accepted a one-sided test at the .05 level, and other regulatory agencies who have requested a two-sided test at the .05 level, or equivalently, a one-sided test at the .025 level. In order to facilitate the review of the final study report, two-sided p-values will be presented in addition to the one-sided p-values.

4.3.5. Nominal P-value Adjustments

When there are multiple outcomes, and the study drug is declared to be effective when at least one of these outcomes achieves statistical significance in comparison with a placebo control, a downward adjustment to the nominal α-level is necessary. A well-known simple method is the Bonferroni method, that divides the overall Type I error rate, usually .05, by the number of multiple outcomes. So, for example, if there are two multiple outcomes, the study drug is declared to be effective if at least one of the two outcomes is significant at the .05/2 or .025 level.

However, when one has the situation that is present in this study, where there are 2 (or 3 for Europe) outcome variables, each of which must be statistically significant, then the adjustment of the nominal levels is in the opposite direction, that is upwards, in order to maintain an overall Type 1 error rate of .05.

In the case of two outcomes, ADAS-Cog (11) and CIBIC+, if the two variables were completely independent, then each variable should be tested at the nominal α-level of $.05^{1/2} = .2236$ level. So if both variables resulted in a nominal p-value less than or equal to .2236, then we would declare the study drug to be effective at the overall Type 1 error rate of .05.

We expect these two outcome measures to be correlated. From the first large-scale efficacy study of oral xanomeline, Study MC-H2Q-LZZA, the correlation between CIBIC+ and the change in ADAS-Cog(11) from baseline was .252. Consequently, we

plan to conduct a randomization test to combine these two dependent dose-response p-values into a single test, which will then be at the .05 Type I error level. Because there will be roughly 300!/(3 * 100!) possible permutations of the data, random data permutations will be sampled (10,000 random permutations).

Designate the dose response p-values as p1 and p2 (computed as one-sided p-values), for ADAS-Cog(11) and CIBIC+, respectively. The rejection region is defined as

   [{p1 ≤ α and p2 ≤ α}].

The critical value, α, will be determined from the 10,000 random permutations by choosing the value of α to be such that 2.5% of the 10,000 computed pairs of dose response p-values fall in the rejection region. This will correspond to a one-sided test at the .025 level, or equivalently a two-sided test at the .05 level. In addition, by determining the percentage of permuted samples that are more extreme than the observed data, a single p-value is obtained.

4.4. Safety Analyses

Although safety data is collected at the 24 week visit for retrieved dropouts, these data will not be included in the primary analysis of safety.

Pearson's chi-square test will be used to analyze 3 reasons for study discontinuation (protocol completed, lack of efficacy, and adverse event), the incidence of abnormal (high or low) laboratory measures during the postrandomization phase, and the incidence of treatment-emergent adverse events. The analysis of laboratory data is conducted by comparing the measures to the normal reference ranges (based on a large Lilly database), and counting patients in the numerator if they ever had a high (low) value during the postrandomization phase.

Additionally, for the continuous laboratory tests, an analysis of change from baseline to endpoint will be conducted using the same ANOVA model described for the efficacy measures in Section 4.3. Because several laboratory analytes are known to be non-normally distributed (skewed right), these ANOVAs will be conducted on the ranks.

Several outcome measures will be extracted and analyzed from the Ambulatory ECG tapes, including number of pauses, QT interval, and AV block (first, second, or third degree). The primary consideration will be the frequency of pauses. The number of pauses greater than or equal to 2, 3, 4, 5 and 6 seconds will be tabulated. Primary analysis will focus on the number of pauses greater than or equal to 3 seconds. Due to possible outliers, these data will be analyzed as the laboratory data, by ANOVA on the ranks.

Treatment-emergent adverse events (also referred to as treatment-emergent signs and symptoms, or TESS) are defined as any event reported during the postrandomization

period (Weeks 0 - 26) that is worse in severity than during the baseline period, or one that occurs for the first time during the postrandomization period.

4.5. Subgroup Analyses

The effect of age, gender, origin, baseline disease severity as measured by MMSE, Apo E, and patient education level upon efficacy will be evaluated if sample sizes are sufficient to warrant such analyses. For example, if all patients are Caucasian, then there is no need to evaluate the co-factor origin. The ANCOVA and ANOVA models described above will be supplemented with terms for the main effect and interaction with treatment. Each co-factor will be analyzed in separate models. The test for treatment-by-subgroup interaction will address whether the response to xanomeline, compared with placebo, is different or consistent between levels of the co-factor.

4.6. Interim Efficacy Analyses

Two interim efficacy analyses are planned. The first interim analysis will occur when approximately 50% of the patients have completed 8 weeks; the second interim analysis is to be conducted when approximately 50% of the patients have completed 24 weeks of the study. The purpose of these interim analyses is to provide a rationale for the initiation of subsequent studies of xanomeline TTS, or if the outcome is negative to stop development of xanomeline TTS. The method developed by Enas and Offen (1993) will be used as a guideline as to whether or not to stop one treatment arm, or the study, to declare ineffectiveness. The outcome of the interim analyses will not affect in any way the conduct, results, or analysis of the current study, unless the results are so negative that they lead to a decision to terminate further development of xanomeline TTS in AD. Hence, adjustments to final computed p-values are not appropriate.

Planned interim analyses, and any unplanned interim analyses, will be conducted under the auspices of the data monitoring board assigned to this study. Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results only if absolutely necessary. Any such dissemination will be documented and described in the final study report. Study sites will not receive information about interim results unless they need to know for the safety of their patients.

4.7. Interim Safety Analyses

An analysis of the cardiovascular safety monitoring (see section 3.9.4) will be performed when approximately 25 patients from each treatment arm have completed at least 2 weeks at the treatment arms' respective full dosage (Visit 5). If necessary, this analysis will be repeated every 25 patients per arm. This analysis will be conducted under the auspices of the DSMB. This board membership will be composed of 3 external

cardiologists who will be the voting members of the board, a Lilly cardiologist, a Lilly statistician, and the Lilly research physician in charge of the study. Only the DSMB is authorized to review completely unblinded cardiovascular safety analyses and, if necessary, to disseminate those results. The outcome of the cardiovascular safety analyses will determine the need for further Ambulatory ECGs.

4.8. Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentrations of xanomeline will be determined from samples obtained at selected visits (Section 3.9.2). The plasma concentration data for xanomeline, dosing information, and patient characteristics such as weight, gender and origin will be pooled and analyzed using a population pharmacokinetic analysis approach (for example, NONMEM). This approach preserves the individual pharmacokinetic differences through structural and statistical models. The population pharmacokinetic parameters through the structural model, and the interindividual and random residual variability through the components of the statistical models will be estimated. An attempt will also be made to correlate plasma concentrations with efficacy and safety data by means of population pharmacokinetic/pharmacodynamic modeling.

5. Informed Consent, Ethical Review, and Regulatory Considerations

5.1. Informed Consent

In the United States and Canada, the investigator is responsible for preparing the informed consent document. The investigator will use information provided in the current [Clinical Investigator's Brochure or product information] to prepare the informed consent document.

The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

As used in this protocol, the term "informed consent" includes all consent and/or assent given by subjects, patients, or their legal representatives.

In addition to the elements required by all applicable laws, the 3 numbered paragraphs below must be included in the informed consent document. The language may be altered to match the style of the informed consent document, providing the meaning is unchanged. In some circumstances, local law may require that the text be altered in a way that changes the meaning. These changes can be made only with specific Lilly approval. In these cases, the ethical review board may request from the investigator documentation evidencing Lilly's approval of the language in the informed consent document, which would be different from the language contained in the protocol. Lilly shall, upon request, provide the investigator with such documentation.

1. "I understand that the doctors in charge of this study, or Lilly, may stop the study or stop my participation in the study at any time, for any reason, without my consent."

2. "I hereby give permission for the doctors in charge of this study to release the information regarding, or obtained as a result of, my participation in this study to Lilly, including its agents and contractors; the US Food and Drug Administration (FDA) and other governmental agencies; and to allow them to inspect all my medical records. I understand that medical records that reveal my identity will remain confidential, except that they will be provided as noted above or as may be required by law."

3.   "If I follow the directions of the doctors in charge of this study and I am physically injured because of any substance or procedure properly given me under the plan for this study, Lilly will pay the medical expenses for the treatment of that injury which are not covered by my own insurance, by a government program, or by any other third party. No other compensation is available from Lilly if any injury occurs."

The investigator is responsible for obtaining informed consent from each patient or legal representative and for obtaining the appropriate signatures on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

5.2. Ethical Review

The name and address of the ethical review board are listed on the Investigator/Contacts cover pages provided with this protocol.

The investigator will provide Lilly with documentation of ethical review board approval of the protocol and the informed consent document *before* the study may begin at the site or sites concerned. The ethical review board(s) will review the protocol as required.

The investigator must provide the following documentation:

- The ethical review board's annual reapproval of the protocol

- The ethical review board's approvals of any revisions to the informed consent document or amendments to the protocol.

5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign 2 protocol signature pages and return 1 of the signed pages to a Lilly representative (see Attachment LZZT.10).

6. References

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Fisher A, Barak D. 1994. Promising therapeutic strategies in Alzheimer's disease based on functionally selective M_1 muscarinic agonists. Progress and perspectives in new muscarinic agonists. DN&P 7(8):453-464.

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Protocol Attachment LZZT.1
Schedule of Events for Protocol H2Q-MC-LZZT(c)

Protocol Attachment LZZT.1
Schedule of Events for Protocol H2Q-MC-LZZT(c)

ACTIVITY	VISIT / WEEK	1 / -2	2 / -.3	3 / 0	4 / 2	5 / 4		7 / 6	8 / 8
Informed consent		X							
Patient number assigned		X							
Hachinski ≤4		X							
MMSE 10-23		X							
Physical examination		X							
Medical History		X							
Habits		X							
Chest x-ray		X							
Apo E genotyping					X				
Patient randomized				X					
Vital signs/Temperature		X	X	X	X	X		X	X
Ambulatory ECG placed			X						
Ambulatory ECG removed				X					
ECG		X			X	X		X	X
Placebo TTS test		X							
CT Scan (if not within last year and patient passes all other screens)		X							
Concomitant Medications		X		X	X	X		X	X
Laboratory (Chem/Hemat):		X			X	X		X	X
Laboratory (Urinalysis)		X			X				
Plasma Specimen (Xanomeline)				X	X	X		X	
Hemoglobin A_{1C}		X^a							
Study drug record Medications dispensed Medications returned				X	X	X		X	X
TTS Acceptability Survey									
ADAS-Cog		P		X					X
CIBIC+		P		X					X
DAD		P		X					X
NPI-X		P		X	X	X		X	X^b
Adverse events		X	X	X	X	X		X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram

X = Performed at this visit.

X^a = Performed at this visit if patient is an insulin-dependent diabetic.

X^b = Performed at this visit and via telephone interview 2 weeks following this visit.

P = Practice only - It is recommended that a sampling of the CIBIC+, ADAS-Cog, DAD, and NPI-X be administered at Visit 1. Data from this sampling would not be considered as study data and would not be collected.

Schedule of Events for Protocol H2Q-MC-LZZT(c) (concluded)

	VISIT	9	10	11	12	13	ET	RT
ACTIVITY	WEEK	12	16	20	24	26		
Informed consent								
Patient number assigned								
Hachinski ≤4								
MMSE 10-23								
Physical examination							X	X	
Medical History								
Habits								
Chest x-ray								
Apo E genotyping								
Patient randomized								
Vital signs/Temperature		X	X	X	X	X	X	X
Ambulatory ECG placed								
Ambulatory ECG removed								
ECG		X	X	X	X	X	X	
Placebo TTS test								
CT Scan (if not within last year and patient passes all other screens)								
Concomitant Medications		X	X	X	X	X	X	X
Laboratory (Chem/Hemat):		X	X	X	X	X	X	
Laboratory (Urinalysis)		X			X		X	
Plasma Specimen (Xanomeline)		X		X			X	
Hemoglobin A_{1c}								
Study drug record Medications dispensed Medications returned		X	X	X	X	X	X	
TTS Acceptability Survey						X	X	
ADAS-Cog			X		X		X	X
CIBIC+			X		X		X	X
DAD			X		X		X	X
NPI-X		X[b]	X[b]	X[b]	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ET = Early
    Termination; RT = Retrieval

X = Performed at this visit.

X[b] = Performed at this visit and via telephone interview 2 weeks following this visit.

Protocol Attachment LZZT.2
Alzheimer's Disease Assessment Scale
(ADAS-Cog) With Attention/Concentration Tasks

Protocol Attachment LZZT.2
Alzheimer's Disease Assessment Scale (ADAS-Cog)
With Attention/Concentration Tasks

Background Information

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) is an instrument devised to assess the severity of cognitive impairment in patients with Alzheimer's Disease (AD). The scale includes short neuropsychological tests in which the patient performs simple tasks such as word recall, word recognition, and constructional praxis. The cognitive section of the ADAS consists of 11 items which assess the following: memory, language (aphasia), and motor skills (praxis).

Rosen et al (1984) evaluated the test-retest and interrater reliabilities of the individual scale items and the entire scale in patients with dementia of the Alzheimer's type. The ADAS was shown to be valid (Rosen et al, 1984) in the ability to detect patients with clinically diagnosed AD from matched nondemented controls. Kramer-Ginzberg et al (1988) demonstrated at 12 month and 24 month retesting that higher scores on the ADAS correlated with disease progression. Because both of the above cognitive and noncognitive parameters are assessed, the ADAS is a reliable instrument for use in psychopharmacologic trials involving patients with AD.

Three additional items have been incorporated into this scale to asses the attention/concentration level of the patient. The three additional tasks are delayed word recall, attention/visual search task, and maze solution. These tasks and their rating scales were developed by the author of the ADAS-Cog.

Equipment Needed:

The following props are needed to carry out the ADAS-Cog with attention/concentration tasks:

1. Toys which are replicas of the objects to be named.

2. Sets of index cards for the word recall, delayed word recall and word recognition items. For each administration of the ADAS there is a designated set of cards specific for that visit and the words are different for each visit.

3. Scaled drawings of the forms that the patients will copy.

4. Sets of mazes for the maze solution task.

5. Sets of numbers and letters for the attention/visual search task.

All of these items will be supplied by Eli Lilly and Company.

Test Administration and Scoring

The ADAS-Cog with attention/concentration tasks should be administered by a health care professional trained to do so. The test will take approximately 30-45 minutes to complete and involves interviewing the patient alone.

There are a total of 11 items which assess cognitive function and 3 which assess attention/concentration. The maximum total score is 90. 70 points are possible on the cognitive section and 20 points on the attention/concentration section. The higher the score, the greater is the degree of cognitive impairment.

The following is the sequence in which the ADAS-Cog with attention/concentration tasks is to be administered along with test instructions and scoring guidelines:

1. Word Recall

The patient reads aloud 10 high imagery-words exposed for 2 seconds each. The patient then recalls the words aloud. Three trials of reading and recall are given. On the worksheet, check each word recalled correctly. The words not checked are added and the total score is divided by 3 to generate a score for this item. The score equals the mean number of words not recalled on the 3 trials (maximum = 10).

2. Naming Objects and Fingers

The patient is asked to name 12 randomly presented real objects, with frequency identification levels of high, medium, and low. For those patients having difficulty naming objects, standard clues may be used. The following is a list of the objects, their frequency of identification, and clues:

High Frequency:

Object	Clue
Flower	grows in a garden
Bed	used for sleeping
Whistle	makes a sound when blown
Pencil	used for writing

Medium Frequency:

Object	Clue
Rattle	a baby's toy
Mask	hides your face
Scissors	cuts paper
Comb	used on hair

Low Frequency:

Object	Clue
Wallet	holds your money
Harmonica	a musical instrument
Stethoscope	doctor uses it to listen to your heart
Tongs	picks up food

Also, ask the patient to name the fingers of his dominant hand; thumb, pinky (little finger), index (pointer, forefinger), middle and ring fingers.

Check each object/finger on the worksheet named correctly. In order to correctly score, the patient must name each object exactly as stated on the worksheet, exceptions include wallet which could also be called a billfold, index finger which could also be referred to as the pointer or forefinger and pinky which could also be called little finger.

Add the number of empty boxes and then score this item using the following scale:

Items = objects and fingers named

0 = 0-2 items named incorrectly

1 = 3-5 items named incorrectly

2 = 6-8 items named incorrectly

3 = 9-11 items named incorrectly

4 = 12-14 items named incorrectly

5 = 15-17 items named incorrectly

3. Delayed Word Recall

The patient is asked if they remember any of the 10 words used in the first task. On the worksheet, check each word recalled correctly. The words not checked are added to generate a score for this task. (maximum = 10)

4. Commands

The patient is instructed to perform the following 5 commands. Receptive speech is assessed based on the patient's ability to carry out 1 to 5 step commands.

1. Make a <u>fist</u>.

2. Point to the <u>ceiling</u> and then to the <u>floor</u>.

   Line up a pencil, watch, and card on the table in front of the patient.

3. Put the <u>pencil on top of the card</u> and then <u>put it back</u>.

4. Put the <u>watch</u> on the <u>other side of the pencil</u> and then <u>turn over the card</u>.

5. Tap each shoulder twice, with two fingers, keeping your eyes shut.

Each underlined word represents a single step. The command may be repeated once by the interviewer. Each command is scored as a whole. That is, each part of the command must be performed accurately to obtain credit for that item. One the worksheet, check each command performed correctly and then add up the empty boxes. The scale for scoring this item is as follows:

0 = no errors, all 5 commands correct

1 = 1 command incorrect, 4 commands correct

2 = 2 commands incorrect, 3 commands correct

3 = 3 commands incorrect, 2 commands correct

4 = 4 commands incorrect, 1 command correct

5 = all 5 commands incorrect

5. Constructional Praxis

This item assesses the patient's ability to copy 4 geometric forms. These forms, in the order of presentation are:

1. Circle: approximately 2.0 cm in diameter

2. Two overlapping rectangles: the vertical rectangle is 2.0 cm x 2.5 cm, and the horizontal rectangle is 1.0 cm x 3.5 cm.

3. Rhombus: each side = 2.0 cm, acute angle = 50 degrees, obtuse angle = 130 degrees

4. Cube: each side = 2.0 cm, internal lines are present.

Each figure is located in the upper middle of a 5 1/2 x 8 1/2 sheet of paper. The patient is instructed: **"Do you see this figure? Make one that looks like the one anywhere on the paper."** Two attempts are permitted. One the worksheet check each figure drawn correctly. The scoring of this item is as follows:

1 = 1 form drawn incorrectly

2 = 2 forms drawn incorrectly

3 = 3 forms drawn incorrectly

4 = 4 forms drawn incorrectly

5 = no figures drawn: scribbles, parts of forms, words instead of forms

Scoring criteria for each form:

1. Circle: a closed figure

2. Two overlapping rectangles: forms must be 4-sided and overlap must be similar to presented form. Changes in size are not scored.

3. Rhombus (diamond): figure must be 4-sided obliquely oriented, and the sides approximately equal in length. Four measurements are taken.

   These are: ac, a'c, bc, b'c.

   The ratio of ac/a'c or a'c/ac ranges from 0.75 to 1.00.

   The ratio of bc/b'c or b'c/bc ranges from 0.60 to 1.00.

   The ratio bb'/aa' ranges from 0.30 to 0.75.

   The figure is incorrect if any ratio is outside these ranges.

4. Cube: the form is 3-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. If opposite sides of faces are not parallel by more than 20 degrees, it is incorrect (insert examples of drawings).

6. Ideational Praxis

The patient is given a 8 1/2" x 11" sheet of paper and a long envelope. The patient is instructed to pretend to send a letter to himself. The patient is told to fold the paper, put the paper into the envelope, seal it, address it to himself, and to indicate where the stamp goes.

If the patient forgets part of the task or is having difficulty, reinstruction should be given. Impairment on this term should only reflect dysfunction in executing an overlearned task only and not recall difficulty. The 5 components to this task are:

1. fold letter

2. put letter in envelope

3. seal envelope

4. address envelope (any address containing: name, street, city, state, and zip code is correct)

5. mark where stamp goes

On the worksheet check each step completed correctly. Scoring this item is as follows:

        0 = able to perform all components

        1 = failure to perform 1 component

        2 = failure to perform 2 components

        3 = failure to perform 3 components

        4 = failure to perform 4 components

        5 = failure to perform 5 components

7.   Orientation

The patient is asked questions which assess orientation. The components of orientation assessed are: full name, month, date, year, day, season, place, and time of day. On the worksheet check each correct response. One point is given for each incorrect response (maximum of 8). Acceptable answers include 1 day either way within the date: within 1 hour for the hour, partial name for place, naming the upcoming season if it is 1 week prior to its onset, or naming the previous season for two weeks after its termination.

8.   Word Recognition Task

The patient reads aloud 12 high-imagery words presented on index cards. Then these words are mixed in randomly with 12 new words. The patient indicates if he has previously seen the word by saying "yes" or "old" and if the word is new by saying "no" or "new." Two more trials of reading the original words and recognition are given. On the worksheet check each word recalled correctly. Words that are starred are the original words and patients should answer by saying "yes" or "old." Words that are not starred are new words and the patient should respond by saying "no" or "new." The score equals the mean number of <u>incorrect</u> responses for 3 trials (maximum 12).

9.   Attention/Visual Search Task

Place the example face up in front of the subject. Say to the subject "This is an example of the task we are about to do. On the top of this page is a number (or in some cases a number and letter). Throughout the page you will find this number mixed in with the other numbers. I'd like you to begin here (point to the beginning of the first line), and going across line by line, cross out any number that matches the number at the top of the page. Please work as quickly as you can." Discontinue the example after 30 seconds.

Prior to each task, you may repeat the instructions to the subject. Discontinue each task after 60 seconds. (maximum = 40 targets)

10. Maze Solution Task

The subject will be required to attempt each maze in order of difficulty. Difficulty was varied by manipulating features of the maze such as the number of turns, number of

decision points, and length of dead end routes. There is a time limit of 240 seconds for each maze. Two errors, or reaching the 240 second time limit constitutes a failure.

Show the example. Tell them to start where it says "start" and find their way outside the maze. Show them where they would come out. Tell them to try not to run into any dead ends or cross solid lines. You can help them in the example if they hit a dead end. If they hit a dead end during the test you may show them the correct path once. (maximum = 240 seconds)

Language

Language abilities are evaluated throughout the interview and on specific tests. Questions eliciting "yes" or "no" answers assess comprehension on a very basic level. Other questions require recall of specific information and well developed communication skills. The following 4 items (8-11) assess spoken language ability, comprehension, remembering test instructions and word finding difficulty in spontaneous speech.

11. Spoken Language Ability

This item is a global rating of the quality of the patient's speech such as clarity and difficulty in making oneself understood. Quantity and word finding difficulty are not rated on this item. The scoring for this item is as follows:

> 0 = no impairment: patient speaks clearly and is understandable
>
> 1 = very mild: 1 instance of lack of understandability
>
> 2 = mild: patient has difficulty <25% of the time
>
> 3 = moderate: patient has difficulty 25-50% of the time
>
> 4 = moderately severe: patient has difficulty more than 50% of the time
>
> 5 = severe: only 1 or 2 utterances, clued by empty speech, mute

12. Comprehension

This item evaluates the patient's ability to understand speech. Do not include responses to commands. The scoring for this item is as follows:

> 0 = no impairment: patient understands
>
> 1 = very mild: 1 instance of misunderstanding
>
> 2 = mild: 2-5 instances of misunderstanding
>
> 3 = moderate: requires several repetitions and rephrasing
>
> 4 = moderately severe: patient only occasionally responds correctly (that is, to yes questions)
>
> 5 = severe: patient rarely responds to questions appropriately, not due to poverty of speech

13. Word-Finding Difficulty in Spontaneous Speech

This item assesses whether the patient has difficulty in finding the desired word in spontaneous speech. The problem may be circumlocution (that is, giving explanatory phrases) or substituting nearly satisfactory synonyms. The score represents a subjective rating by the interviewer. Do not include responses to the finger or object naming during the testing in this rating. The scoring for this item is as follows:

0 = none

1 = very mild: 1 or 2 instances, not clinically significant

2 = mild: noticeable circumlocution or synonym substitution

3 = moderate: loss of words without compensation on occasion

4 = moderately severe: frequent loss of words without compensation

5 = severe: nearly total loss of content words, speech sounds empty, 1-2 word utterances

14. Recall of Test Instructions

The patient's ability to remember the requirements of the word recognition task is evaluated. On each recognition trial, the patient is asked prior to presentation of the first 2 words, **"Did you see this word before or is this a new word?"** For the third word, the patient is asked, **"How about this one?"** If the patient responds appropriately (that is, "yes" or "no") then the recall of the instruction is accurate. If the patient fails to respond, this signifies that the instructions have been forgotten. Then instruction is repeated. The procedure used for the third word is repeated for words 4-24. Each instance of recall failure is noted. The scoring for this item is as follows:

0 = no impairment

1 = very mild: forgets once

2 = mild: must be reminded 2 times

3 = moderate: must be reminded 3 or 4 times

4 = moderately severe: must be reminded 5 or 6 times

5 = severe: must be reminded 7 or more times

References

Kramer-Ginzberg E, Mohs RC, Ayran M, et al. 1988. Predictors of course for Alzheimer patients in a longitudinal study. Psychopharmacol Bull 24:458-62.

Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's disease. Am J Psychiatry 141:1356-64.

Protocol Attachment LZZT.3
Video-referenced Clinician's Interview-Based Impression of Change (CIBIC+)

Protocol Attachment LZZT.3
Video-referenced Clinician's Interview-Based Impression of Change CIBIC+ Rating Scale

Background Information

Global ratings are intended to provide an index of clinical importance of change that cannot be obtained from quantitative assessment measures such as mental status examinations. The Video-referenced Clinician's Interview-Based Impression of Change (CIBIC+) has been designed to observe the patient's behavior in a cumulative global sense (as opposed to rating each behavior for the purpose of deriving a scored severity). The majority of the interview appears somewhat conversational (except for certain items, for example, those items seeking evidence of disturbed praxis) yet it samples behaviors that might be affected by AD. The seemingly informal tone of the CIBIC+ interview is designed to reduce the discomfort that a patient might feel when placed in a traditional testing environment. Since the interview is not scored and it's intent is to elicit standardized patient behaviors that will provide the clinician with a global impression of change.

Test Administration

A semi-structured interview should be used to assess global change. Provided are worksheets to be used by the clinician to assess 3 domains: cognitive/mental status, functioning, and behaviors. The worksheets provided should be used as a tool and not to exclude any other method of assessment used by a clinician. No particular format or order is suggested for the interview.

Video-referenced Clinician's Interview Based Impression of Change
CIBIC+ Rating Scale

Circle the number that indicates the extent of change, if any, observed since the initial baseline interview.

Marked improvement	1
Moderate improvement	2
Minimal improvement	3
No Change	4
Minimal worsening	5
Moderate worsening	6
Marked worsening	7

ADCS - Clinical Global Impression of Change Worksheets
Baseline Evaluation for Both Subject and Informant

Area	Probes
Relevant History	recent relevant clinical events, illnesses?
Observation/ Evaluation	appearance

Notes

Subject

Informant

MENTAL/COGNITIVE STATE:	[structured exam if used:_____]
Areas	**Probes**
Arousal, Alertness, Attention, Concentration	confusion/clarity, state of consciousness, excitement/reactivity
Orientation	time, place person
Memory	registration, recall long term/remote, recall for past events
Language/speech	fluency/expressive & receptive language, comprehension, paraphasia/word finding, naming, amount, repetition, follows directions
Praxis	constructional ability, ideational praxis, ideomotor/imitation
Judgment/Problem Solving/Insight	patient's behavior in situations requiring judgments
Notes	
Subject	
Informant	
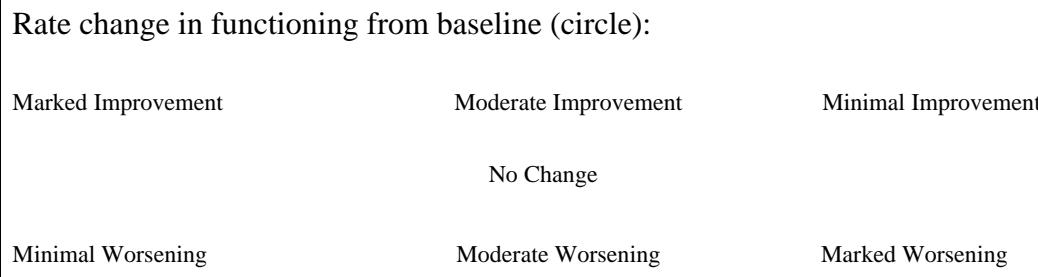
BEHAVIOR	
Areas	**Probes**
Thought content	organization, appropriateness
Hallucinations, Delusions, Illusions	auditory/visual, misperceptions, systematized/developed, suspiciousness/paranoia, fearful
Behavior/Mood	affect/lability, apathy, tearful, depression-related, anxiety-related, compulsive, motivation/energy, agitation/aggression, hostility/vocal outbursts, appropriateness, cooperativeness, unusual/bizarre, uninhibited
Sleep/Appetite	sleep disorder, insomnia, nocturnal activity, hypersomnia, hyposomnia, appetite/weight change
Psychomotor activity	wandering, pacing, posture, gait
Notes	
Subject	
Informant	

FUNCTIONING	
Areas	**Probes**
Complex (instrumental) functional ability and basic	finances, shopping, driving, household chores/hobbies, dressing, hygiene/grooming, self-feeding, mobility
Social function	participation in social interactions and community activities, independence, helplessness

Notes
Subject
Informant

ADCS - Clinical Global Impression of Change Worksheets
Subsequent Visits - Evaluation for Both Subject and Informant

MENTAL/COGNITIVE STATE:	[structured exam if used:_____]
Areas	**Probes**
Arousal, Alertness, Attention, Concentration	confusion/clarity, state of consciousness, excitement/reactivity
Orientation	time, place person
Memory	registration, recall long term/remote, recall for past events
Language/speech	fluency/expressive & receptive language, comprehension, paraphasia/word finding, naming, amount, repetition, follows directions
Praxis	constructional ability, ideational praxis, ideomotor/imitation
Judgment/Problem Solving/Insight	patient's behavior in situations requiring judgments

Notes	
Subjects	
Informant	

Rate change in mental status from baseline (circle):

Marked Improvement   Moderate Improvement   Minimal Improvement

No Change

Minimal Worsening   Moderate Worsening   Marked Worsening

(ADCS Worksheet—Subsequent Visits, continued)

BEHAVIOR	
Areas	**Probes**
Thought content	organization, appropriateness
Hallucinations, Delusions, Illusions	auditory/visual, misperceptions, systematized/developed, suspiciousness/paranoia, fearful
Behavior/Mood	affect/lability, apathy, tearful, depression-related, anxiety-related, compulsive, motivation/energy, agitation/aggression, hostility/vocal outbursts, appropriateness, cooperativeness, unusual/bizarre, uninhibited
Sleep/Appetite	sleep disorder, insomnia, nocturnal activity, hypersomnia, hyposomnia, appetite/weight change
Psychomotor activity	wandering, pacing, posture, gait
Notes	
Subject	
Informant	

Rate change in behavior from baseline (circle):

Marked Improvement   Moderate Improvement   Minimal Improvement

No Change

Minimal Worsening   Moderate Worsening   Marked Worsening

(ADCS Worksheet—Subsequent Visits, concluded)

FUNCTIONING	
Areas	**Probes**
Complex (instrumental) functional ability and basic	finances, shopping, driving, household chores/hobbies, dressing, hygiene/grooming, self-feeding, mobility
Social function	participation in social interactions and community activities, independence, helplessness

Notes

Subject

Informant

Rate change in functioning from baseline (circle):

Marked Improvement	Moderate Improvement	Minimal Improvement
	No Change	
Minimal Worsening	Moderate Worsening	Marked Worsening

Protocol Attachment LZZT.4
Revised Neuropsychiatric Inventory (NPI-X)

Protocol Attachment LZZT.4
Revised Neuropsychiatric Inventory (NPI-X)

Background Information

The neuropsychiatric inventory (NPI) (Cummings et al. 1994) was developed to assess behavioral disturbances occurring in dementia patients: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability, aberrant motor activity, sleep, and appetite and eating disorders. The NPI uses a screening strategy to immunize administration, examining and scoring only those behavioral domains with positive responses to screening questions. Frequency, severity and caregiver distress of each behavior are determined.

Test Administration

The NPI should be administered by a health care professional trained to do so. Information for the inventory may be obtained from the spouse or other person intimately familiar with the patients behavior. The NPI is administered at every clinic visit, plus twice via the telephone when patients are not required to come to the clinic.

Questions should be asked exactly as written. Clarification's should be provided if the caregiver does not understand the questions. The answers pertain to changes in patient's behavior that have appeared since the onset of the illness.

Delusions

Does the patient have beliefs that you know are not true? For example, insisting that people are trying to harm him/her. Has he/she said that family members are not who they say they are; or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

Hallucinations

Does the patient have hallucinations such as false visions or voices? Does he/she seem to see, hear or experience things that are not present? By this questions we do not mean just mistaken beliefs such as stating that someone who has died is still alive: rather we are asking if the patient actually has abnormal experiences of sounds, or visions.

Agitation/Aggression

Does the patient does have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

Depression/Dysphoria

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

Anxiety

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

Elation/Euphoria

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

Apathy/Indifference

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

Disinhibition

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or did in public? Does he/she do things that are embarrassing to you or others?

Irritability/Lability

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability , impatience, or rapid emotional changes different from his/her usual self.

Aberrant Motor Behavior

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

Night-time Behaviors

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he she wander at night, get dressed, or disturb your sleep?

Appetite and Eating Disorders

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

Frequency:

1. Occasionally - less than once per week.

2. Often - about once per week.

3. Frequently - several times per week but less than every day.

4. Very Frequently - once or more per day.

Severity:

1. Mild - delusions present but seem harmless and produce little

   distress in the patient.

2. Moderate - delusions are distressing and disruptive.

3. Marked - delusions are very disruptive and are a major source of

   behavioral disruption. (If PRN medications are prescribed,

   their use signals that the delusions are of marked severity.)

Distress: **How emotionally distressing do you find this behavior?**

0. Not at all

1. Minimally

2. Mildly

3. Moderately

4. Severely

5. Very severely or extremely

References

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. 1994. The Neuropsychological inventory: Comprehensive assessment of psychopathology in dementia. Neurology 44(Dec):2308-2314.

Protocol Attachment LZZT.5
Disability Assessment for Dementia (DAD)

Protocol Attachment LZZT.5
Disability Assessment for Dementia (DAD)

Background Information

The Disability Assessment for Dementia (DAD) scale quantitatively measures functional abilities in activities of daily living (ADL) in individuals with cognitive impairments such as dementia of the Alzheimer type (DAT). Basic and instrumental ADLs are examined in relation to executive skills to delineate areas of cognitive deficits which may impair performance in ADL. The DAD is intended specifically for the assessment of disability in community residing individuals with cognitive deficits such as DAT and other dementias.

This measure of functional disability is based on the model of health proposed by the World Health Organization (WHO). In accordance with this model, functional disability refers to any restriction in the ability to perform an activity, a task or a behavior of every day life such as basic self-care or instrumental activities.

Functional disability is measured with the DAD scale through the assessment of basic, instrumental, and leisure activities. The DAD scale includes:

> Basic activities of daily living: Activities that are important for self-care which are dressing, hygiene, continence, and eating.

> Instrumental activities of daily living: Activities that are important for maintenance in a specific environment which are meal preparation, telephoning, housework, taking care of finance and correspondence, going on an outing, taking medications, and ability to stay safely at home.

> Leisure activities: Activities that are beyond the mean of self maintenance and for the purpose of recreation which are assessed in terms of interest that is shown towards these activities.

To understand the cognitive dimensions of disabilities in ADL within the DAD scale, the above measured ADLs have been further subdivided according to executive functions which have showed regression patterns in dementias. These are initiation, planning, and organization, and effective performance.

> Initiation consists of the ability to decide and/or start an action. This requires spontaneity on the part of the individual and must be accomplished at an appropriate moment and place.

> Planning and organization consists of the ability to identify the different components of a task, to be able to structure them in an appropriate sequence, to elaborate a strategy for action, and to be able to prepare the required material

prior to the action. It also includes the ability to monitor actions during the activity which involves problem solving and decision making abilities to make appropriate corrections when needed.

Effective performance consists of the ability to complete an action. The quality of the performance with regards to whether the task is done in a safe and acceptable manner is also an important component.

Test Administration and Scoring

The DAD is administered through interview with the caregiver in a quiet environment. Administration takes approximately 15 minutes. The DAD is a measure of the actual performance in ADLs of the individual as observed over a period of 2 weeks up to the time of the interview. Activities are evaluated as performed **without any assistance or reminder** being provided from caregivers.   Questions must be formulated and clarified in this sense.

**** **Questions should be given as follows:**

> **"During the past two weeks, did Mr./Ms. X without help or reminder ...."**

It is essential to use the exact wording in order to respect content validity. Elements in brackets should be read. The choice of answer should be specified at the beginning of the interview and should be repeated throughout. Scoring for each question is determined as follows:

Yes = 1

No = 0

Non applicable (N/A) = 96

Yes indicates that the person has performed the activity without help or reminder in the last two weeks even if it was only performed once.
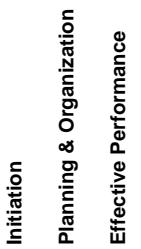
No signifies that the person could not perform the activity without help or reminder. Therefore, if a person has performed the activity with some assistance from the caregiver, verbal or physical, he/she is scored as a No.

N/A signifies that the individual never used to do it before the occurrence of DAT or did not have the opportunity to do it in the past two weeks.

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)
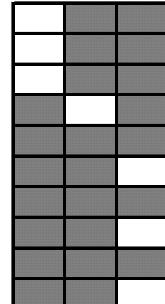
SCORING: YES=1   NO=0   Not Applicable=N/A

**During the past two weeks, did (name) _____,
without help or reminder**

	Initiation	Planning & Organization	Effective Performance
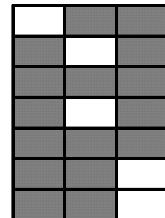
HYGIENE
- Undertake to wash himself/herself or to take a bath or a shower
- Undertake to brush his/her teeth or care for his/her dentures
- Decide to care for his/her hair (wash and comb)
    - Prepare the water, towels, and soap for washing, taking a bath or a shower
        - Wash and dry completely all parts of his/her body safely
        - Brush his/her teeth or care for his/her dentures appropriately
        - Care for his/her hair (wash and comb)
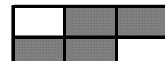
DRESSING
- Undertake to dress himself/herself
    - Choose appropriate clothing (with regard to the occasion, neatness, the weather and color combination)
    - Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)
        - Dress himself/herself completely
        - Undress himself/herself completely
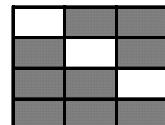
CONTINENCE
- Decide to use the toilet at appropriate times
        - Use the toilet without "accidents"

EATING
- Decide that he/she needs to eat
    - Choose appropriate utensils and seasonings when eating
        - Eat his/her meals at a normal pace and with appropriate manners

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

SCORING: YES=1   NO=0   Not Applicable=N/A

**During the past two weeks, did (name) _____,
without help or reminder**

	Initiation	Planning & Organization	Effective Performance
MEAL PREPARATION			
- Undertake to prepare a light meal or snack for himself/herself	☐		
- Adequately plan a light meal or snack (ingredients, cookware)		☐	
- Prepare or cook a light meal or a snack safely			☐
TELEPHONING			
- Attempt to telephone someone at a suitable time	☐		
- Find and dial a telephone number correctly		☐	
- Carry out an appropriate telephone conversation			☐
- Write and convey a telephone message adequately			☐
GOING ON AN OUTING			
- Undertake to go out (walk, visit, shop) at an appropriate time	☐		
- Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list		☐	
- Go out and reach a familiar destination without getting lost			☐
- Safely take the adequate mode of transportation (car, bus, taxi)			☐
- Return from the store with the appropriate items			☐
FINANCE & CORRESPONDENCE			
- Show an interest in his/her personal affairs such as his/her finances and written correspondence	☐		
- Organize his/her finance to pay his/her bills (cheques, bankbook, bills)		☐	
- Adequately organize his/her correspondence with respect to stationery, address, stamps		☐	
- Handle adequately his/her money (make change)			☐

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

SCORING: YES=1   NO=0   Not Applicable=N/A

During the past two weeks, did (name) _____,
without help or reminder

	Initiation	Planning & Organization	Effective Performance

MEDICATIONS
- Decide to take his/her medications at the correct time
    - Take his/her medications as prescribed
    (according to the right dosage)

LEISURE AND HOUSEWORK
- Show an interest in leisure activity (ies)
- Take an interest in household chores that he/she used
 to perform in the past
        - Plan and organize adequately household chores
        that he/she used to perform in the past
            - Complete household chores adequately
            as he/she used to perform in the past
            - Stay safely at home by himself/herself
            when needed

Protocol Attachment LZZT.6
Mini-Mental State Examination (MMSE)

Protocol Attachment LZZT.6
Mini-Mental State Examination (MMSE)

Background Information

The MMSE is a brief assessment instrument used to assess cognitive function in elderly patients. The MMSE can be used to screen for cognitive impairment and as a measurement of cognition over time and with pharmacologic treatment. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention: the maximum score is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures: the maximum score is 9. The scoring range for the MMSE is 0-30.

Folstein et al (1975) demonstrated the MMSE to be both reliable and valid in a group of elderly subjects: including those with dementia, depression with cognitive impairment, depression and "normal" elderly patients. The validity of the MMSE is demonstrated by a positive correlation between the patients' MMSE scores and their scores on both the verbal and performance sections of the Wechsler Adult Intelligence Scale (WAIS). The MMSE has been shown to possess sensitivity and specificity in various populations. Although the MMSE alone is unable to provide diagnostic information, the data on its sensitivity and specificity in cognitively impaired patients demonstrates its utility as a screening instrument.

Test Administration

The MMSE should be administered by a health care professional trained in its use. The MMSE will be administered at Visit 1 (screening visit). The administration item of the MMSE requires no more than 10 to 15 minutes. The interviewer should make the patient comfortable and establish rapport. Inform the patient that you would like to ask him questions to test his memory and concentration. It is important to acknowledge correct responses, and to avoid applying pressure when a patient finds an item to be difficult. Patients must score between 10 and 23 on this scale to be eligible for participation in this study.

Dialogue for the Standardized Administration of the MMSE

Introduce the test by saying: **"I would like to ask you some questions to test your memory and concentration. Most of the questions will be easy, just follow my instruction."**

1. *Orientation (1 point each)*
   a. "What year is it?"

   b. "What season is it?"

   c. "What is today's date?"

   d. "What day of the week is today?"

   e. "What is the month?"

   f. "What state are we in?"

   g. "What county are we in?"

   h. "What town are we in?"

   i. "Can you tell me the name of this hospital?"

   j. "What floor of the building are we on?"

If the patient answered the above items correctly, indicate so by scoring 1 point for each item correctly identified.

2. *Registration (3 points)*

Say to the patient **"Now I'd like to test your memory... I'm going to name 3 objects. After I have said them, I want you to repeat them. Remember what they are because I'm going to ask you to name them again in a few minutes."** Then say the names of the items slowly and clearly. After you have said all 3 objects, ask the patient to repeat them.

The first repetition determines the score, but keep saying all 3 words (up to 6 trials) until the patient can repeat all 3. One point is given for each correct response.

3. *Attention and Calculation (5 points)*

Instruct the patient: **"Begin with 100 and count backwards by 7 and keep subtracting until I tell you to stop."**

Stop after 5 subtractions (93, 86, 79, 72, 65). One point is given for each sequential correct response. For example, 93, 86, 77, 72 score = 2; 93, 85, 78, 71, 64 score = 1.

If the patient cannot or refuses to perform this test, ask him to spell the word "world" backwards. Score 1 point for each letter named in correct order. For example, dlrwo score = 3; drlow = 1.

4. Recall (3 points)

Ask the patient if he can recall the 3 objects you asked him to remember earlier. Give 1 point for each correct response.

5. Naming (2 points)

Show the patient a wrist watch and ask **"What is this called?"**

Next **s**how the patient a pencil and ask **"What is this called?"**

Score 1 point for each item named correctly.

6. Repetition (1 point)

Ask the patient to repeat this phrase for you: **"No if ands or buts."** Allow only 1 trial. Score 1 point if the phrase is repeated correctly.

7. Three Stage Command (3 points)

Have the patient follow this command, Point to a piece of paper which is on top of the desk and say to the patient:

"Please take that piece of <u>paper in your right hand</u>, <u>fold the paper in half with both hands</u>, and <u>put the paper down on the floor</u>." Score 1 point for each underlined segment correctly executed.

8. Reading (1 point)

On a blank piece of paper print the sentence: "Close your eyes." in letters large enough for the patient to see clearly. Ask him to read the words on it and do what it says. Score 1 point if he actually closes his eyes.

9. Writing (1 point)

Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence, it has to be written spontaneously. The sentence should have a   subject and a verb and make sense. Correct grammar and punctuation are not necessary.

10. Copying (1 point)

Instruct the patient to copy the intersecting pentagons exactly as they are drawn. All 10 angles must be present and 2 must intersect forming a quadrangle to score 1 point. Tremor and rotation are ignored.

References

Folstein MF, Folstein SE, McHugh PR. 1975. Mini-mental state: A practical method for   grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-98.

Protocol Attachment LZZT.7
NINCDS/ADRDA Guidelines

Attachment LZZT.7
NINCDS/ADRDA GUIDELINES

Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in 2 or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:
- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:

    normal lumbar puncture as evaluated by standard techniques;

    normal pattern or nonspecific changes in EEG, such as increased slow-wave activity; and

    evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
- the clinical criteria for probable Alzheimer's disease and
- histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
- familial occurrence;
- onset before age of 65;

- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

McKhann et al.,

Neurology, 34: 939-44, 1984

Protocol Attachment LZZT.8
Hachinski Ischemic Scale

Protocol Attachment LZZT.8
Hachinski Ischemic Scale

Background Information

The Hachinski Ischemic Score (Hachinski et al. 1975) was devised to better distinguish multi-infarct dementia (MID) from other types of dementia such as primary degenerative dementia (PDD) and is commonly used as a screening tool to exclude patients with MID from entrance into clinical trials assessing neuropsychopharmacologic therapy in patients with AD. The Ischemic Score is based on a 13-item scale, which consists of clinical features which may be consistent with vascular dementia.

Test Administration

The Hachinski Ischemic Score is to be completed at Visit 1 (screening visit). The scale should be completed by the physician based on clinical information obtained from diagnostic information and physical examination. The scale takes about 10 to 15 minutes to complete depending on the availability of the data needed. Scores for the 13 items are added together for a total score. <u>Patients who score 5 or greater are more likely to have a dementia of vascular etiology and are excluded from participating in the trial.</u>

Hachinski Ischemic Scale

Feature	Present	Absent
1. Abrupt onset	2	0
2. Stepwise deterioration	1	0
3. Fluctuating course	2	0
4. Nocturnal confusion	1	0
5. Relative preservation of personality	1	0
6. Depression	1	0
7. Somatic complaints	1	0
8. Emotional incontinence	1	0
9. History of hypertension	1	0
10. History of strokes	2	0
11. Evidence of associated atherosclerosis	1	0
12. Focal neurologic symptoms	2	0
13. Focal neurologic signs	2	0

References

Hachinski VC, Iliff LD, Zilhka E, et al. 1975. Cerebral blood flow in dementia. Arch Neurol 32:632-37.

Protocol Attachment LZZT.9
TTS Acceptability Survey

Protocol Attachment LZZT.9
TTS Acceptability Survey

ACCEPTABILITY: **CAREGIVER'S RESPONSE ABOUT THE PATCH**

INFORMATION NOT OBTAINED   ☐

The following questions are intended to be answered by the caregiver and to address the patch's design and wearability. Focus on the act of wearing and removing the transdermal patch. On each scale below, circle one number (do not circle on the scale between numbers) that best describes your feelings about the patch:

1. The <u>appearance</u> of the patch while being worn is acceptable:

1	2	3	4	5	6	7

Strongly   Neutral   Strongly
Disagree   Agree

2. The <u>size</u> of the patch is acceptable:

1	2	3	4	5	6	7

Strongly   Neutral   Strongly
Disagree   Agree

3. The patches were durable (eg, did not discolor, tear) while being worn:

1	2	3	4	5	6	7

Strongly   Neutral   Strongly
Disagree   Agree

ACCEPTABILITY: **CAREGIVER'S RESPONSE ABOUT THE PATCH**

INFORMATION NOT OBTAINED ☐

Based on the experience of applying and wearing this patch, if the patient was prescribed a drug for Alzheimer's disease and was given the choice of this patch or an oral pill given twice daily (assume that both formulations are equally effective), would you (the caregiver):

☐   Insist that the patient receive an oral pill

☐   Prefer that the patient receive an oral pill

☐   Have no preference (neutral) for an oral or patch formulation

☐   Prefer that the patient receive a patch

☐   Insist that the patient receive a patch

Appendix 2.   Sample Case Report Form

Lilly

Date: _____/_____/_____

ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT

Inclusion Criteria: The answers for Items 1-8 must be YES to qualify for study.

Yes No

☐ ☐ 1. Males and postmenopausal females at least 50 years of age.

☐ ☐ 2. Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Protocol Attachment LZZT.7).

☐ ☐ 3. MMSE score of 10 to 23.

☐ ☐ 4. Modified Hachinski Ischemic Scale score of £4. (Protocol Attachment LZZT.8).

☐ ☐ 5. CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year.

   The following findings are incompatible with AD.

   1. Large vessel strokes

      a. Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory.

      b. Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts.

   The above are exclusionary. Exceptions are made for small areas of cortical asymmetry which may represent a small cortical stroke or a focal area of atrophy provided there is no abnormal signal intensity in the immediately underlying parenchyma. Only one such questionable area allowed per scan, and size is restricted to £1 cm in frontal/parietal/temporal cortices and £2 cm in occipital cortex.

   2. Small vessel ischemia

      a. Lacunar infarct is defined as an area of abnormal intensity seen on CT scan or on both T1 and T2 weighted MRI images in the basal ganglia, thalamus or deep white matter which is £1 cm in maximal diameter. A maximum of one lacune is allowed per scan.

      b. Leukoariosis or leukoencephalopathy is regarded as an abnormality seen on T2 but not T1 weighted MRIs, or on CT. This is accepted if mild or moderate in extent, meaning involvement of less than 25% of cortical white matter.

   3. Miscellaneous

      a. Benign small extra-axial tumors (ie, meningiomas) are accepted if they do not contact or indent the brain parenchyma.

      b. Small extra-axial arachnoid cysts are accepted if they do not indent or deform the brain parenchyma.

ENTRY PROCEDURES AND CRITERIA FOR ENROLLMENT

Inclusion Criteria: The answers for Items 1-8 must be YES to qualify for study.

Yes No

☐ ☐ 6. Investigator has obtained informed consent signed by the patient (and/or legal representative) and by the caregiver.

☐ ☐ 7. Geographic proximity to investigator's site that allows adequate follow-up.

☐ ☐ 8. A reliable caregiver who is in frequent or daily contact with the patient and who will accompany the patient to the office and/or be available by telephone at designated times, will monitor administration of prescribed medications, and will be responsible for the overall care of the patient at home. The caregiver and the patient must be able to communicate in English and willing to comply with 26 weeks of transdermal therapy.

Exclusion Criteria: The answers for Items 9-31 must be NO to qualify for study.

Yes No

☐ ☐ 9. Persons who have previously completed or withdrawn from this study or any other investigating xanomeline TTS or the oral formulation of xanomeline.

☐ ☐ 10. Use of any investigational agent or approved Alzheimer's therapeutic medication within 30 days prior to enrollment into the study.

☐ ☐ 11. Serious illness which required hospitalization within 3 months of screening.

☐ ☐ 12. Diagnosis of serious neurological conditions, including

a) Stroke or vascular dementia documented by clinical history and/or radiographic findings interpretable by the investigator as indicative of these disorders

b) Seizure disorder other than simple childhood febrile seizures

c) Severe head trauma resulting in protracted loss of consciousness within the last 5 years, or multiple episodes of head trauma

d) Parkinson's disease

e) Multiple sclerosis

f) Amyotrophic lateral sclerosis

g) Myasthenia gravis.

☐ ☐ 13. Episode of depression meeting DSM-IV criteria within 3 months of screening.

☐ ☐ 14. A history within the last 5 years of the following:

a) Schizophrenia

b) Bipolar Disease

c) Ethanol or psychoactive drug abuse or dependence.

Exclusion Criteria: The answers for Items 9-31 must be NO to qualify for study.

Yes No

☐ ☐ 15. A history of syncope within the last 5 years.

☐ ☐ 16. Evidence from ECG recording at screening of any of the following conditions:

    a) Left bundle branch block

    b) Bradycardia £50 beats per minute

    c) Sinus pauses >2 seconds

    d) Second or third degree heart block unless treated with a pacemaker

    e) Wolff-Parkinson-White syndrome

    f) Sustained supraventricular tachyarrhythmia

☐ ☐ 17. A history within the last 5 years of a serious cardiovascular disorder, including

    a) Clinically significant arrhythmia

    b) Symptomatic sick sinus syndrome not treated with a pacemaker

    c) Congestive heart failure refractory to treatment

    d) Angina except angina controlled with PRN nitroglycerin

    e) Resting heart rate <50 or >100 beats per minute, on physical exam

    f) Uncontrolled hypertension

☐ ☐ 18. A history within the last 5 years of a serious gastrointestinal disorder, including

    a) Chronic peptic/duodenal/gastric/esophageal ulcer that are untreated or refractory to treatment

    b) Symptomatic diverticular disease

    c) Inflammatory bowel disease

    d) Pancreatitis

    e) Hepatitis

    f) Cirrhosis of the liver

Exclusion Criteria: The answers for Items 9-31 must be NO to qualify for study.

Yes No

19. A history within the last 5 years of a serious endocrine disorder, including

    a) Uncontrolled Insulin Dependent Diabetes Mellitus (IDDM)

    b) Diabetic ketoacidosis

    c) Untreated hyperthyroidism

    d) Untreated hypothyroidism

    e) Other untreated endocrinological disorder

20. A history within the last 5 years of a serious respiratory disorder, including

    a) Asthma with bronchospasm refractory to treatment

    b) Decompensated chronic obstructive pulmonary disease.

21. A history within the last 5 years of a serious genitourinary disorder, including

    a) Renal failure

    b) Uncontrolled urinary retention

22. A history within the last 5 years of a serious rheumatologic disorder, including

    a) Lupus

    b) Temporal arteritis

    c) Severe rheumatoid arthritis

23. A known history of human immunodeficiency virus (HIV) within the last 5 years.

24. A history within the last 5 years of a serious infectious disease including

    a) Neurosyphilis

    b) Meningitis

    c) Encephalitis

25. A history within the last 5 years of a primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with a normal PSA postresection.

26. Visual, hearing, or communication disabilities impairing the ability to participate in the study; (for example, inability to speak or understand English, illiteracy).

Yes No   **Exclusion Criteria:** The answers for Items 9-31 must be NO to qualify for study.

☐ ☐ 27. Laboratory test values exceeding the Lilly Reference Range III for the patient's age in any of the following analytes: -creatinine, -total bilirubin, - SGOT, - SGPT, - alkaline phosphatase, - GGT, -ˉ hemoglobin, -ˉ white blood cell count, -ˉ platelet count, -ˉserum sodium, potassium or calcium.

If values exceed these laboratory reference ranges, clinical significance will be judged by the monitoring physicians.

☐ ☐ 28. Central laboratory test values below reference range for folate, and vitamin B_{12}, and outside reference range for thyroid function tests.

☐ ☐ 29. Positive syphilis screening with confirmatory testing.

☐ ☐ 30. Central laboratory test value above reference range for glycosylated hemoglobin (A_{1C}) (insulin dependent diabetes mellitus patients only)

☐ ☐ 31. Treatment with the following medications within 1 month prior to enrollment

a) Anticonvulsants including but not limited to
- Tegretolâ (carbamazepine)
- Depakoteâ (valproic acid)

b) Alpha receptor blockers including but not limited to
- Catapresâ (clonidine)
- Aldometâ (methyldopa)

c) Calcium channel blockers that are CNS active including but not limited to
- Nimotopâ (nimodipine)

d) Beta blockers including but not limited to
- Inderalâ (propranolol)
-Tenorminâ (atenolol)

e) Beta sympathomimetics (unless inhaled) including but not limited to
- Proventil Repetabsâ , Ventolinâ tablets (albuterol tablets)
- Dopamineâ

f) Parasympathomimetics (cholinergics) (unless ophthalmic) including but not limited to
- Urecholineâ (bethanechol)
-Reglanâ (metoclopramide)

g) Muscle relaxants-centrally active including but not limited to
- Flexerilâ (cyclobenzaprine)
- Somaâ (carisoprodol)

h) Monoamine oxidase inhibitors (MAOI) including but not limited to
- Nardilâ (phenelzine)
- Eldeprylâ (selegiline)
- Parnateâ (tranylcypromine)

Exclusion Criteria: The answers for Items 9-31 must be NO to qualify for study.

i) Parasympatholytics (anticholinergics) including but not limited to
- Ditropanâ (oxybutynin)
- Urispasâ (flavoxate)
- Antivertâ (meclizine)

j) Antidepressants including but not limited to
- Prozacâ (fluoxetine)
- Elavilâ (amitriptyline)

k) Systemic corticosteroids including but not limited to
- Depo-medrolâ (methylprednisolone)

l) Xanthine derivatives including but not limited to
- Theo-Durâ (theophylline)

m) Histamine (H$_2$) antagonists including but not limited to
- Tagametâ (cimetidine)
- Axidâ (nizatidine)

n) Narcotic Analgesics including but not limited to
- Darvocet-N 100â , Propacetâ (propoxyphene + acetaminophen)

Percocet (oxycodone with acetaminophen) and Tylenolâ with codeine #2, #3, #4 (acetaminophen + codeine) ARE allowed in the month prior to enrollment, but are not permitted in the 4 days prior to enrollment.

o) Neuroleptics (antipsychotics) including but not limited to
- Haldolâ (haloperidol)
- Mellarilâ (thioridazine)

The use of neuroleptics on an as needed basis is permitted during the month prior to enrollment, but are to be discontinued at least 7 days prior to enrollment.

p) Antianxiety agents including but not limited to
- BuSparâ (buspirone)
- Libriumâ (chlordiazepoxide)

Ativanâ (lorazepam) is allowed on an as needed basis in the month prior to enrollment, but is not permitted in the 24 hours prior to enrollment.

q) Hypnotics/Sedatives including but not limited to
- Restorilâ (temazepam)

Chloral Hydrate is allowed on an as needed basis in the month prior to enroll-ment, but is not permitted in the 24 hours prior to enrollment.

r) Histamine (H$_1$) antagonists including but not limited to
- Benadrylâ (diphenhydramine)
- Seldaneâ (terfenadine)

Intermittent use of these antihistamines is permitted during the month prior to enrollment, but is not permitted in the 4 days prior to enrollment.

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Visit 1
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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                    First   Middle   Last

Visit date _____/_____/_____
             MM   DD   YY

INFORMED CONSENT

Date patient and caregiver signed the consent document _____/_____/_____
                                                          MM   DD   YY

DEMOGRAPHICS

Date of birth _____/_____/_____
                MM   DD   YY

Sex ☐$_F$ Female   ☐$_M$ Male

Origin ☐$_{CA}$ Caucasian (European, Mediterranean, Middle Eastern)

☐$_{AF}$ African Descent (Negro, Black)

☐$_{EA}$ East/Southeast Asian (Burmese, Chinese, Japanese, Korean, Mongolian, Vietnamese)

☐$_{AS}$ Western Asian (Pakistani, Indian Sub-continent)

☐$_{HP}$ Hispanic (Mexican-American, Mexico, Central and South America)

☐$_O$ Other (Mixed-racial parentage, American Indian, Eskimo)

REMINDER

Record the patient's pre-existing conditions on the Pre-existing
Conditions and Study Adverse Events page.

Record all medications the patient is currently taking on the
Concomitant Medication page.

A physical examination must be performed at this visit. Any
clinically significant abnormalities must be listed on the
Pre-existing Conditions and Study Adverse Events page.

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EDUCATION

Number of years of education completed   _____
                                                    years

HABITS : SMOKING

INFORMATION NOT OBTAINED ☐

> Enter the average current <u>daily</u> use
> **0** = None
> **L** = Less than one *(eg, cigar or pipe smoker*
> *who smokes only 1 or 2x a week)*
> **1, 2, 3, etc** = Whole numbers ONLY

Number of cigarettes   _____

Number of cigars   _____

Number of pipesful   _____

Enter the number of years (past or current) patient
has smoked. If patient has never smoked, enter 0.   _____
                                                          years

**(If the patient has NEVER smoked or is still smoking,
leave the following question blank.)**

Enter the month and year that the patient quit smoking.   _____/_____
                                                              MM   YY

HABITS : ALCOHOL

INFORMATION NOT OBTAINED ☐

> Enter the average current <u>weekly</u> consumption
> **0** = None
> **L** = Less than one
> **1, 2, 3,** etc = Whole numbers ONLY

Number of beers or wine coolers/spritzers   _____

Number of glasses of wine   _____

Number of drinks containing distilled spirits   _____

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HABITS **: CAFFEINE**

INFORMATION NOT OBTAINED ☐

> Enter the average current <u>daily</u> consumption
> **0** = None
> **L** = Less than one
> **1, 2, 3, etc** = Whole numbers ONLY

Number of cups of coffee   _____

Number of cups of tea   _____

Number of colas   _____

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MINI-MENTAL STATE

INFORMATION NOT OBTAINED ☐

Score   Maximum
             Score

Orientation

1. ___   (5)   What is the (year) (season) (date) (day) (month)?

2. ___   (5)   Where are we: (state) (county) (town) (hospital) (floor)?

Registration

3. ___   (3)   Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he learns all 3. Count trials and record.

Attention and Calculation

4. ___   (5)   Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively, spell "world" backwards.

Recall

5. ___   (3)   Ask for the 3 objects repeated above. Give 1 point for each correct.

Language

6. ___   (9)   Name a pencil, and watch (2 points)

Repeat the following "No ifs, ands, or buts." (1 point)

Follow a 3-stage command:
    "Take a paper in your right hand, fold it in half, and put it on the floor" (3 points)

Read and obey the following:
    Close your eyes (1 point)

Write a sentence (1 point)

Copy design (1 point)

(DNDE)

Total score _____   NOTE: Patient must have a score of 10-23 on the MMSE at Visit 1 to be enrolled in this study.

ASSESS level of consciousness along a continuum _____

                    Alert   Drowsy   Stupor   Coma

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MODIFIED HACHINSKI ISCHEMIC SCORE

INFORMATION NOT OBTAINED ☐

Circle the score that corresponds to the feature being present or absent.

Feature	Present	Absent
1. Abrupt onset	2	0
2. Stepwise deterioration	1	0
3. Fluctuating course	2	0
4. Nocturnal confusion	1	0
5. Relative preservation of personality	1	0
6. Depression	1	0
7. Somatic complaints	1	0
8. Emotional incontinence	1	0
9. History of hypertension	1	0
10. History of strokes	2	0
11. Evidence of associated atherosclerosis	1	0
12. Focal neurological symptoms	2	0
13. Focal neurological signs	2	0

(DNDE)

Total Score _____

NOTE: Patient must have a score of £4 on the Modified Hachinski
Ischemic Scale at Visit 1 to be enrolled in this study.

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 Arch Neurol 1975;32:632-37.

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PATIENT HISTORY : ALZHEIMER'S DISEASE ONSET DATE

Date of onset of the <u>first definite symptoms</u>
of Alzheimer's Disease   _____/_____/_____
                                    MM   DD   YY

CLINICAL FEATURES : ALZHEIMER'S DISEASE

INFORMATION NOT OBTAINED ☐

Does the patient display or has the patient displayed the following clinical features:

1. Extrapyramidal features (masked facies, bradykinesia, slowed rapid alternating movements, flexed posture, gait difficulty) without a resting tremor   ☐₁ Yes   ☐₂ No

2. Essential tremor (action or postural)   ☐₁ Yes   ☐₂ No

3. Sensitivity to neuroleptics   ☐₁ Yes   ☐₂ No

4. Marked deficit of attention and/or fluctuations in level of attention and alertness; confusional episodes   ☐₁ Yes   ☐₂ No

5. Visual hallucinations and/or paranoid delusions   ☐₁ Yes   ☐₂ No

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EXTRAPYRAMIDAL FINDINGS

INFORMATION NOT OBTAINED ☐

1. Masked facies

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

2. Rigidity of upper extremity

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

3. Essential tremor

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

4. Ambulation

   How long did it take the patient to walk 25 yards? _____

   seconds

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SIGNIFICANT HISTORICAL DIAGNOSIS

NO SIGNIFICANT HISTORICAL DIAGNOSIS ☐

List each clinically significant (at the discretion of the investigator) historical diagnosis that is
NO LONGER PRESENT. If exact date is unknown, enter the month and year. A year MUST be entered.

Historical Diagnosis COSTART Class Term	Date Recovered/Date of Surgical Procedure		
	MM	DD	YY
0.			
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			

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SIGNIFICANT HISTORICAL DIAGNOSIS

List each clinically significant (at the discretion of the investigator) historical diagnosis that is
NO LONGER PRESENT. If exact date is unknown, enter the month and year. A year MUST be entered.

Historical Diagnosis COSTART Class Term	Date Recovered/Date of Surgical Procedure		
	MM	DD	YY

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

HEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth inch</u> or <u>tenth centimeter</u>.

Height ___ ___ ___ . ___   ☐ cm Centimeter   ☐ in Inch

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

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VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ $_F$ Fahrenheit   ☐ $_C$ Centigrade

Method   ☐ $_{PO}$ Oral   ☐ $_R$ Rectal   ☐ $_A$ Axillary   ☐ $_E$ Ear   ☐ $_O$ Other

ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   _____/_____/_____
                              MM   DD   YY

Electrocardiogram result   ☐ $_{12}$ Acceptable   ☐ $_{13}$ Not Acceptable

> NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on
>   the Pre-existing Conditions and Study Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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                                                                Page 11 of 14

CHEST X-RAY

NOT DONE ☐

Was the chest x-ray   ☐ $_1$ Taken for this visit   ☐ $_{611}$ Historical (within the previous 6 months)

Date of chest x-ray   _____/_____/_____
                       MM   DD   YY

Chest x-ray result   ☐ $_{12}$ Acceptable   ☐ $_{13}$ Not Acceptable

> NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on the Pre-existing Conditions and Study Adverse Events page. Note non-relevant abnormalities in the Chest X-ray Comments section below.

COMMENTS : **NON-RELEVANT CHEST X-RAY ABNORMALITIES**

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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PROCEDURE **: MRI**

NOTE: **Either** a CT scan **OR** MRI of the brain, which is compatible with Alzheimer's Disease, is required to enter this trial.

NOT DONE ☐

Was the MRI   ☐ 1 Taken for this visit   ☐ 2 Historical (within the previous 12 months)

Date of MRI   _____/_____/_____
                  MM   DD   YY

NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on the Pre-existing Conditions and Study Adverse Events page. Note non-relevant abnormalities in the MRI Comments section below.

COMMENTS **: NON-RELEVANT MRI ABNORMALITIES**

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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PROCEDURE : **CT SCAN**

NOTE: **Either** a CT scan **OR** MRI of the brain, which is compatible with Alzheimer's Disease, is required to enter this trial.

NOT DONE ☐

Was the CT scan   ☐ $_1$ Taken for this visit   ☐ $_2$ Historical (within the previous 12 months)

Date of CT scan   _____/_____/_____
                    MM   DD   YY

NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on the Pre-existing Conditions and Study Adverse Events page. Note non-relevant abnormalities in the CT Scan Comments section below.

COMMENTS : **NON-RELEVANT CT SCAN ABNORMALITIES**

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

_____

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The information reported for this visit is accurate and complete.

_____ _____/_____/_____
                Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                    First   Middle   Last

Visit date   _____/_____/_____
               MM   DD   YY

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication page, record new medications the patient has taken since the previous visit and record a stop date for any medication the patient is no longer taking.

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VITAL SIGNS : **TEMPERATURE**

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

PROCEDURE : **AMBULATORY ECG**

NOT DONE ☐

Date of ambulatory ECG   _____/_____/_____
                            MM   DD   YY

> NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on
>   the Pre-existing Conditions and Study Adverse Events page. Note non-relevant
>   abnormalities in the Ambulatory ECG Comments section below.

COMMENTS : **NON-RELEVANT AMBULATORY ECG ABNORMALITIES**

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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COMMENTS : **VISIT**

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

The information reported for this visit is accurate and complete.

_____   _____/_____/_____
              Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                    First   Middle Last

Visit date   _____/_____/_____
              MM   DD   YY

KIT NUMBER

NONE DISPENSED ☐

Kit number dispensed   _____

STUDY DRUG : **DAILY PRESCRIBED DOSAGE**

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                               25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                               50-cm^2 patches

---

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
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ALZHEIMER'S DISEASE ASSESSMENT SCALE : COGNITIVE with ATTENTION/ CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                         First   Middle   Last

1.	Word Recall Task	(max = 10)	_____
2.	Naming Objects and Fingers (refer to 5 categories in manual)	(max = 5)	_____
3.	Delayed Word Recall	(max = 10)	_____
4.	Commands	(max = 5)	_____
5.	Constructional Praxis	(max = 5)	_____
6.	Ideational Praxis	(max = 5)	_____
7.	Orientation	(max = 8)	_____
8.	Word Recognition	(max = 12)	_____
9.	Attention/Visual Search Task	(max = 40)	_____
10.	Maze Solution	(max = 240)	_____ (seconds)
11.	Spoken Language Ability	(max = 5)	_____
12.	Comprehension of Spoken Language	(max = 5)	_____
13.	Word Finding Difficulty in Spontaneous Speech	(max = 5)	_____
14.	Recall of Test Instructions	(max = 5)	_____

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 American Journal of Psychiatry 1984;141:1356-64.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency				Severity			Distress					
A. Delusions	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
B. Hallucinations	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
C. Agitation/Agression	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
D. Depression/ Dysphoria	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
E. Anxiety	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
F. Euphoria/Elation	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
G. Apathy/ Indifference	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
H. Disinhibition	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
I. Irritability/Lability	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
J. Aberrant Motor Behavior	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
K. Night-Time Behavior	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
L. Appetite/Eating Change	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

During the past two weeks, did the patient without help or reminder:

SCORING: Yes = 1 No = 0 Not Applicable = 96	Initiation	Planning & Organization	Effective Performance
HYGIENE			
1. Undertake to wash himself/herself or to take a bath or a shower			
2. Undertake to brush his/her teeth or care for his/her dentures			
3. Decide to care for his/her hair (wash and comb)			
4. Prepare the water, towels, and soap for washing, taking a bath, or a shower			
5. Wash and dry completely all parts of his/her body safely			
6. Brush his/her teeth or care for his/her dentures appropriately			
7. Care for his/her hair (wash and comb)			
DRESSING			
8. Undertake to dress himself/herself			
9. Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)			
10. Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)			
11. Dress himself/herself completely			
12. Undress himself/herself completely			
CONTINENCE			
13. Decide to use the toilet at appropriate times			
14. Use the toilet without "accidents"			
EATING			
15. Decide that he/she needs to eat			
16. Choose appropriate utensils and seasonings when eating			
17. Eat his/her meals at a normal pace and with appropriate manners			
MEAL PREPARATION			
18. Undertake to prepare a light meal or snack for himself/herself			
19. Adequately plan a light meal or snack (ingredients, cookware)			
20. Prepare or cook a light meal or a snack safely			

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Lilly

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

#	Item	Initiation	Planning & Organization	Effective Performance
TELEPHONING				
21.	Attempt to telephone someone at a suitable time		▨	▨
22.	Find and dial a telephone number correctly	▨		▨
23.	Carry out an appropriate telephone conversation	▨	▨	
24.	Write and convey a telephone message adequately	▨	▨	
GOING ON AN OUTING				
25.	Undertake to go out (walk, visit, shop) at an appropriate time		▨	▨
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▨		▨
27.	Go out and reach a familiar destination without getting lost	▨	▨	
28.	Safely take the adequate mode of transportation (car, bus, taxi)	▨	▨	
29.	Return from the store with the appropriate items	▨	▨	
FINANCE AND CORRESPONDENCE				
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence		▨	▨
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▨		▨
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	▨		▨
33.	Handle adequately his/her money (make change)	▨	▨	
MEDICATIONS				
34.	Decide to take his/her medications at the correct time		▨	▨
35.	Take his/her medications as prescribed (according to the right dosage)	▨	▨	
LEISURE AND HOUSEWORK				
36.	Show an interest in leisure activity(ies)		▨	▨
37.	Take an interest in household chores that he/she used to perform in the past		▨	▨
38.	Plan and organize adequately household chores that he/she used to perform in the past	▨		▨
39.	Complete household chores adequately as he/she used to perform in the past	▨	▨	
40.	Stay safely at home by himself/herself when needed	▨	▨	

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

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H2Q-MC-LZZT

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle   Last

Visit date _____/_____/_____
             MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                  days

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                                 25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                                 50-cm^2 patches

---

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
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VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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PROCEDURE : AMBULATORY ECG

NOT DONE ☐

Date of ambulatory ECG   _____/_____/_____
                                         MM   DD   YY

NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on
           the Pre-existing Conditions and Study Adverse Events page. Note non-relevant
           abnormalities in the Ambulatory ECG Comments section below.

COMMENTS : NON-RELEVANT AMBULATORY ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
                Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle   Last

Visit date _____/_____/_____
             MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                 days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
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STUDY DRUG : PATCH ADHERENCE - PREVIOUS THREE DOSES

INFORMATION NOT OBTAINED ☐

For the previous three doses of study drug (patch administration), give the date and the number of hours that a patch was NOT applied (if applicable).

	Date	Number of hours 25-cm^2 patch **NOT** applied	Number of hours 50-cm^2 patch **NOT** applied
1. Today's (visit) date	____/____/____ MM DD YY	_____ hours	_____ hours
2. Yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours
3. Day before yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches) that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                                  25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                                  50-cm^2 patches

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials	_____	_____	_____
	First	Middle	Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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H2Q-MC-LZZT

Visit 4
Page 4 of 6

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

NOTE: Blood pressure and pulse must be taken after the
patient has been lying down for 5 minutes
(supine) and after standing for 1 minute (standing)
and 3 minutes.

Position
SU = Supine
ST = Standing

(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0. 5 minutes	815	SU		/
1. 1 minute	816	ST		/
2. 3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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H2Q-MC-LZZT   Visit 4
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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   _____/_____/_____
                             MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the Pre-existing Conditions and Adverse Events page. Note non-relevant abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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Visit 4
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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
            Signature   MM   DD   YY

Clinical Report Form
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  Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

Visit 5
Page 1 of 7

PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle   Last

Visit date _____/_____/_____
             MM   DD   YY

STUDY DRUG **: COMPLIANCE**

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                  days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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Visit 5
Page 2 of 7

STUDY DRUG : PATCH ADHERENCE - PREVIOUS THREE DOSES

INFORMATION NOT OBTAINED ☐

For the previous three doses of study drug (patch administration), give the date and the number of hours that a patch was NOT applied (if applicable).

	Date	Number of hours 25-cm^2 patch **NOT** applied	Number of hours 50-cm^2 patch **NOT** applied
1. Today's (visit) date	____/____/____ MM DD YY	_____ hours	_____ hours
2. Yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours
3. Day before yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches) that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                           25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                           50-cm^2 patches

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Visit 5
Page 3 of 7

NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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Visit 5
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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   _____/_____/_____
                                MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
> Pre-existing Conditions and Adverse Events page. Note non-relevant
> abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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                                                                 Page 6 of 7

PROCEDURE : **AMBULATORY ECG**

NOT DONE ☐

Date of ambulatory ECG _____/_____/_____
                          MM   DD   YY

> NOTE: If abnormality present and clinically relevant, enter the diagnosis or symptom on
>   the Pre-existing Conditions and Study Adverse Events page. Note non-relevant
>   abnormalities in the Ambulatory ECG Comments section below.

COMMENTS : **NON-RELEVANT AMBULATORY ECG ABNORMALITIES**

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
            Signature   MM   DD   YY

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H2Q-MC-LZZT

Visit 6
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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle   Last

Visit date _____/_____/_____
             MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy? _____
                                               days

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day _____
                                            25-cm^2 patches

Number of 50-cm^2 patches prescribed/day _____
                                            50-cm^2 patches

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
                        Signature   MM   DD   YY

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H2Q-MC-LZZT   Visit 7
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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                      First   Middle   Last

Visit date   _____/_____/_____
                       MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                    days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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H2Q-MC-LZZT

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Lilly

STUDY DRUG : PATCH ADHERENCE - PREVIOUS THREE DOSES

INFORMATION NOT OBTAINED ☐

For the previous three doses of study drug (patch administration), give the date and the number of hours that a patch was NOT applied (if applicable).

	Date	Number of hours 25-cm^2 patch **NOT** applied	Number of hours 50-cm^2 patch **NOT** applied
1. Today's (visit) date	___/___/___ MM DD YY	_____ hours	_____ hours
2. Yesterday's date	___/___/___ MM DD YY	_____ hours	_____ hours
3. Day before yesterday's date	___/___/___ MM DD YY	_____ hours	_____ hours

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches) that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                            25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                            50-cm^2 patches

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Visit 7
Page 3 of 6

NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                               First Middle Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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Lilly (logo)

WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure ☐ F Fahrenheit ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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Page 5 of 6

ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date _____/_____/_____
                         MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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   Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT   Visit 7
                                                               Page 6 of 6

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
                Signature   MM   DD   YY

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  Transdermal Therapeutic System (TTS) in
  Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                          First   Middle   Last

Visit date   _____/_____/_____
                      MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                       days

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                                   25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                                   50-cm^2 patches

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REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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ALZHEIMER'S DISEASE ASSESSMENT SCALE : COGNITIVE with ATTENTION/ CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

1. Word Recall Task   (max = 10)   _____

2. Naming Objects and Fingers
    (refer to 5 categories in manual)   (max = 5)   _____

3. Delayed Word Recall   (max = 10)   _____

4. Commands   (max = 5)   _____

5. Constructional Praxis   (max = 5)   _____

6. Ideational Praxis   (max = 5)   _____

7. Orientation   (max = 8)   _____

8. Word Recognition   (max = 12)   _____

9. Attention/Visual Search Task   (max = 40)   _____

10. Maze Solution   (max = 240)   _____ (seconds)

11. Spoken Language Ability   (max = 5)   _____

12. Comprehension of Spoken Language   (max = 5)   _____

13. Word Finding Difficulty in Spontaneous Speech (max = 5)   _____

14. Recall of Test Instructions   (max = 5)   _____

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CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

Check one box to indicate the extent of change, if any, observed since the initial baseline interview.

☐ 1 Marked improvement

☐ 2 Moderate improvement

☐ 3 Minimal improvement

☐ 4 No change

☐ 5 Minimal worsening

☐ 6 Moderate worsening

☐ 7 Marked worsening

The clinical interview-based impression of change scale in this study is from a pilot instrument, the Clinical Global Impression of Change, developed and currently undergoing validity studies by the National Institute on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator), and is in the public domain.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

During the past two weeks, did the patient without help or reminder:

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

		Initiation	Planning & Organization	Effective Performance
HYGIENE				
1.	Undertake to wash himself/herself or to take a bath or a shower		▓	▓
2.	Undertake to brush his/her teeth or care for his/her dentures		▓	▓
3.	Decide to care for his/her hair (wash and comb)		▓	▓
4.	Prepare the water, towels, and soap for washing, taking a bath, or a shower	▓		▓
5.	Wash and dry completely all parts of his/her body safely	▓		
6.	Brush his/her teeth or care for his/her dentures appropriately	▓		
7.	Care for his/her hair (wash and comb)	▓	▓	
DRESSING				
8.	Undertake to dress himself/herself		▓	▓
9.	Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)	▓		▓
10.	Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)	▓		
11.	Dress himself/herself completely	▓		
12.	Undress himself/herself completely	▓	▓	
CONTINENCE				
13.	Decide to use the toilet at appropriate times		▓	▓
14.	Use the toilet without "accidents"	▓	▓	
EATING				
15.	Decide that he/she needs to eat		▓	
16.	Choose appropriate utensils and seasonings when eating	▓		
17.	Eat his/her meals at a normal pace and with appropriate manners	▓	▓	
MEAL PREPARATION				
18.	Undertake to prepare a light meal or snack for himself/herself		▓	▓
19.	Adequately plan a light meal or snack (ingredients, cookware)	▓		▓
20.	Prepare or cook a light meal or a snack safely	▓	▓	

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

SCORING: **Yes = 1** **No = 0** **Not Applicable = 96**

Columns: Initiation | Planning & Organization | Effective Performance
(Shaded cells = ▨)

TELEPHONING

#	Item	Initiation	Planning & Organization	Effective Performance
21.	Attempt to telephone someone at a suitable time		▨	▨
22.	Find and dial a telephone number correctly	▨		▨
23.	Carry out an appropriate telephone conversation	▨	▨	
24.	Write and convey a telephone message adequately	▨	▨	

GOING ON AN OUTING

#	Item	Initiation	Planning & Organization	Effective Performance
25.	Undertake to go out (walk, visit, shop) at an appropriate time		▨	▨
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▨		▨
27.	Go out and reach a familiar destination without getting lost	▨	▨	
28.	Safely take the adequate mode of transportation (car, bus, taxi)	▨	▨	
29.	Return from the store with the appropriate items	▨	▨	

FINANCE AND CORRESPONDENCE

#	Item	Initiation	Planning & Organization	Effective Performance
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence		▨	▨
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▨		▨
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	▨		▨
33.	Handle adequately his/her money (make change)	▨	▨	

MEDICATIONS

#	Item	Initiation	Planning & Organization	Effective Performance
34.	Decide to take his/her medications at the correct time		▨	▨
35.	Take his/her medications as prescribed (according to the right dosage)	▨	▨	

LEISURE AND HOUSEWORK

#	Item	Initiation	Planning & Organization	Effective Performance
36.	Show an interest in leisure activity(ies)		▨	▨
37.	Take an interest in household chores that he/she used to perform in the past		▨	▨
38.	Plan and organize adequately household chores that he/she used to perform in the past	▨		▨
39.	Complete household chores adequately as he/she used to perform in the past	▨	▨	
40.	Stay safely at home by himself/herself when needed	▨	▨	

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date _____/_____/_____
                          MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____
_____
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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

_____

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_____

The information reported for this visit is accurate and complete.

_____   _____/_____/_____
              Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle Last

Visit date   _____/_____/_____
              MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                    days

<div style="border:1px solid">

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

</div>

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STUDY DRUG : PATCH ADHERENCE - PREVIOUS THREE DOSES

INFORMATION NOT OBTAINED ☐

For the previous three doses of study drug (patch administration), give the date and the number of hours that a patch was NOT applied (if applicable).

	Date	Number of hours 25-cm^2 patch **NOT** applied	Number of hours 50-cm^2 patch **NOT** applied
1. Today's (visit) date	____/____/____ MM DD YY	_____ hours	_____ hours
2. Yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours
3. Day before yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches) that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day _____
25-cm^2 patches

Number of 50-cm^2 patches prescribed/day _____
50-cm^2 patches

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date _____/_____/_____
                           MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

_____

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_____

The information reported for this visit is accurate and complete.

_____   _____/_____/_____
           Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
                   First   Middle   Last

Visit date   _____/_____/_____
                    MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                   days

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                                25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                                50-cm^2 patches

---

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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ALZHEIMER'S DISEASE ASSESSMENT SCALE : COGNITIVE with ATTENTION/ CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                     First   Middle   Last

1. Word Recall Task   (max = 10)   _____

2. Naming Objects and Fingers
    (refer to 5 categories in manual)   (max = 5)   _____

3. Delayed Word Recall   (max = 10)   _____

4. Commands   (max = 5)   _____

5. Constructional Praxis   (max = 5)   _____

6. Ideational Praxis   (max = 5)   _____

7. Orientation   (max = 8)   _____

8. Word Recognition   (max = 12)   _____

9. Attention/Visual Search Task   (max = 40)   _____

10. Maze Solution   (max = 240)   _____ (seconds)

11. Spoken Language Ability   (max = 5)   _____

12. Comprehension of Spoken Language   (max = 5)   _____

13. Word Finding Difficulty in Spontaneous Speech   (max = 5)   _____

14. Recall of Test Instructions   (max = 5)   _____

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CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First Middle Last

Check one box to indicate the extent of change, if any, observed since the initial baseline interview.

☐ 1 Marked improvement

☐ 2 Moderate improvement

☐ 3 Minimal improvement

☐ 4 No change

☐ 5 Minimal worsening

☐ 6 Moderate worsening

☐ 7 Marked worsening

The clinical interview-based impression of change scale in this study is from a pilot instrument, the Clinical
Global Impression of Change, developed and currently undergoing validity studies by the National Institute
on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator),
and is in the public domain.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

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B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

During the past two weeks, did the patient without help or reminder:

SCORING: Yes = 1 No = 0 Not Applicable = 96	Initiation	Planning & Organization	Effective Performance
HYGIENE			
1. Undertake to wash himself/herself or to take a bath or a shower			
2. Undertake to brush his/her teeth or care for his/her dentures			
3. Decide to care for his/her hair (wash and comb)			
4. Prepare the water, towels, and soap for washing, taking a bath, or a shower			
5. Wash and dry completely all parts of his/her body safely			
6. Brush his/her teeth or care for his/her dentures appropriately			
7. Care for his/her hair (wash and comb)			
DRESSING			
8. Undertake to dress himself/herself			
9. Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)			
10. Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)			
11. Dress himself/herself completely			
12. Undress himself/herself completely			
CONTINENCE			
13. Decide to use the toilet at appropriate times			
14. Use the toilet without "accidents"			
EATING			
15. Decide that he/she needs to eat			
16. Choose appropriate utensils and seasonings when eating			
17. Eat his/her meals at a normal pace and with appropriate manners			
MEAL PREPARATION			
18. Undertake to prepare a light meal or snack for himself/herself			
19. Adequately plan a light meal or snack (ingredients, cookware)			
20. Prepare or cook a light meal or a snack safely			

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

#	Item	Initiation	Planning & Organization	Effective Performance
	TELEPHONING			
21.	Attempt to telephone someone at a suitable time	□	▓	▓
22.	Find and dial a telephone number correctly	▓	□	▓
23.	Carry out an appropriate telephone conversation	▓	▓	□
24.	Write and convey a telephone message adequately	▓	▓	□
	GOING ON AN OUTING			
25.	Undertake to go out (walk, visit, shop) at an appropriate time	□	▓	▓
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▓	□	▓
27.	Go out and reach a familiar destination without getting lost	▓	▓	□
28.	Safely take the adequate mode of transportation (car, bus, taxi)	▓	▓	□
29.	Return from the store with the appropriate items	▓	▓	□
	FINANCE AND CORRESPONDENCE			
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence	□	▓	▓
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▓	□	▓
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	▓	□	▓
33.	Handle adequately his/her money (make change)	▓	▓	□
	MEDICATIONS			
34.	Decide to take his/her medications at the correct time	□	▓	▓
35.	Take his/her medications as prescribed (according to the right dosage)	▓	▓	□
	LEISURE AND HOUSEWORK			
36.	Show an interest in leisure activity(ies)	□	▓	▓
37.	Take an interest in household chores that he/she used to perform in the past	□	▓	▓
38.	Plan and organize adequately household chores that he/she used to perform in the past	▓	□	▓
39.	Complete household chores adequately as he/she used to perform in the past	▓	▓	□
40.	Stay safely at home by himself/herself when needed	▓	▓	□

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H2Q-MC-LZZT

Visit 10
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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐_{kg} Kilogram   ☐_{lb} Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0. 5 minutes	815	SU		/
1. 1 minute	816	ST		/
2. 3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐_F Fahrenheit   ☐_C Centigrade

Method   ☐_{PO} Oral   ☐_R Rectal   ☐_A Axillary   ☐_E Ear   ☐_O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date _____/_____/_____
                            MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the Pre-existing Conditions and Adverse Events page. Note non-relevant abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

_____

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
               Signature   MM   DD   YY

Clinical Report Form
Safety and Efficacy of the Xanomeline
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H2Q-MC-LZZT

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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                     First   Middle   Last

Visit date   _____/_____/_____
               MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                    days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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STUDY DRUG **: PATCH ADHERENCE - PREVIOUS THREE DOSES**

INFORMATION NOT OBTAINED ☐

For the previous three doses of study drug (patch administration), give the date and the number of hours that a patch was NOT applied (if applicable).

	Date	Number of hours 25-cm^2 patch **NOT** applied	Number of hours 50-cm^2 patch **NOT** applied
1. Today's (visit) date	____/____/____ MM DD YY	_____ hours	_____ hours
2. Yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours
3. Day before yesterday's date	____/____/____ MM DD YY	_____ hours	_____ hours

STUDY DRUG **: DAILY PRESCRIBED DOSAGE**

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches) that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day _____
25-cm^2 patches

Number of 50-cm^2 patches prescribed/day _____
50-cm^2 patches

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral
change is present or absent in the patient. If the answer to the screening question is negative (NO)
or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96]
or Absent [0]) and proceed to the next screening question without asking the subquestions to deter-
mine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency				Severity			Distress					
A. Delusions	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
B. Hallucinations	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
C. Agitation/Agression	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
D. Depression/ Dysphoria	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
E. Anxiety	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
F. Euphoria/Elation	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
G. Apathy/ Indifference	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
H. Disinhibition	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
I. Irritability/Lability	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
J. Aberrant Motor Behavior	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
K. Night-Time Behavior	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5
L. Appetite/Eating Change	96	0	1	2	3	4	1	2	3	0	1	2	3	4	5

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

NOTE: Blood pressure and pulse must be taken after the
        patient has been lying down for 5 minutes
        (supine) and after standing for 1 minute (standing)
        and 3 minutes.

Position
SU = Supine
ST = Standing

(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0. 5 minutes	815	SU		/
1. 1 minute	816	ST		/
2. 3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   _____/_____/_____
                            MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____

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COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
                  Signature   MM   DD   YY

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Telephone Visit   Visit 11t
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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                        First   Middle   Last

Visit (telephone) date   _____/_____/_____
                             MM   DD   YY

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Telephone Visit | Visit 11t
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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                    First   Middle   Last

Visit date   _____/_____/_____
                     MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                  days

STUDY DRUG : DAILY PRESCRIBED DOSAGE

For this visit interval, record the number of patches (25-cm^2 and 50-cm^2 patches)
that the patient is to wear per day.

Number of 25-cm^2 patches prescribed/day   _____
                                                25-cm^2 patches

Number of 50-cm^2 patches prescribed/day   _____
                                                50-cm^2 patches

---

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

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ALZHEIMER'S DISEASE ASSESSMENT SCALE : **COGNITIVE with ATTENTION/ CONCENTRATION TASKS**

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First Middle Last

1. Word Recall Task   (max = 10)   _____

2. Naming Objects and Fingers
   (refer to 5 categories in manual)   (max = 5)   _____

3. Delayed Word Recall   (max = 10)   _____

4. Commands   (max = 5)   _____

5. Constructional Praxis   (max = 5)   _____

6. Ideational Praxis   (max = 5)   _____

7. Orientation   (max = 8)   _____

8. Word Recognition   (max = 12)   _____

9. Attention/Visual Search Task   (max = 40)   _____

10. Maze Solution   (max = 240)   _____ (seconds)

11. Spoken Language Ability   (max = 5)   _____

12. Comprehension of Spoken Language   (max = 5)   _____

13. Word Finding Difficulty in Spontaneous Speech (max = 5)   _____

14. Recall of Test Instructions   (max = 5)   _____

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 American Journal of Psychiatry 1984;141:1356-64.

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CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)

INFORMATION NOT OBTAINED ☐

Clinician's initials ＿＿＿ ＿＿＿ ＿＿＿
                     First Middle Last

Check one box to indicate the extent of change, if any, observed since the initial baseline interview.

☐ 1 Marked improvement

☐ 2 Moderate improvement

☐ 3 Minimal improvement

☐ 4 No change

☐ 5 Minimal worsening

☐ 6 Moderate worsening

☐ 7 Marked worsening

The clinical interview-based impression of change scale in this study is from a pilot instrument, the Clinical
Global Impression of Change, developed and currently undergoing validity studies by the National Institute
on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator),
and is in the public domain.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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Lilly

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

During the past two weeks, did the patient without help or reminder:

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

		Initiation	Planning & Organization	Effective Performance
HYGIENE				
1.	Undertake to wash himself/herself or to take a bath or a shower			
2.	Undertake to brush his/her teeth or care for his/her dentures			
3.	Decide to care for his/her hair (wash and comb)			
4.	Prepare the water, towels, and soap for washing, taking a bath, or a shower			
5.	Wash and dry completely all parts of his/her body safely			
6.	Brush his/her teeth or care for his/her dentures appropriately			
7.	Care for his/her hair (wash and comb)			
DRESSING				
8.	Undertake to dress himself/herself			
9.	Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)			
10.	Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)			
11.	Dress himself/herself completely			
12.	Undress himself/herself completely			
CONTINENCE				
13.	Decide to use the toilet at appropriate times			
14.	Use the toilet without "accidents"			
EATING				
15.	Decide that he/she needs to eat			
16.	Choose appropriate utensils and seasonings when eating			
17.	Eat his/her meals at a normal pace and with appropriate manners			
MEAL PREPARATION				
18.	Undertake to prepare a light meal or snack for himself/herself			
19.	Adequately plan a light meal or snack (ingredients, cookware)			
20.	Prepare or cook a light meal or a snack safely			

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Lilly

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

	SCORING: **Yes = 1** **No = 0** **Not Applicable = 96**	Initiation	Planning & Organization	Effective Performance
TELEPHONING				
21.	Attempt to telephone someone at a suitable time		▒	▒
22.	Find and dial a telephone number correctly	▒		▒
23.	Carry out an appropriate telephone conversation	▒	▒	
24.	Write and convey a telephone message adequately	▒	▒	
GOING ON AN OUTING				
25.	Undertake to go out (walk, visit, shop) at an appropriate time		▒	▒
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▒		▒
27.	Go out and reach a familiar destination without getting lost	▒		
28.	Safely take the adequate mode of transportation (car, bus, taxi)	▒		
29.	Return from the store with the appropriate items	▒	▒	
FINANCE AND CORRESPONDENCE				
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence		▒	▒
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▒		▒
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	▒		
33.	Handle adequately his/her money (make change)	▒	▒	
MEDICATIONS				
34.	Decide to take his/her medications at the correct time		▒	▒
35.	Take his/her medications as prescribed (according to the right dosage)	▒	▒	
LEISURE AND HOUSEWORK				
36.	Show an interest in leisure activity(ies)		▒	▒
37.	Take an interest in household chores that he/she used to perform in the past		▒	▒
38.	Plan and organize adequately household chores that he/she used to perform in the past	▒		▒
39.	Complete household chores adequately as he/she used to perform in the past	▒	▒	
40.	Stay safely at home by himself/herself when needed	▒	▒	

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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H2Q-MC-LZZT

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   ____ / ____ / ____
                                 MM DD YY

Electrocardiogram result   ☐ $_{12}$ Acceptable   ☐ $_{13}$ Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the Pre-existing Conditions and Adverse Events page. Note non-relevant abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____

_____

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Clinical Report Form
Safety and Efficacy of the Xanomeline
   Transdermal Therapeutic System (TTS) in
   Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

Visit 12
Page 9 of 9

COMMENTS : VISIT

NO COMMENTS ☐

Comments should address any clinical report form items that require further explanation. Repeating information from the clinical report form is discouraged.

Comment on all clinically significant lab values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values.

If the patient is ending participation in the study at this visit, enter only comments that apply to this visit; then complete the Patient Summary and Study Summary Comments pages.

Print legibly and do not use abbreviations or symbols.

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The information reported for this visit is accurate and complete.

_____   _____/_____/_____
              Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
First   Middle   Last

Visit date _____/_____/_____
MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

A physical examination must be performed at this visit. Any clinically
significant abnormalities must be listed on the Pre-existing Conditions and
Study Adverse Events page.

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EXTRAPYRAMIDAL FINDINGS

INFORMATION NOT OBTAINED ☐

1. Masked facies

   ☐ $_0$ None

   ☐ $_1$ Mild

   ☐ $_2$ Moderate

   ☐ $_3$ Severe

2. Rigidity of upper extremity

   ☐ $_0$ None

   ☐ $_1$ Mild

   ☐ $_2$ Moderate

   ☐ $_3$ Severe

3. Essential tremor

   ☐ $_0$ None

   ☐ $_1$ Mild

   ☐ $_2$ Moderate

   ☐ $_3$ Severe

4. Ambulation

   How long did it take the patient to walk 25 yards? _____

                                                           seconds

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                      First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

	(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0.	5 minutes	815	SU		/
1.	1 minute	816	ST		/
2.	3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date _____/_____/_____
                          MM   DD   YY

Electrocardiogram result ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

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ACCEPTABILITY : CAREGIVER'S RESPONSE ABOUT THE PATCH

INFORMATION NOT OBTAINED ☐

The following question is to be answered by the caregiver.

Based on the experience of applying and wearing this patch, if the patient were prescribed a drug for Alzheimer's disease and was given the choice of this patch or an oral pill given twice daily (assume that both formulations are equally effective), would you (the caregiver):

☐₁ Insist that the patient receive an oral pill

☐₂ Prefer that the patient receive an oral pill

☐₃ Have no preference (neutral) for an oral or patch formulation

☐₄ Prefer that the patient receive a patch

☐₅ Insist that the patient receive a patch

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ACCEPTABILITY : CAREGIVER'S RESPONSE ABOUT THE PATCH

INFORMATION NOT OBTAINED ☐

The following questions are intended to be answered by the caregiver and address the patch's design and wearability. Focus only on the act of wearing and removing the transdermal patch. On each scale below, circle one number (do not circle on the scale between numbers) that best describes your feelings about the patch:

1. The appearance of the patch while being worn is acceptable:

   1   **2**   **3**   **4**   **5**   **6**   **7**

   Strongly   Neutral   Strongly
   Disagree   Agree

2. The size of the patch is acceptable:

   1   **2**   **3**   **4**   **5**   **6**   **7**

   Strongly   Neutral   Strongly
   Disagree   Agree

3. The patches were durable (eg, did not discolor, tear) while being worn:

   1   **2**   **3**   **4**   **5**   **6**   **7**

   Strongly   Neutral   Strongly
   Disagree   Agree

STUDY DRUG THERAPY : DATE OF FINAL DOSE

Date of final dose of study drug   _____/_____/_____
                                    MM   DD   YY

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PATIENT SUMMARY

Patient Initials _____ _____ _____
First   Middle   Last

CHECK ONE <u>PRIMARY</u> REASON FOR ENDING PARTICIPATION IN THE STUDY

☐₁ Protocol completed

☐₃ Adverse event E __ __
             E__ Code

☐₄ Death* E __ __
             E__ Code

> If **# 4** is checked, enter date of death.
>
> Date of Death   ____/_____/____
>   MM   DD   YY

☐₈ Lack of efficacy, patient/caregiver perception
☐₉ Lack of efficacy, physician perception

☐₁₁ Unable to contact patient (lost to follow-up)

☐₁₃ Personal conflict or other patient/caregiver decision _____
                                                        Specify

☐₂₂ Physician decision _____
                      Specify

☐₁₄ Protocol entry criteria not met _____ (Specify number from entry criteria checklist)
                                  Specify

☐₂₄₃ Protocol violation

☐₁₈ Sponsor decision (study or patient discontinued by the Sponsor)

---

* **Contact the Quintiles Drug Safety Unit immediately in event of death.** Obtain a copy of the autopsy report (if autopsy performed) or hospital discharge summary. Forward to Quintiles Drug Safety Unit as soon as possible. Explain circumstances of the death on the Study Summary Comments page.

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COMMENTS : **STUDY SUMMARY**

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

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All information reported for this patient is accurate and complete.

_____ _____/_____/_____
Investigator Signature   MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials _____ _____ _____
              First   Middle   Last

Visit date   _____/_____/_____
                MM   DD   YY

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication page, record new medications the patient has taken since the previous visit and record a stop date for any medication the patient is no longer taking.

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ALZHEIMER'S DISEASE ASSESSMENT SCALE : COGNITIVE with ATTENTION/ CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle Last

1. Word Recall Task   (max = 10)   _____

2. Naming Objects and Fingers
    (refer to 5 categories in manual)   (max = 5)   _____

3. Delayed Word Recall   (max = 10)   _____

4. Commands   (max = 5)   _____

5. Constructional Praxis   (max = 5)   _____

6. Ideational Praxis   (max = 5)   _____

7. Orientation   (max = 8)   _____

8. Word Recognition   (max = 12)   _____

9. Attention/Visual Search Task   (max = 40)   _____

10. Maze Solution   (max = 240) _____ (seconds)

11. Spoken Language Ability   (max = 5)   _____

12. Comprehension of Spoken Language   (max = 5)   _____

13. Word Finding Difficulty in Spontaneous Speech   (max = 5)   _____

14. Recall of Test Instructions   (max = 5)   _____

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 American Journal of Psychiatry 1984;141:1356-64.

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CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First   Middle   Last

Check one box to indicate the extent of change, if any, observed since the initial baseline interview.

☐ $_1$ Marked improvement

☐ $_2$ Moderate improvement

☐ $_3$ Minimal improvement

☐ $_4$ No change

☐ $_5$ Minimal worsening

☐ $_6$ Moderate worsening

☐ $_7$ Marked worsening

The clinical interview-based impression of change scale in this study is from a pilot instrument, the Clinical Global Impression of Change, developed and currently undergoing validity studies by the National Institute on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator), and is in the public domain.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                        First   Middle   Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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Lilly

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

During the past two weeks, did the patient without help or reminder:

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

		Initiation	Planning & Organization	Effective Performance
HYGIENE				
1.	Undertake to wash himself/herself or to take a bath or a shower		▨	▨
2.	Undertake to brush his/her teeth or care for his/her dentures		▨	▨
3.	Decide to care for his/her hair (wash and comb)		▨	▨
4.	Prepare the water, towels, and soap for washing, taking a bath, or a shower	▨		▨
5.	Wash and dry completely all parts of his/her body safely	▨	▨	
6.	Brush his/her teeth or care for his/her dentures appropriately	▨	▨	
7.	Care for his/her hair (wash and comb)	▨	▨	
DRESSING				
8.	Undertake to dress himself/herself		▨	▨
9.	Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)	▨		▨
10.	Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)	▨		▨
11.	Dress himself/herself completely	▨	▨	
12.	Undress himself/herself completely	▨	▨	
CONTINENCE				
13.	Decide to use the toilet at appropriate times		▨	▨
14.	Use the toilet without "accidents"	▨	▨	
EATING				
15.	Decide that he/she needs to eat		▨	▨
16.	Choose appropriate utensils and seasonings when eating	▨		▨
17.	Eat his/her meals at a normal pace and with appropriate manners	▨	▨	
MEAL PREPARATION				
18.	Undertake to prepare a light meal or snack for himself/herself		▨	▨
19.	Adequately plan a light meal or snack (ingredients, cookware)	▨		▨
20.	Prepare or cook a light meal or a snack safely	▨	▨	

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

	SCORING: **Yes = 1** **No = 0** **Not Applicable = 96**	Initiation	Planning & Organization	Effective Performance
TELEPHONING				
21.	Attempt to telephone someone at a suitable time		░	░
22.	Find and dial a telephone number correctly	░		░
23.	Carry out an appropriate telephone conversation	░	░	
24.	Write and convey a telephone message adequately	░	░	
GOING ON AN OUTING				
25.	Undertake to go out (walk, visit, shop) at an appropriate time		░	░
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	░		░
27.	Go out and reach a familiar destination without getting lost	░	░	
28.	Safely take the adequate mode of transportation (car, bus, taxi)	░	░	
29.	Return from the store with the appropriate items	░	░	
FINANCE AND CORRESPONDENCE				
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence		░	░
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	░		░
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	░		░
33.	Handle adequately his/her money (make change)	░	░	
MEDICATIONS				
34.	Decide to take his/her medications at the correct time		░	░
35.	Take his/her medications as prescribed (according to the right dosage)	░	░	
LEISURE AND HOUSEWORK				
36.	Show an interest in leisure activity(ies)		░	░
37.	Take an interest in household chores that he/she used to perform in the past		░	░
38.	Plan and organize adequately household chores that he/she used to perform in the past	░		░
39.	Complete household chores adequately as he/she used to perform in the past	░	░	
40.	Stay safely at home by himself/herself when needed	░	░	

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VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position	
SU = Supine	
ST = Standing	

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0. 5 minutes	815	SU		/
1. 1 minute	816	ST		/
2. 3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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COMMENTS : STUDY SUMMARY

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

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All information reported for this patient is accurate and complete.

_____ _____/_____/_____
        Investigator Signature   MM   DD   YY

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Adverse Event Follow-up | Visit 501
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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                    First   Middle   Last

Visit date   _____/_____/_____
              MM   DD   YY

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new events that occurred since the previous visit and re-evaluate any on-going conditions or events.

On the Concomitant Medication page, record new medications the patient has taken since the previous visit and record a stop date for any medication the patient is no longer taking.

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Adverse Event Follow-up | Visit 501
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ADVERSE EVENT FOLLOW-UP

1. Patient initials   _____ _____ _____
                       First   Middle   Last

2. Primary event causing discontinuation   _____
                                (E _ _ Code from
                                Patient Summary page)

3. Check one PRIMARY reason for ending the ADVERSE EVENT follow-up period

   ☐101 Event resolved | Date resolved ____/_____/____
                               | MM   DD   YY

   ☐102 Laboratory test result returned to acceptable range

   ☐11 Patient is lost to follow-up

   ☐103 Event or condition is stable and not expected to change

   ☐99 Other _____
                         Specify

4. Check one patient outcome

   ☐104 No residual effect

   ☐105 Impairment or disability

   ☐4 Death*

   ☐99 Other _____
                         Specify

---

* **Contact the Quintiles Drug Safety Unit immediately in event of death.** Obtain a copy
   of the autopsy report (if autopsy performed) or hospital discharge summary. Forward to Lilly
   as soon as possible. Explain circumstances of the death on the Adverse Event Follow-Up
   Comments page.

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Adverse Event Follow-up | Visit 501
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COMMENTS **: STUDY SUMMARY**

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

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_____

All information reported for this patient is accurate and complete.

_____   _____/_____/_____
   Investigator Signature   MM   DD   YY

Safety and Efficacy of the Xanomeline
   Transdermal Therapeutic System (TTS) in
   Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

PROCEDURE : MRSI

NOT DONE ☐

Date of MRSI   _____/_____/_____
                   MM   DD   YY

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Addendum Study | Visit 3
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PROCEDURE : MRSI

NOT DONE ☐

Date of MRSI _____/_____/_____
　　　　　　　　MM　　DD　　YY

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PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

NO CONDITIONS OR EVENTS ☐

· List all pre-existing conditions or symptoms present at entry to study.

· List all clinically relevant abnormalities found on the physical exam, ECG, chest x-ray, or Holter monitor.

· List all events that occur during study.

*Serious Codes
1 = Fatal
2 = Life-threatening
3 = Permanently disabling
4 = Hospitalization
5 = Congenital anomaly
6 = Cancer
7 = Overdose
8 = Other reason

* If Event is serious, notify the Quintiles Drug Safety Unit immediately.

Severity Codes
1 = Mild
2 = Moderate
3 = Severe

Evaluate when event stops or at end of patient's participation in study

Code	Description of Condition/Event / COSTART Class Term	Onset Date MM DD YY / Stop Date MM DD YY	Serious* during trial?	Severity of Condition/Event — Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.							Relationship to Study Drug
E01			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E02			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E03			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E04			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E05			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E06			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							
E07			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None 2 = Remote (Unlikely) 3 = Possible 4 = Probable
				Severity							

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PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

Continue listing all pre-existing
conditions and events that occur
during the study.

*Serious Codes
1 = Fatal
2 = Life-threatening
3 = Permanently disabling
4 = Hospitalization
5 = Congenital anomaly
6 = Cancer
7 = Overdose
8 = Other reason

*** If Event is serious,
notify the Quintiles Drug
Safety Unit immediately.**

Severity Codes
1 = Mild
2 = Moderate
3 = Severe

Evaluate when
event stops or at
end of patient's
participation in
study

Code	Description of Condition/Event / COSTART Class Term	Onset Date MM DD YY / Stop Date MM DD YY	Serious* during trial?	Severity of Condition/Event — Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.							Relationship to Study Drug
E08			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None
				Severity							2 = Remote (Unlikely) / 3 = Possible / 4 = Probable
E09			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable
E10			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable
E11			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable
E12			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable
E13			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable
E14			☐ N No If **Yes**, enter Serious Code(s) _____	Visit Number							1 = None / 2 = Remote (Unlikely)
				Severity							3 = Possible / 4 = Probable

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PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS

Continue listing all pre-existing conditions and events that occur during the study.

*Serious Codes
1 = Fatal
2 = Life-threatening
3 = Permanently disabling
4 = Hospitalization
5 = Congenital anomaly
6 = Cancer
7 = Overdose
8 = Other reason

* If Event is serious, notify the Quintiles Drug Safety Unit immediately.

Severity Codes	Evaluate when event stops or at end of patient's participation in study
1 = Mild	
2 = Moderate	
3 = Severe	

Code	Description of Condition/Event / COSTART Class Term	Onset Date MM DD YY / Stop Date MM DD YY	Serious* during trial?	Severity of Condition/Event — Record the onset visit number and *maximum severity* at that visit. **Then** record the *maximum severity* in each subsequent visit **ONLY** if there is a change in severity.							Relationship to Study Drug
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable
E__			☐ N No If **Yes**, enter Serious Code(s) ____	Visit Number							1 = None
											2 = Remote (Unlikely)
				Severity							3 = Possible
											4 = Probable

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CONCOMITANT MEDICATION

NO CONCOMITANT MEDICATIONS ☐

Enter all medications, other than study drug, the patient
is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page.
E__ = Pre-Existing Condition or Event (eg, E01)
or
X1 = Primary study condition
X2 = Prophylaxis or non-therapeutic use

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	IFU
0.								
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								

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CONCOMITANT MEDICATION

Continue entering all medications, other than study drug,
the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page.
E__ = Pre-Existing Condition or Event (eg, E01)
or
X1 = Primary study condition
X2 = Prophylaxis or non-therapeutic use

	Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	IFU
12.								
13.								
14.								
15.								
16.								
17.								
18.								
19.								
20.								
21.								
22.								
23.								

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CONCOMITANT MEDICATION

Continue entering all medications, other than study drug,
the patient is taking at **entry** and **during the study**.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Study Adverse Events page.
E__ = Pre-Existing Condition or Event (eg, E01)
or
X1 = Primary study condition
X2 = Prophylaxis or non-therapeutic use

Brand or Trade Name (Use generic if brand or trade name unknown)	Dose	Unit	Fre-quency	Route	Start Date MM DD YY	Stop Date MM DD YY	IFU

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DOSING CHANGE Visit _____
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STUDY DRUG DOSE CHANGE : **START DATE (12-14 hour patch)**

Start date of the new study drug dosing regimen (12-14 hour patch)   _____/_____/_____

MM   DD   YY

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PATIENT AND VISIT IDENTIFICATION

Patient initials   _____ _____ _____
                      First   Middle   Last

Visit date   _____/_____/_____
                MM   DD   YY

STUDY DRUG : COMPLIANCE

INFORMATION NOT OBTAINED ☐

Since the previous visit, on how many days was
the patient unable to complete the therapy?   _____
                                                days

REMINDER

On the Pre-existing Conditions and Study Adverse Events page, record new
events that occurred since the previous visit and re-evaluate any on-going
conditions or events.

On the Concomitant Medication page, record new medications the patient has
taken since the previous visit and record a stop date for any medication the
patient is no longer taking.

A physical examination must be performed at this visit. Any clinically
significant abnormalities must be listed on the Pre-existing Conditions and
Study Adverse Events page.

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EXTRAPYRAMIDAL FINDINGS

INFORMATION NOT OBTAINED ☐

1. Masked facies

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

2. Rigidity of upper extremity

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

3. Essential tremor

   ☐ 0 None

   ☐ 1 Mild

   ☐ 2 Moderate

   ☐ 3 Severe

4. Ambulation

   How long did it take the patient to walk 25 yards? _____
                                                        seconds

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ALZHEIMER'S DISEASE ASSESSMENT SCALE : COGNITIVE with ATTENTION/ CONCENTRATION TASKS

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

1. Word Recall Task   (max = 10)   _____

2. Naming Objects and Fingers
    (refer to 5 categories in manual)   (max = 5)   _____

3. Delayed Word Recall   (max = 10)   _____

4. Commands   (max = 5)   _____

5. Constructional Praxis   (max = 5)   _____

6. Ideational Praxis   (max = 5)   _____

7. Orientation   (max = 8)   _____

8. Word Recognition   (max = 12)   _____

9. Attention/Visual Search Task   (max = 40)   _____

10. Maze Solution   (max = 240)   _____ (seconds)

11. Spoken Language Ability   (max = 5)   _____

12. Comprehension of Spoken Language   (max = 5)   _____

13. Word Finding Difficulty in Spontaneous Speech (max = 5)   _____

14. Recall of Test Instructions   (max = 5)   _____

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 American Journal of Psychiatry 1984;141:1356-64.

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CLINICIAN'S INTERVIEW-BASED IMPRESSION OF CHANGE (CIBIC+)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                     First   Middle   Last

Check one box to indicate the extent of change, if any, observed since the initial baseline interview.

☐ 1 Marked improvement

☐ 2 Moderate improvement

☐ 3 Minimal improvement

☐ 4 No change

☐ 5 Minimal worsening

☐ 6 Moderate worsening

☐ 7 Marked worsening

The clinical interview-based impression of change scale in this study is from a pilot instrument, the Clinical Global Impression of Change, developed and currently undergoing validity studies by the National Institute on Aging Alzheimer's Disease Study Units Program (1 U01 AG10483; Leon Thal, Principal Investigator), and is in the public domain.

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NEUROPSYCHIATRIC INVENTORY - REVISED (NPI-X)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                     First Middle Last

The screening question (from worksheet) is asked of the caregiver to determine if the behavioral change is present or absent in the patient. If the answer to the screening question is negative (NO) or if the question is not applicable to the patient, circle the appropriate response (Not Applicable [96] or Absent [0]) and proceed to the next screening question without asking the subquestions to determine frequency, severity, and distress.

Item	Not Applicable	Absent	Frequency	Severity	Distress
A. Delusions	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
B. Hallucinations	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
C. Agitation/Agression	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
D. Depression/ Dysphoria	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
E. Anxiety	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
F. Euphoria/Elation	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
G. Apathy/ Indifference	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
H. Disinhibition	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
I. Irritability/Lability	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
J. Aberrant Motor Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
K. Night-Time Behavior	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5
L. Appetite/Eating Change	96	0	1 2 3 4	1 2 3	0 1 2 3 4 5

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
                       First Middle Last

During the past two weeks, did the patient without help or reminder:

SCORING: **Yes = 1**   **No = 0**   **Not Applicable = 96**

	Initiation	Planning & Organization	Effective Performance
HYGIENE			
1. Undertake to wash himself/herself or to take a bath or a shower			
2. Undertake to brush his/her teeth or care for his/her dentures			
3. Decide to care for his/her hair (wash and comb)			
4. Prepare the water, towels, and soap for washing, taking a bath, or a shower			
5. Wash and dry completely all parts of his/her body safely			
6. Brush his/her teeth or care for his/her dentures appropriately			
7. Care for his/her hair (wash and comb)			
DRESSING			
8. Undertake to dress himself/herself			
9. Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)			
10. Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)			
11. Dress himself/herself completely			
12. Undress himself/herself completely			
CONTINENCE			
13. Decide to use the toilet at appropriate times			
14. Use the toilet without "accidents"			
EATING			
15. Decide that he/she needs to eat			
16. Choose appropriate utensils and seasonings when eating			
17. Eat his/her meals at a normal pace and with appropriate manners			
MEAL PREPARATION			
18. Undertake to prepare a light meal or snack for himself/herself			
19. Adequately plan a light meal or snack (ingredients, cookware)			
20. Prepare or cook a light meal or a snack safely			

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DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

	Initiation	Planning & Organization	Effective Performance
SCORING: **Yes = 1** **No = 0** **Not Applicable = 96**			

TELEPHONING

		Initiation	Planning & Organization	Effective Performance
21.	Attempt to telephone someone at a suitable time		▓	▓
22.	Find and dial a telephone number correctly	▓		▓
23.	Carry out an appropriate telephone conversation	▓	▓	
24.	Write and convey a telephone message adequately	▓	▓	

GOING ON AN OUTING

		Initiation	Planning & Organization	Effective Performance
25.	Undertake to go out (walk, visit, shop) at an appropriate time		▓	▓
26.	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▓		▓
27.	Go out and reach a familiar destination without getting lost	▓	▓	
28.	Safely take the adequate mode of transportation (car, bus, taxi)	▓	▓	
29.	Return from the store with the appropriate items	▓	▓	

FINANCE AND CORRESPONDENCE

		Initiation	Planning & Organization	Effective Performance
30.	Show an interest in his/her personal affairs such as his/her finances and written correspondence		▓	▓
31.	Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▓		▓
32.	Adequately organize his/her correspondence with respect to stationery, address, stamps	▓		▓
33.	Handle adequately his/her money (make change)	▓	▓	

MEDICATIONS

		Initiation	Planning & Organization	Effective Performance
34.	Decide to take his/her medications at the correct time		▓	▓
35.	Take his/her medications as prescribed (according to the right dosage)	▓	▓	

LEISURE AND HOUSEWORK

		Initiation	Planning & Organization	Effective Performance
36.	Show an interest in leisure activity(ies)		▓	▓
37.	Take an interest in household chores that he/she used to perform in the past		▓	▓
38.	Plan and organize adequately household chores that he/she used to perform in the past	▓		▓
39.	Complete household chores adequately as he/she used to perform in the past	▓	▓	
40.	Stay safely at home by himself/herself when needed	▓	▓	

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WEIGHT

INFORMATION NOT OBTAINED ☐

Measure with shoes off. Round up or down to the nearest <u>tenth kilogram</u> or <u>tenth pound</u>.

Weight ___ ___ ___ . ___   ☐ kg Kilogram   ☐ lb Pound

VITAL SIGNS : HEART RATE AND BLOOD PRESSURE

INFORMATION NOT OBTAINED ☐

Position
SU = Supine
ST = Standing

NOTE: Blood pressure and pulse must be taken after the patient has been lying down for 5 minutes (supine) and after standing for 1 minute (standing) and 3 minutes.

(DNDE) Reference Time	Timing Code	Position	Heart Rate (bpm)	Blood Pressure (mmHg) Systolic/Diastolic
0. 5 minutes	815	SU		/
1. 1 minute	816	ST		/
2. 3 minutes	817	ST		/

VITAL SIGNS : TEMPERATURE

INFORMATION NOT OBTAINED ☐

Temperature   ___ ___ ___ . ___

Unit of measure   ☐ F Fahrenheit   ☐ C Centigrade

Method   ☐ PO Oral   ☐ R Rectal   ☐ A Axillary   ☐ E Ear   ☐ O Other

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ELECTROCARDIOGRAM

NOT DONE ☐

Electrocardiogram date   _____/_____/_____
                           MM   DD   YY

Electrocardiogram result   ☐ 12 Acceptable   ☐ 13 Not Acceptable

> NOTE: Any clinically relevant change from Visit 1 (baseline) ECG must be recorded on the
>   Pre-existing Conditions and Adverse Events page. Note non-relevant
>   abnormalities in the ECG Comments section below.

COMMENTS : NON-RELEVANT ECG ABNORMALITIES

NO COMMENTS ☐

Print legibly and do not use abbreviations or symbols.

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

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ACCEPTABILITY : CAREGIVER'S RESPONSE ABOUT THE PATCH

INFORMATION NOT OBTAINED ☐

The following question is to be answered by the caregiver.

Based on the experience of applying and wearing this patch, if the patient were prescribed a drug for Alzheimer's disease and was given the choice of this patch or an oral pill given twice daily (assume that both formulations are equally effective), would you (the caregiver):

☐₁ Insist that the patient receive an oral pill

☐₂ Prefer that the patient receive an oral pill

☐₃ Have no preference (neutral) for an oral or patch formulation

☐₄ Prefer that the patient receive a patch

☐₅ Insist that the patient receive a patch

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ACCEPTABILITY : CAREGIVER'S RESPONSE ABOUT THE PATCH

INFORMATION NOT OBTAINED ☐

The following questions are intended to be answered by the caregiver and address the patch's design and wearability. Focus only on the act of wearing and removing the transdermal patch. On each scale below, circle one number (do not circle on the scale between numbers) that best describes your feelings about the patch:

1. The appearance of the patch while being worn is acceptable:

1	**2**	**3**	**4**	**5**	**6**	**7**
Strongly Disagree			Neutral			Strongly Agree

2. The size of the patch is acceptable:

1	**2**	**3**	**4**	**5**	**6**	**7**
Strongly Disagree			Neutral			Strongly Agree

3. The patches were durable (eg, did not discolor, tear) while being worn:

1	**2**	**3**	**4**	**5**	**6**	**7**
Strongly Disagree			Neutral			Strongly Agree

STUDY DRUG THERAPY : DATE OF FINAL DOSE

Date of final dose of study drug   _____/_____/_____
                                    MM   DD   YY

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Safety and Efficacy of the Xanomeline
  Transdermal Therapeutic System (TTS) in
  Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

Early Termination Visit ____
Page 12 of 13

PATIENT SUMMARY

Patient Initials _____ _____ _____
               First   Middle   Last

CHECK ONE <u>PRIMARY</u> REASON FOR ENDING PARTICIPATION IN THE STUDY

☐₁ Protocol completed

☐₃ Adverse event E __ __
                  E__ Code

☐₄ Death* E __ __
            E__ Code

If **# 4** is checked, enter date of death.
Date of Death ____/____/____   MM   DD   YY

☐₈ Lack of efficacy, patient/caregiver perception
☐₉ Lack of efficacy, physician perception

☐₁₁ Unable to contact patient (lost to follow-up)

☐₁₃ Personal conflict or other patient/caregiver decision _____
                                                     Specify

☐₂₂ Physician decision _____
                               Specify

☐₁₄ Protocol entry criteria not met _____ (Specify number from entry criteria checklist)
                                Specify

☐₂₄₃ Protocol violation

☐₁₈ Sponsor decision (study or patient discontinued by the Sponsor)

> * **Contact the Quintiles Drug Safety Unit immediately in event of death.** Obtain a copy of the autopsy report (if autopsy performed) or hospital discharge summary. Forward to Quintiles Drug Safety Unit as soon as possible. Explain circumstances of the death on the Study Summary Comments page.

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Clinical Report Form
Safety and Efficacy of the Xanomeline
  Transdermal Therapeutic System (TTS) in
  Patients with Mild to Moderate Alzheimer's Disease
H2Q-MC-LZZT

Early Termination Visit ___
Page 13 of 13

COMMENTS : STUDY SUMMARY

NO COMMENTS ☐

Repeating information from the clinical report form is discouraged. If the patient is ending participation in the study for any reason other than protocol complete (Reason 1 on Patient Summary page) give a brief description of the circumstances.

Enter comments below. Print legibly and do not use abbreviations or symbols.

_____

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All information reported for this patient is accurate and complete.

_____   _____/_____/_____
Investigator Signature   MM   DD   YY

TRIAL – Adverse Event Reporting Form

Page ___ of ___

International ID No. _____   **DEN Mfr. Control No.** _____

Research Code: **H2Q**   Facility Code: **MC**   Study Code: **LZZT** | Investigator No: | Indication: **Alzheimer's**

Patient Identification
Patient Number _____   **Kit Number** _____

Concomitant Medication(s) Information (Exclude those medications used to treat the event)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Name of Concomitant Medication _____
Dose _____ Unit _____ Frequency_____ Route _____

Start Date ____/_____/____   Stop Date ____/_____/____   Indication for Use _____
　　　　　(DD　MMM　YY)　　　　　　　(DD　MMM　YY)
Duration Drug taken____day(s) week(s) month(s) year(s) (circle one unit)

Comments:

Instructions for Administration of the NPI

The purpose of the Neuropsychiatric Inventory (NPI) is to obtain information on the presence of psychopathology in patients with brain disorders. The NPI was developed for application to patients with Alzheimer's disease and other dementias, but it may be useful in the assessment of behavioral changes in other conditions. Twelve behavioral areas are included in the NPI:

Delusions	Apathy
Hallucinations	Disinhibition
Agitation	Irritability
Depression	Aberrant motor behavior
Anxiety	Night-time behaviors
Euphoria	Appetite and eating changes

The NPI is based on responses from an informed caregiver, preferably one living with the patient. If an informed observer is not available, this instrument cannot be used or must be modified. The interview is best conducted with the caregiver in the absence of the patient to facilitate an open discussion of behaviors that may be difficult to describe with the patient present. Several points should be made when you introduce the NPI interview to the caregiver:

- Purpose of the interview
- Ratings - frequency, severity, distress (described below)
- Answers apply to behaviors that are new since the onset of the disease and have been present for the past two weeks or other defined period
- Questions can usually be answered with "yes" or "no" and responses should be brief

When beginning the inventory, say to the caregiver "These questions are designed to evaluate your [husband's/wife's/etc] behavior. They can usually be answered 'yes' or 'no' so please try to be brief in your responses." If the caregiver lapses into elaborate responses that provide little useful information, they may be reminded of the need to be brief. Some of the issues raised with this are very emotionally disturbing to caregivers and the interviewer should reassure the caregiver that they will discuss the problems in more detail after completion of the inventory.

Questions should be asked exactly as written. Clarification should be provided if the caregiver does not understand the question. Acceptable clarifications are restatements of the questions in alternate terms.

The questions pertain to <u>changes</u> in the patient's behavior that have appeared since the onset of the illness. Behaviors that have been present throughout the patient's life and have not changed in the course of the illness are not scored even if they are abnormal (e.g., anxiety, depression). Behaviors that have been present throughout life but have <u>changed</u> since the illness are scored (e.g., the patient has always been apathetic but there has been a notable increase in apathy during the period of inquiry).

The NPI is typically used to assess changes in the patient's behavior that have appeared in a defined period of time (e.g., in the past four weeks or other defined interval). In some studies, the NPI may be used to address changes occurring in response to treatment or that have changed since the last clinic visit. The time frame of the question would then be revised to reflect this interest in recent changes. Emphasize to the caregiver that the questions pertain to behaviors that have appeared or changed since the onset of the illness. For example, the questions might be phrased "Since he/she began treatment with the new medications . . ." or "Since our last interview . . ."

The screening question is asked to determine if the behavioral change is present or absent. If the answer to the screening question is negative, mark NO and proceed to the next screening question without asking the subquestions. If the answer to the screening question is positive or if there are any

uncertainties in the caregiver's response or any inconsistencies between the response and other information known by the clinician (e.g., the caregiver responds negatively to the euphoria screening question but the patient appears euphoric to the clinician), the category is marked YES and is explored in more depth with the subquestions. If the subquestions confirm the screening question, the severity and frequency of the behavior are determined according to the criteria provided with each behavior. When determining frequency and severity, use the behaviors identified by the subquestions as most aberrant. For example, if the caregiver indicates that resistive behavior is particularly problematic when you are asking the subquestions of the agitation section, then use resistive behavior to prompt judgments regarding the frequency and severity of agitation. If two behaviors are very problematic, use the frequency and severity of both behaviors to score the item. For example, if the patient has two or more types of delusions, then use the severity and frequency of all delusional behaviors to phrase the questions regarding severity and frequency.

In some cases, the caregiver will provide a positive response to the screening question and a negative reply to all subquestions. If this happens, ask the caregiver to expand on why they re-sponded affirmatively to the screen. If they provide information relevant to the behavioral domain but in different terms, the behavior should be scored for severity and frequency as usual. If the original affirmative response was erroneous, leading to a failure to endorse any subquestions, then the behavior is changed to "NO" on the screen.

Some sections such as the questions pertaining to appetite are framed so as to capture whether there is an increase or decrease in the behavior (increased or decreased appetite or weight). If the caregiver answer "yes" to the first member of the paired question (such as has the patient's weight decreased?), do not ask the second question (has the patient's weight increased?) since the answer to the second question is contained in the answer to the first. If the caregiver answers "no" to the first member of the pair of questions, then the second question must be asked.

When determining frequency, say to the person being interviewed "Now I want to find out how often these things [define using description of the behaviors they noted as most problematic on the subquestions] occur. Would you say that they occur less than once per week, about once per week, several times per week but not every day, or essentially every day?" Some behaviors, such as apathy eventually become continuously present, and then "are constantly present" can be substituted for "every day." When determining severity, tell the person being interviewed "Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are mild, moderate, or marked?" Additional descriptors are provided in each section that may be used to help the interviewer clarify each grade of severity. In each case, be sure that the caregiver provides you with a definite answer as to the frequency and severity of the behaviors. Do not guess what you think the caregiver would say based on your discussion. We have found it helpful to provide the caregiver with a piece of paper on which is written the frequency and severity descriptions (less than once per week, about once per week, several times per week and daily or continuously for frequency and mild, moderate, and severe for severity) to allow them to visually see the response alternatives. This also saves the examiner from reiterating the alternatives with each question.

In very impaired patients or patients with special medical circumstances, a set of questions may not be applicable. For example, bed-bound patients may exhibit hallucinations or agitation but could not exhibit aberrant motor behavior. If the clinician or the caregiver believes that the questions are inappropriate, then the section should be marked NA (upper right corner of each section), and no further data are not recorded for the section. Likewise, if the clinician feels that the responses are invalid (e.g., the caregiver did not seem to understand the particular set of questions asked), NA should also be marked.

When each domain is completed and the caregiver has completed the frequency and severity rating, you may want to ask the associated caregiver distress question if your protocol includes the distress assessment. To do this, ask the caregiver how much, if any, "emotional or psychological" distress the behavior he or she just discussed causes him or her (the caregiver). The caregiver must rate their own distress on a five point scale from 0 - no distress, 1 - minimal, 2 - mild,

3 - moderate, 4 - moderately severe, 5 - very severe or extreme. The distress scale of this instrument was developed by Daniel Kaufer, M.D.

<u>Scoring the NPI</u>

<u>Frequency</u> is rated as:

1 - Occasionally - less than once per week
2 - Often - about once per week
3 - Frequently - several times per week but less than every day
4 - Very frequently - daily or essentially continuously present

<u>Severity</u> is rated as:

1 - Mild - produce little distress in the patient
2 - Moderate - more disturbing to the patient but can be redirected by the caregiver
3 - Marked - very disturbing to the patient and difficult to redirect

The score for each domain is: domain score = frequency x severity

<u>Distress</u> is scored as:

0 - no distress
1 - minimal
2 - mild
3 - moderate
4 - moderately severe
5 - very severe to extreme

Thus, for each behavioral domain there are four scores:

• Frequency
• Severity
• Total (frequency x severity)
• Caregiver distress

A <u>total NPI score</u> can be calculated by adding all domain scores together. The distress score is not included in the total NPI score.

<u>Instructional Videotape</u>

An instructional videotape demonstrating the use of the NPI is available through the UCLA Alzheimer's Disease Center, Neuropsychiatric Institute, 740 Westwood Plaza, Los Angeles, California, 90024. The cost of the videotape is $25.00 (subject to change).

<u>Reference</u>
Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308-2314.

A. Delusions

Does the patient have beliefs that you know are not true? For example, insisting that people are try to harm him/her or steal from him/her. Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspicious-ness; I am interested if the patient is <u>convinced</u> that these things are happening to him/her.

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient believe that he/she is in danger - that others are planning to hurt him/her?   _____

2. Does the patient believe that others are stealing from him/her?   _____

3. Does patient believe that his/her spouse is having an affair?   _____

4. Does patient believe that unwelcome guests are living in his/her house?   _____

5. Does the patient believe that his/her spouse or others are not who they claim to be? _____

6. Does the patient believe that his/her house is not his/her home?   _____

7. Does the patient believe that family members plan to abandon him/her?   _____

8. Does the patient believe that television or magazine figures are actually present in the home? [Does he/she try to talk or interact with them?]   _____

9. Does the he/she believe any other unusual things that I haven't asked about?   _____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency: 1.   Occasionally - less than once per week.
                      2.   Often - about once per week.
                      3.   Frequently - several times per week but less than every day.
                      4.   Very frequently - once or more per day.

Severity: 1.   Mild - delusions present but seem harmless and produce little distress in the patient.
                      2.   Moderate - delusions are distressing and disruptive.
                      3.   Marked - delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

Distress: How emotionally distressing do you find this behavior:
                      0.   Not at all
                      1.   Minimally
                      2.   Mildly
                      3.   Moderately
                      4.   Severely
                      5.   Very severely or extremely

B. Hallucinations

Does the patient have hallucinations such as false visions or voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sound, or visions.

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient describe hearing voices or act as if he/she hears voices?   _____

2. Does the patient talk to people who are not there?   _____

3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc)?   _____

4. Does the patient report smelling odors not smelled by others?   _____

5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or toughing him/her?   _____

6. Does the patient describe tastes that are without any known cause?   _____

7. Does the patient describe any other unusual sensory experiences?   _____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency: 1.   Occasionally - less than once per week.
              2.   Often - about once per week.
              3.   Frequently - several times per week but less than every day.
              4.   Very frequently - once or more per day.

Severity: 1.   Mild - hallucinations present but seem harmless and produce little distress in the patient.
             2.   Moderate - hallucinations are distressing and disruptive to the patient.
             3.   Marked - hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior:
               0.   Not at all
               1.   Minimally
               2.   Mildly
               3.   Moderately
               4.   Severely
               5.   Very severely or extremely

C. Agitation/Aggression

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient get upset with those trying to care for him/her or resist activities
    such as bathing or changing clothes?   _____

2. Is the patient stubborn, having to have things his/her way?   _____

3. Is the patient uncooperative, resistive to help from others?   _____

4. Does the patient have any other behaviors that make him hard to handle?   _____

5. Does the patient shout or curse angrily?   _____

6. Does the patient slam doors, kick furniture, throw things?   _____

7. Does the patient attempt to hurt or hit others?   _____

8. Does the patient have any other aggressive or agitated behaviors?   _____

If the screening question is confirmed, determine the frequency and severity of the agitation.

Frequency: 1.   Occasionally - less than once per week.
             2.   Often - about once per week.
             3.   Frequently - several times per week but less than every day.
             4.   Very frequently - once or more per day.

Severity: 1.   Mild - behavior is disruptive but can be managed with redirection or
                  reassurance.
             2.   Moderate - behaviors disruptive and difficult to redirect or control.
             3.   Marked - agitation is very disruptive and a major source of difficulty;
                  there may be a threat of personal harm. Medications are often
                  required.

Distress: How emotionally distressing do you find this behavior:
             0.   Not at all
             1.   Minimally
             2.   Mildly
             3.   Moderately
             4.   Severely
             5.   Very severely or extremely

D. Depression/Dysphoria

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate
    sadness?   _____

2. Does the patient say or act as if he/she is sad or in low spirits?   _____

3. Does the patient put him/herself down or say the he/she feels like a failure?   _____

4. Does the patient say that he/she is a bad person or deserves to be punished?   _____

5. Does the patient seem very discouraged or say that he/she has no future?   _____

6. Does the patient say he/she is a burden to the family or that the family would be
    better off without him/her?   _____

7. Does the patient express a wish for death or talk about killing him/herself?   _____

8. Does the patient show any other signs of depression or sadness?   _____

If the screening question is confirmed, determine the frequency and severity of the depression.

Frequency: 1.   Occasionally - less than once per week.
             2.   Often - about once per week.
             3.   Frequently - several times per week but less than every day.
             4.   Very frequently - once or more per day.

Severity: 1.   Mild - depression is distressing but usually responds to redirection
                  or reassurance.
             2.   Moderate - depression is distressing, depressive symptoms are
                  spontaneously voiced by the patient and difficult to alleviate.
             3.   Marked - depression is very distressing and a major source of
                  suffering for the patient.

Distress: How emotionally distressing do you find this behavior:
             0.   Not at all
             1.   Minimally
             2.   Mildly
             3.   Moderately
             4.   Severely
             5.   Very severely or extremely

E. Anxiety

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1.   Does the patient say that he/she is worried about planned events?   _____

2.   Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense?   _____

3.   Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness?   _____

4.   Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health]   _____

5.   Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds?   _____

6.   Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?]   _____

7.   Does the patient show any other signs of anxiety?   _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency: 1.   Occasionally - less than once per week.
2.   Often - about once per week.
3.   Frequently - several times per week but less than every day.
4.   Very frequently - once or more per day.

Severity: 1.   Mild - anxiety is distressing but usually responds to redirection or reassurance.
2.   Moderate - anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
3.   Marked - anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior:
0.   Not at all
1.   Minimally
2.   Mildly
3.   Moderately
4.   Severely
5.   Very severely or extremely

F. Elation/Euphoria

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and <u>abnormally</u> good mood or finds humor where others do not.

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self?   _____

2. Does the patient find humor and laugh at things that others do not find funny?   _____

3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? _____

4. Does the patient tell jokes or make remarks that have little humor for others but seem funny to him/her?   _____

5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it?   _____

6. Does the patient "talk big" or claim to have more abilities or wealth than is true?   _____

7. Does the patient show any other signs of feeling too good or being too happy?   _____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

<u>Frequency</u>:   1.   Occasionally - less than once per week.
2.   Often - about once per week.
3.   Frequently - several times per week but less than every day.
4.   Very frequently - once or more per day.

<u>Severity</u>:   1.   Mild - elation is notable to friends and family but is not disruptive.
2.   Moderate - elation is notably abnormal.
3.   Marked - elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

<u>Distress</u>:   How emotionally distressing do you find this behavior:
0.   Not at all
1.   Minimally
2.   Mildly
3.   Moderately
4.   Severely
5.   Very severely or extremely

G. Apathy/Indifference

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient seem less spontaneous and less active than usual?   _____

2. Is the patient less likely to initiate a conversation?   _____

3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self?   _____

4. Does the patient contribute less to household chores?   _____

5. Does the patient seem less interested in the activities and plans of others?   _____

6. Has the patient lost interest in friends and family members?   _____

7. Is the patient less enthusiastic about his/her usual interests?   _____

8. Does the patient show any other signs that he/she doesn't care about doing new things?   _____

If the screening question is confirmed, determine the frequency and severity of the apathy/ indifference.

Frequency: 1.   Occasionally - less than once per week.
2.   Often - about once per week.
3.   Frequently - several times per week but less than every day.
4.   Very frequently - once or more per day.

Severity: 1.   Mild - apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
2.   Moderate - apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
3.   Marked - apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior:
0.   Not at all
1.   Minimally
2.   Mildly
3.   Moderately
4.   Severely
5.   Very severely or extremely

H. Disinhibition

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1.   Does the patient act impulsively without appearing to consider the consequences?   _____

2.   Does the patient talk to total strangers as if he/she knew them?   _____

3.   Does the patient say things to people that are insensitive or hurt their feelings?   _____

4.   Does the patient say crude things or make sexual remarks that they would not usually
      have said?   _____

5.   Does the patient talk openly about very personal or private matters not usually
      discussed in public?   _____

6.   Does the patient take liberties or touch or hug others in way that is out of character
      for him/her?   _____

7.   Does the patient show any other signs of loss of control of his/her impulses?   _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency: 1.   Occasionally - less than once per week.
                  2.   Often - about once per week.
                  3.   Frequently - several times per week but less than every day.
                  4.   Very frequently - once or more per day.

Severity: 1.   Mild - disinhibition is notable but usually responds to redirection and
                        guidance.
                  2.   Moderate - disinhibition is very evident and difficult to overcome by the
                        caregiver.
                  3.   Marked - disinhibition usually fails to respond to any intervention by
                        the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior:
                  0.   Not at all
                  1.   Minimally
                  2.   Mildly
                  3.   Moderately
                  4.   Severely
                  5.   Very severely or extremely

I. Irritability/Lability

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1.   Does the patient have a bad temper, flying "off the handle" easily over little things?   _____

2.   Does the patient rapidly change moods from one to another, being fine one minute
      and angry the next?   _____

3.   Does the patient have sudden flashes of anger?   _____

4.   Is the patient impatient, having trouble coping with delays or waiting for planned
      activities?   _____

5.   Is the patient cranky and irritable?   _____

6.   Is the patient argumentative and difficult to get along with?   _____

7.   Does the patient show any other signs of irritability?   _____

If the screening question is confirmed, determine the frequency and severity of the irritability/ lability.

Frequency: 1.   Occasionally - less than once per week.
             2.   Often - about once per week.
             3.   Frequently - several times per week but less than every day.
             4.   Very frequently - once or more per day.

Severity: 1.   Mild - irritability or lability is notable but usually responds to
                  redirection and reassurance.
             2.   Moderate - irritability and lability are very evident and difficult to
                  overcome by the caregiver.
             3.   Marked - irritability and lability are very evident, they usually fail to
                  respond to any intervention by the caregiver, and they are a major
                  source of distress.

Distress: How emotionally distressing do you find this behavior:
             0.   Not at all
             1.   Minimally
             2.   Mildly
             3.   Moderately
             4.   Severely
             5.   Very severely or extremely

J. <u>Aberrant Motor Behavior</u>

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient pace around the house without apparent purpose?   _____

2. Does the patient rummage around opening and unpacking drawers or closets?   _____

3. Does the patient repeatedly put on and take off clothing?   _____

4. Does the patient have repetitive activities or "habits" that he/she performs over and over?   _____

5. Does the patient engage in repetitive activities such as handling buttons, picking wrapping string, etc?   _____

6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?   _____

7. Does the patient do any other activities over and over?   _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

<u>Frequency</u>:   1.   Occasionally - less than once per week.
                2.   Often - about once per week.
                3.   Frequently - several times per week but less than every day.
                4.   Very frequently - once or more per day.

<u>Severity</u>:   1.   Mild - abnormal motor activity is notable but produce little interference with daily routines.
                2.   Moderate - abnormal motor activity is very evident; can be overcome by the caregiver.
                3.   Marked - abnormal motor activity is very evident, it usually fails to respond to any intervention by the caregiver and is are a major source of distress.

<u>Distress</u>:   How emotionally distressing do you find this behavior:
                0.   Not at all
                1.   Minimally
                2.   Mildly
                3.   Moderately
                4.   Severely
                5.   Very severely or extremely

K. Sleep

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Does the patient have difficulty falling asleep?   _____

2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?   _____

3. Does the patient wander, pace, or get involved in inappropriate activities at night?   _____

4. Does the patient awaken you during the night?   _____

5. Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day?   _____

6. Does the patient awaken too early in the morning (earlier that was his/her habit)?   _____

7. Does the patient sleep excessively during the day?   _____

8. Does the patient have any other night-time behaviors that bother you that we haven't talked about?   _____

If the screening question is confirmed, determine the frequency and severity of the night-time behavior disturbance.

Frequency: 1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day.

Severity: 1. Mild - night-time behaviors occur but they are not particularly disruptive.
2. Moderate - night-time behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of night-time behavior may be present.
3. Marked - night-time behaviors occur; several types of night-time behaviors may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior:
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

L. Appetite and eating disorders

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

NO (If no, proceed to the next screening question)   YES (If yes, proceed to subquestions).

1. Has he/she had a loss of appetite?   _____

2. Has he/she had an increase in appetite?   _____

3. Has he/she had a loss of weight?   _____

4. Has he/she gained weight?   _____

5. Has he/she had a change in eating behavior such as putting too much food in his/her
     mouth at once?   _____

6. Has he/she had a change in the kind of food he/she likes such as eating too many
     sweets or other specific types of food?   _____

7. Has he/she developed eating behaviors such as eating exactly the same types of food
     each day or eating the food in exactly the same order?   _____

8. Have there been any other changes in appetite or eating that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency: 1.   Occasionally - less than once per week.
                  2.   Often - about once per week.
                  3.   Frequently - several times per week but less than every day.
                  4.   Very frequently - once or more per day.

Severity: 1.   Mild - changes in appetite or eating are present but have not led to changes
                       in weight and are not disturbing
                  2.   Moderate - changes in appetite or eating are present and cause minor
                       fluctuations in weight.
                  3.   Marked - obvious changes in appetite or eating are present and cause
                       fluctuations in weight, are embarrassing, or otherwise disturb the
                       patient.

Distress: How emotionally distressing do you find this behavior:
                  0.   Not at all
                  1.   Minimally
                  2.   Mildly
                  3.   Moderately
                  4.   Severely
                  5.   Very severely or extremely

Investigator No. _____

Patient No. _____

Visit _____

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

INFORMATION NOT OBTAINED ☐

Clinician's initials _____ _____ _____
First   Middle   Last

During the past two weeks, did the patient without help or reminder:

		Initiation	Planning & Organization	Effective Performance
	SCORING: **Yes = 1** **No = 0** **Not Applicable = 96**			
HYGIENE				
1.	Undertake to wash himself/herself or to take a bath or a shower		�	▓
2.	Undertake to brush his/her teeth or care for his/her dentures		▓	▓
3.	Decide to care for his/her hair (wash and comb)		▓	▓
4.	Prepare the water, towels, and soap for washing, taking a bath, or a shower	▓		▓
5.	Wash and dry completely all parts of his/her body safely	▓		
6.	Brush his/her teeth or care for his/her dentures appropriately	▓		
7.	Care for his/her hair (wash and comb)	▓	▓	
DRESSING				
8.	Undertake to dress himself/herself		▓	▓
9.	Choose appropriate clothing (with regard to the occasion, neatness, the weather, and color combination)	▓		▓
10.	Dress himself/herself in the appropriate order (undergarments, pant/dress, shoes)	▓		
11.	Dress himself/herself completely	▓	▓	
12.	Undress himself/herself completely	▓	▓	
CONTINENCE				
13.	Decide to use the toilet at appropriate times		▓	▓
14.	Use the toilet without "accidents"	▓	▓	
EATING				
15.	Decide that he/she needs to eat		▓	▓
16.	Choose appropriate utensils and seasonings when eating	▓		
17.	Eat his/her meals at a normal pace and with appropriate manners	▓	▓	
MEAL PREPARATION				
18.	Undertake to prepare a light meal or snack for himself/herself		▓	▓
19.	Adequately plan a light meal or snack (ingredients, cookware)	▓		
20.	Prepare or cook a light meal or a snack safely	▓	▓	

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

	Initiation	Planning & Organization	Effective Performance
SCORING: Yes = 1 No = 0 Not Applicable = 96			
TELEPHONING			
21. Attempt to telephone someone at a suitable time	☐	▨	▨
22. Find and dial a telephone number correctly	▨	☐	▨
23. Carry out an appropriate telephone conversation	▨	▨	☐
24. Write and convey a telephone message adequately	▨	▨	☐
GOING ON AN OUTING			
25. Undertake to go out (walk, visit, shop) at an appropriate time	☐	▨	▨
26. Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list	▨	☐	▨
27. Go out and reach a familiar destination without getting lost	▨	▨	☐
28. Safely take the adequate mode of transportation (car, bus, taxi)	▨	▨	☐
29. Return from the store with the appropriate items	▨	▨	☐
FINANCE AND CORRESPONDENCE			
30. Show an interest in his/her personal affairs such as his/her finances and written correspondence	☐	▨	▨
31. Organize his/her finances to pay his/her bills (cheques, bankbook, bills)	▨	☐	▨
32. Adequately organize his/her correspondence with respect to stationery, address, stamps	▨	☐	▨
33. Handle adequately his/her money (make change)	▨	▨	☐
MEDICATIONS			
34. Decide to take his/her medications at the correct time	☐	▨	▨
35. Take his/her medications as prescribed (according to the right dosage)	▨	▨	☐
LEISURE AND HOUSEWORK			
36. Show an interest in leisure activity(ies)	☐	▨	▨
37. Take an interest in household chores that he/she used to perform in the past	☐	▨	▨
38. Plan and organize adequately household chores that he/she used to perform in the past	▨	☐	▨
39. Complete household chores adequately as he/she used to perform in the past	▨	▨	☐
40. Stay safely at home by himself/herself when needed	▨	▨	☐

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Appendix 3.   List of IECs or IRBs

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 4.   List of Investigators and Other Key Personnel Involved in the Design, Conduct, Analysis, and Reporting of the Study

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 5.   Signature of Coordinating Investigator

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 6.   Subject Listing of Batch Numbers for Investigational Product

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 7. Randomization Scheme and Codes

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 8.   Audit Certificates

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 9.   Statistical Analysis Plan

Title:

Statistical Analysis Plan for CDISCPILOT01 – Initial Case Study of the CDISC SDTM/ADaM Pilot Project

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

Authors:

Cathy Barrows, Joel Hoffman, Susan Kenny, Sandy Lei, and Arline Nakanishi for the CDISC SDTM/ADaM Pilot Project Team

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List of Abbreviations

AD	Alzheimer's Disease
ADaM	Analysis Dataset Model Team
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CIBIC+	Video-referenced Clinician's Interview-based Impression of Change
cm^2	centimeters squared – measure of area
CMH	Cochran-Mantel-Haentzel
DAD	Disability Assessment for Dementia
ECG	Electrocardiogram
ET	Early Termination visit
FDA	Food and Drug Administration
ITT	Intent-to-treat
PT	Preferred Term
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MMRM	Mixed-effects Model Repeated-Measure
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (developed criteria for the diagnosis of Alzheimer's disease)
NPI-X	Revised Neuropsychiatric Inventory
RT	Retrieval visit
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TTS	Transdermal Therapeutic System
XAN	Xanomeline

1.   BACKGROUND

1.1.   CDISC SDTM/ADaM Pilot Project

The CDISC SDTM/ADaM Pilot Project team will produce a case study to demonstrate the effective transformation of legacy data into CDISC SDTM domains and ADaM datasets and their associated metadata. The resulting "pilot submission" will be delivered to FDA reviewers for their evaluation in a mock review, assessing whether data submitted to the FDA using the CDISC Standard will meet the needs and expectations of both medical and statistical FDA reviewers.

The pilot submission will include SDTM datasets, analysis datasets, all relevant metadata, analysis results, and an abbreviated report (including only the necessary documentation).

The legacy data being used in CDISCPILOT01 were provided by Eli Lilly and Company (Legacy Sponsor) for the purposes of this pilot project. The data were de-identified and documents were redacted prior to release to the pilot project team.

The submission will not reproduce all of the Legacy Sponsor's analyses and reports. Instead only the more common elements of a submission will be addressed. These will include safety data, the primary outcome, and at least one secondary outcome. A representative set of analyses will be chosen. Deviations from the protocol-specified analyses are described in Appendix 1. Additional variables and flags may be included in the analysis datasets, but may not be used in the analyses included in the report.

1.2.   Description of Clinical Study

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

The study was a prospective, randomized, multi-center (17), double-blind, placebo-controlled, parallel-group study. 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 patients with mild to moderate Alzheimer's disease.

Xanomeline or placebo was administered daily in the morning, with the application of two adhesive patches, one 50 cm^2 in area, the other 25 cm^2 in area. Doses were measured in terms of the xanomeline base, and were 54mg for the 50 cm^2 patch and 27mg for the 25 cm^2 patch. Placebo was identical in appearance to the primary study material. The total doses being compared are therefore 0 (both patches placebo), 54mg (large patch active drug, small patch placebo), and 81mg (both patches active drug). The treatment groups referred to throughout the pilot submission will be "xanomeline high dose," "xanomeline low dose," and "placebo".

Patients were males or females of non-childbearing potential, 50 years of age or older, had probable Alzheimer's disease according to the NINCDS-ADRDA criteria, and an MMSE score of 10 to 23. The duration of treatment was 26 weeks, with 24 weeks of active treatment. A total of 295 patients were randomized into 1 of 3 treatment groups: xanomeline high dose, 97 patients; xanomeline low dose, 98 patients; and placebo, 100 patients; 166 were females and 129 were males.

2. PURPOSE OF THIS ANALYSIS PLAN

This analysis plan describes the analyses to be performed in the context of the first iteration of the CDISC SDTM/ADaM Pilot Submission, CDISCPILOT01. It should be noted that this document is not meant to represent all of the measures assessed or analyses performed in the original study.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

3.1. Study Objective(s)

3.1.1. Primary

The primary objectives of this study are

- To determine if there is a statistically significant relationship (overall Type 1 error rate, $\alpha=.05$) between the change in both the ADAS-Cog (11) and CIBIC+ scores, and drug dose (0, 50 cm^2 [54 mg], and 75 cm^2 [81 mg]).

- To document the safety profile of the xanomeline TTS.

3.1.2. Secondary

A secondary objective of this study is:

- To assess the dose-dependent improvement in behavior. Improved scores on the Revised Neuropsychiatric Inventory (NPI-X) will indicate improvement in these areas.

3.2. Study Endpoint(s)

3.2.1. Primary

- 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

3.2.2.   Secondary

Secondary Efficacy Endpoints

- Alzheimer's Disease Assessment Scale - Cognitive Subscale, total of 11 items [ADAS-Cog (11)] at Weeks 8 and 16
- Video-referenced Clinician's Interview-based Impression of Change (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

3.3.   Statistical Hypotheses

The statistical hypotheses for the 2 primary endpoints are based on the primary analysis, which is a test for dose response. The primary analysis for ADAS-Cog (11) at Week 24 is based on an ANCOVA model, which includes the baseline score, site, and treatment as continuous variable. The statistical hypothesis is:

H_0: b = 0, where b is the coefficient for treatment

H_1: b ≠ 0, where b is the coefficient for treatment
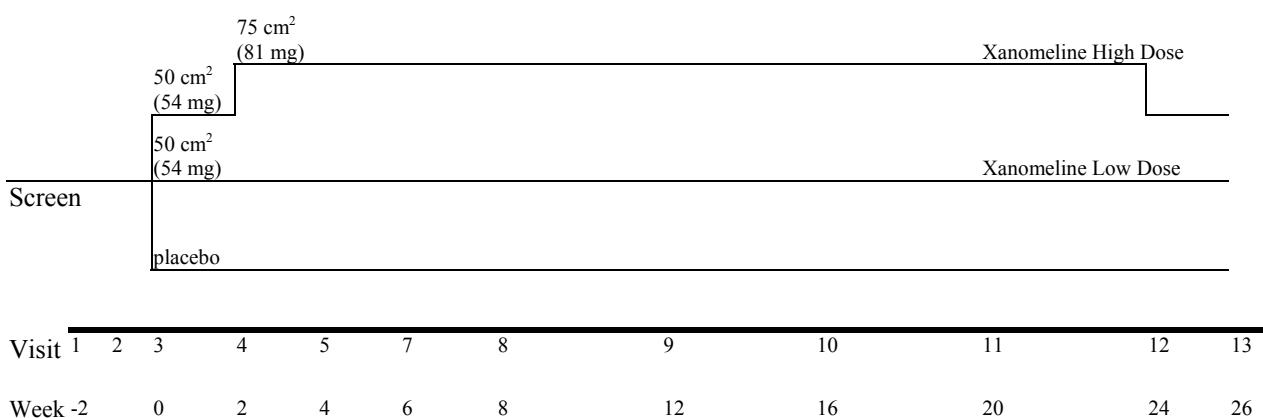
The primary analysis for CIBIC+ at Week 24 is based on an ANOVA model which includes site and treatment as continuous variable. The statistical hypothesis is:

H_0: b = 0, where b is the coefficient for treatment

H_1: b ≠ 0, where b is the coefficient for treatment

4.   STUDY DESIGN

Patients with probable mild to moderate AD will be studied in a randomized, double-blind, parallel (3 arm), placebo-controlled trial of 26 weeks duration. The study will be conducted on an outpatient basis. Approximately 300 patients will be enrolled.

75 cm^2
(81 mg)   Xanomeline High Dose

50 cm^2
(54 mg)

50 cm^2
(54 mg)   Xanomeline Low Dose

Screen

placebo

Visit	1	2	3	4	5	7	8	9	10	11	12	13
Week	-2		0	2	4	6	8	12	16	20	24	26

5.   SAMPLE SIZE CONSIDERATIONS

Approximately 100 patients will be randomized to each of the 3 treatment groups. Previous experience with the oral formulation of xanomeline suggests that this sample size has 90% power to detect a 3.0 mean treatment difference in ADAS-Cog ($p<.05$, two-sided), based on a standard deviation of 6.5. Furthermore, this sample size has 80% power to detect a 0.36 mean treatment difference in CIBIC+ ($p<.05$, two-sided), based on a standard deviation of 0.9.

6.   ANALYSIS POPULATIONS

For this study, the following definitions are used:

Screen Failures   Patients entered into the study are those from whom informed consent for the study has been obtained. Patients entered into the study but not assigned to a treatment group are considered to be screen failures. Demographic data for screen failures will be included in the data tabulation datasets, but not in the analysis datasets or in the analyses.

Randomized   Patients who are enrolled in the study are those who have been assigned to a treatment group. Patients who are entered into the study but fail to meet criteria specified in the protocol for treatment assignment will not be enrolled in the study. Patients are randomly assigned to treatment groups at Week 0 (Visit 3).

ITT Population   All patients randomized

Safety population   All patients randomized and known to have taken at least one dose of randomized drug

Efficacy population   All patients who were randomized and took drug, and have at least 1 post-baseline measure for both ADAS-Cog and CIBIC+

Completers   All patients in the efficacy population who completed their Week 24 visit (Visit 12).

7.   GENERAL CONSIDERATIONS FOR DATA ANALYSES

All statistical tests will be 2-sided with a significance level of 0.05. One-sided p-values will not be reported. Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, minimum, and maximum. Summary statistics for categorical variables will include the frequency and percentage.

7.1.   Multi-center Studies

Sites that enroll fewer than 3 patients in any one treatment group will be grouped together, with a new pooled site identifier assigned for the purpose of analysis. If this combination still results in a treatment group having fewer than 3 patients in any one treatment group, then this group of patients will be combined with the next fewest enrolling site. In the event that there is a tie for fewest-enrolling site, one of these will be chosen at random by a random-number generator.

7.2.   Examination of Subgroups

The effect of gender upon efficacy will be evaluated if sample sizes are sufficient to warrant such analyses.

Covariates for age, race, baseline disease severity as measured by MMSE, and patient education level will be included in analysis datasets as appropriate for exploratory analysis.

7.3.   Multiple Comparisons and Multiplicity

There are 2 primary efficacy endpoints in this study, each of which will be tested at a significance level of 0.05. No adjustments for multiple primary endpoints will be made. Nominal 2-sided p-values will be reported for each primary efficacy endpoint.

The primary analyses for the 2 primary efficacy endpoints will be a test for dose response. Within each primary efficacy endpoint, 3 sets of pairwise comparisons for the 2 active treatment groups and placebo will only be performed if the test for dose response is significant.

8.   DATA HANDLING CONVENTIONS

"End of treatment" will refer to the subject's Week 24 visit or early termination visit. "End of study" will refer to the subject's Week 26 visit or early termination visit.

8.1.   Early Termination and Missing Data

If possible, data for subjects who terminated the study early will be collected at the scheduled Week 24 visit.

Laboratory values collected after the discontinuation of study drug will be used. The assessment date will be compared with the last dose of study drug to determine if the assessment was made within the defined washout period and a flag will be set to indicate this status.

Missing postbaseline efficacy values will be imputed using last observation carried forward (LOCF). Missing baseline values and missing safety data will not be imputed. For the efficacy data, the last observation carried forward will be based on the targeted assessments (i.e. those assigned to be the analyzable assessment based on the assessment windows).

8.2.   Assessment Windows

In general, assessments will be assigned to visits as collected on the CRFs, and will disregard the actual date of the assessment. For example, if an assessment is recorded on the Visit 10 CRF page, the assessment will be assigned to Week 16 (Visit 10).

The ADAS-Cog (11), CIBIC+, and NPI-X assessments will also be assigned to visits based on the actual visit dates, as will laboratory assessments. Actual visit days will be determined relative to the date of randomization, using the algorithm {day = visit date – randomization date}. If multiple assessments fall into the same visit window (windows defined in following table), then the assessment closest to the target day will be selected. [Note that retrieval visits (visit number 201) are included for the purpose of selecting assessments for the week 24 visit window.] If two assessments are equidistant from the target day, then the assessment prior to the target day will be selected. In situations where imputation of missing values is also involved, imputation will use the targeted assessments within the windows.

Variable	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)	Target Time Point (Day)
ADAS-Cog CIBIC+	3	Baseline	≤ 1	1
	8	Week 8	2-84	56
	10	Week 16	85-140	112
	12	Week 24	>140	168
NPI-X	3	Baseline	≤ 1	1
	4	Week 2	2-21	14
	5	Week 4	22-35	28
	7	Week 6	36-49	42
	8	Week 8	50-63	56
	8.1	Week 10 (Tel)	64-77	70
	9	Week 12	78-91	84
	9.1	Week 14 (Tel)	92-105	98
	10	Week 16	106-119	112
	10.1	Week 18 (Tel)	120-133	126
	11	Week 20	134-147	140
	11.1	Week 22 (Tel)	148-161	154
	12	Week 24	162-175	168
	13	Week 26	>175	182

8.3.   Laboratory Data

Multiple laboratory assessments within visit/week windows may be collected. In part, this will be a function of safety monitoring procedures as described in the protocol. Additional and unscheduled labs may also be collected for other reasons. Only planned laboratory values collected at scheduled visits are used for analysis. Additional lab values will be included in datasets, but not incorporated into analyses. A flag will be set to indicate the last on-treatment (prior to or at week 24) observation for each lab parameter.

A change from baseline laboratory value will be calculated as the difference between the baseline lab value and the endpoint value (i.e., the value at the specified visit) and the end of treatment observation.

In addition, each laboratory value, including the baseline value, will be categorized with reference to the lab normal range as
- "L" - less than or equal to the lower limit of normal
- "N" – Greater than the Lower Limit of Normal and less than the Upper Limit of Normal
- "H" – Greater than or equal to the Upper Limit of Normal.

Laboratory values will be assigned a flag of abnormal (high or low) if the value is outside the threshold range (defined as significantly beyond the normal range, i.e., >1.5*ULN or <.5*LLN) or if the value is significantly different from the value observed at the preceding scheduled visit (i.e., absolute value of the change from previous value is larger than the 50% of the normal range, ULN-LLN). In addition, the ratio of the value to its LLN (i.e., value/LLN) and to its ULN (i.e., value/ULN) will be calculated for inclusion in the datasets, but not analyzed. These ratios will allow a quick searching for subjects with values greater than 1.5*ULN, for example, without the use of additional flags.

A separate analysis dataset will be provided containing the lab parameters needed for the assessment of Hy's Law. An abnormal flag will be assigned to indicate whether a subject meets the criteria for a modified Hy's Law assessment of liver function, defined as:
1.   Transaminase (SGPT/ALT or SGOT/AST) elevations (i.e., >1.5*ULN) and
2.   Bilirubin elevated to greater than 1.5*ULN.

8.4.   Values of Clinical Concern

8.4.1.   Laboratory Values

Laboratory values will be assigned a flag of abnormal if the value is significantly beyond the normal range or if the value is significantly different from the proceeding value.

In addition, elevated liver function values will be used to trigger retesting and possible discontinuation of study drug as described in the protocol. These values of clinical concern are:
- Patients with ALT/SGPT levels >120 IU

- Patients with ALT/SGPT values >400 IU, or alternatively, an elevated ALT/SGPT accompanied by GGT and/or ALP values >500 IU

9.   STUDY POPULATION

9.1.   Disposition of Subjects

The number of subjects randomized, number of subjects in the ITT population, number of subjects in the safety population and number of subjects in the efficacy population will be summarized by treatment group. The number and percentage of subjects who complete the study as well as subjects who withdraw prematurely from the study will be displayed. The reasons for early termination will be summarized.

Fisher's exact test will be used to analyze 3 reasons for study discontinuation (protocol completed, lack of efficacy, and adverse event).

9.2.   Demographic and Baseline Characteristics

The following will be summarized by treatment group and across all treatment groups.

- Age
- Age category (<65, 65-80, >80)
- Sex
- Race
- Mini-Mental State
- Duration of disease [computed as months between date of Week -2 (Visit 1) and date of onset of the first definite symptoms of Alzheimer's Disease]
- Years of education
- Weight, height, BMI at Baseline (Visit 3 for weight and BMI, Visit 1 for height)
- BMI category (BMI<25, BMI 25-<30, BMI>=30)

The treatment groups will be compared by analysis of variance (ANOVA) for continuous variables and by Pearson's chi-square test for categorical variables. Note that because patients are randomized to 1 of the 3 treatment groups, any statistically significant treatment group differences are by definition a Type I error; however, the resulting p-values will be used as another descriptive statistic to help focus possible additional analyses (for example, analysis of covariance, subset analyses) on those factors that are most imbalanced (that is, that have the smallest p-values).

Baseline comparisons across treatment groups for the Mini-Mental State Examination (MMSE) will be made using analysis of variance with treatment and site as main effects.

9.3.   Treatment Compliance

Treatment compliance will not be provided.

10.   EFFICACY ANALYSES

Refer to Section 15.1 (Deviations from Protocol-Specified Efficacy Analyses) for a description of how these analyses differ from the protocol-specified efficacy analyses.

A key difference from the protocol is that efficacy assessments are considered valid even if they occur while off study drug.

10.1.   Primary Efficacy Endpoints

10.1.1.   ADAS-COG (11)

The primary analysis of the ADAS-Cog (11) at Week 24 will use the efficacy population with LOCF imputation for any missing values at Week 24. A secondary analysis will be performed for the Week 24 endpoint using the completers subset using observed data. For each of these analyses, an ANCOVA model will be used with the baseline score, site, and treatment included as independent variables. Treatment will be included as a continuous variable, and results for a test of dose response will be produced. Interaction terms will not be investigated. If the test for dose response is statistically significant, pairwise comparisons among the 3 groups will be performed and evaluated at a significance level of 0.05.

Summary statistics will be generated for each visit including baseline using the efficacy population with LOCF imputation. The visits for ADAS-Cog (11) are baseline (Week 0), Week 8, Week 16, and Week 24.

A supportive analysis for the ADAS-Cog (11) will use a likelihood-based repeated measures (MMRM) analysis. In this analysis for the change from baseline in the ADAS-Cog (11) at Week 24, the independent variables included in the model are the fixed, categorical effects of treatment, site, time (week), and treatment by time interaction along with the continuous effects of baseline ADAS-Cog (11) score and baseline ADAS-Cog (11) score by time interaction. Barring a computational singularity, an unstructured covariance matrix will be used to model the within-subject errors in the MMRM analysis. The unstructured covariance matrix is chosen to allow the analysis to be unconstrained by the structure of the covariance. If there is any computational singularity, a Toeplitz covariance matrix will be used. The Toeplitz covariance structure provides reasonable flexibility in estimating correlation between visits.

Additional details regarding scoring and methods for handling missing data for ADAS-Cog (11) are in Appendix 1 of this analysis plan.

10.1.2.   CIBIC+

The primary analysis of CIBIC+ at Week 24 will use the efficacy population with LOCF imputation for any missing values at Week 24. For this endpoint, an ANOVA model will be used with site and treatment included as independent variables. Interaction terms will not be investigated. Treatment will be included as a continuous variable, and results for a test of dose response will be produced. If the test for dose response is statistically significant, pairwise comparisons among the 3 groups will be performed and evaluated at a significance level of 0.05.

Summary statistics will be generated for each visit using the efficacy population with LOCF imputation. The visits for CIBIC+ are Week 8, Week 16, and Week 24.

Additional details regarding scoring for CIBIC+ are in Appendix 1 of this analysis plan.

10.2.   Secondary Efficacy Endpoints

10.2.1.   NPI-X

The primary analysis of mean NPI-X total score from Week 4 to Week 24 will use the efficacy population. This endpoint will be calculated as the mean of all available total scores between Weeks 4 and 24, inclusive. For this endpoint, an ANCOVA model will be used with the baseline score, site, and treatment included as independent variables. Interaction terms will not be investigated. Treatment will be included as a continuous variable, and results for a test of dose response will be produced. If the test for dose response is statistically significant, pairwise comparisons among the 3 groups will be performed and evaluated at a significance level of 0.05.

The visits for NPI-X are baseline (Week 0), Week 2, Week 4, Week 6, Week 8, Week 10 (telephone), Week 12, Week 14 (telephone), Week 16, Week 18 (telephone), Week 20, Week 22 (telephone), Week 24, Week 26.

Additional details regarding scoring and methods for handling missing data for NPI-X are in Appendix 1 of this analysis plan.

11.   SAFETY ANALYSES

11.1.   Extent of Exposure

Average daily dose and cumulative dose at end of study (Week 26 or early termination) will be computed for each subject. Summary statistics will be computed for each of the above quantities for each treatment group.

11.2.   Adverse Events

For this submission, the adverse events will be recoded according to MedDRA. Treatment emergent adverse events will be cross-tabulated by System Organ Class (SOC)

and preferred term (PT). Please refer to Appendix 15.5 for additional information about the MedDRA coding. The incidence of treatment emergent events grouped under preferred terms for each active treatment will be compared to placebo using Fisher's exact test. Treatment emergent adverse events are defined relative to the date of first dose [Week 0 (Visit 3) unless indicated otherwise] as

- events with a start date that is equal to or greater than the date of first dose

- events that start prior to the date of first dose and worsen after that date

- events that start and resolve prior to the date of first dose, but then recur after that the date of first dose.

If the recording of an adverse event start date is not complete, imputation of the start date will be done in a conservative manner. Adverse events will be considered treatment emergent if the year and/or the month is the same as the treatment start year and month. In the case of a completely missing adverse event start date, the start date will be imputed as the day of first dose. No imputation of adverse events dates where the partial date clearly indicates a start prior to the beginning of treatment will be done.

Due to the formulation of the clinical path, it is anticipated that there may be an increase in adverse events that are associated with the application of the skin path. For this reason, additional analysis of dermatological adverse events will be conducted. A category of special events will be created to identify the events that are considered dermatological events. These events will be determined by the medical review of blinded coded adverse event terms and all preferred terms that are considered to be dermatologic in nature, such as rash, pruritus, or dermatitis, will be flagged as adverse events of special interest. A complete list of preferred terms that are considered to be dermatologic events will be provided in the final analysis. The time to the first dermatological event will be compared across the treatment groups using Kaplan-Meier methods. Graphical displays of the survival curves will be presented.

11.3.   Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized by SOC and PT. Incidence of SAEs will be compared between active drug groups and placebo, again using Fisher's exact test.

11.4.   Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

For this submission, no formal summarization of adverse events leading to discontinuation or withdrawal from the study will be conducted. The analysis data will provide variables to identify these adverse events.

11.5.   Clinical Laboratory Evaluations

Hematology, and clinical chemistry will be summarized for Baseline and Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 26 (Visits 1, 4, 5, 7, 8, 9, 10, 11, 12, and 13, respectively). Urinalysis and other lab data will not be summarized, but will be included in the tabulation datasets. The baseline values will be those collected at Week -2 (Visit 1).

Four assessments of abnormality will be identified for each laboratory analyte, as described in Section 8.4.1:
- Values outside the normal range
- Values significantly beyond the normal range (i.e., outside the threshold range)
- Values differing significantly from values at the previous scheduled visit,
- Abnormal values as defined by Hy's Law

The number of subjects with no abnormal measure during treatment and those with at least one abnormal measure during treatment will be summarized for each lab analyte. Two tables will be provided – one defining abnormal as beyond normal range (i.e, below LLN or above ULN) and the other defining abnormal as a clinically significant change from the previous visit. Fisher's exact test will be 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 will be provided. The data will be summarized using sets of 3x3 matrices comparing baseline and on drug categorization for each treatment group for each week for each laboratory analyte.

Shift tables summarizing whether or not a subject's status changed from baseline during the treatment period will be provided for changes based on threshold ranges and changes based on Hy's Law. In these tables a subject will be categorized as normal or abnormal (i.e., outside the threshold range) at baseline. During the treatment phase, the most extreme value will be used to categorize a patient as normal or abnormal during the treatment phase. The shift table will show the number of patients whose on treatment categorization was the same or shifted from the baseline categorization. The treatment perod is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12). A Cochran-Mantel-Haenszel (CMH) test, stratifying by status at baseline, will be performed.

11.6.   Other Safety Measures

Vital sign data (blood pressure supine, blood pressure standing 1 minute, blood pressure standing 3 minutes, heart rate supine, heart rate standing 1 minute, and heart rate standing 3 minutes) at baseline and Week 24 and end of treatment (last visit on or before Week 24 visit) will be summarized by treatment group. Change from baseline will also be summarized.

Weight data at baseline and Week 24 (with and without including early terminations) will be summarized by treatment group. Change from baseline will also be summarized.

The concomitant medication data will be coded using a publicly available sample of WHO Drug. Drugs not matching those in the sample will be considered "uncoded" for the purposes of this submission. The number and percent of subjects receiving each concomitant medication will be summarized. Concomitant medications will be reported by Body System and ingredient. Medications will be sorted in descending order of total incidence across treatment groups for the Body System and in descending order of total incidence for the ingredient within each Body System. If the total incidence for any two or more ingredients is equal, the events will be presented in alphabetical order.

12.   REFERENCES

13.   ATTACHMENTS

13.1.   Table of Contents for Data Display Specifications

13.1.1.   Tables

1.   Summary of Populations (Template 1)

2.   Summary of End of Study Data (Template 2)

3.   Summary of Demographic and Baseline Characteristics (Template 3)

4.   Summary of Number of Subjects by Site (Template 4)

5.   Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 – LOCF (Template 5)

6.   Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 – LOCF (Template 6)

7.   ADAS Cog (11) - Change from Baseline to Week 8 – LOCF (Template 5)

8.   CIBIC+ - Summary at Week 8 – LOCF (Template 6)

9.   ADAS Cog (11) - Change from Baseline to Week 16 – LOCF (Template 5)

10.   CIBIC+ - Summary at Week 16 – LOCF (Template 6)

11.   ADAS Cog (11) - Change from Baseline to Week 24 – Completers at Week 24 - Observed Cases-Windowed (Template 7)

12.   ADAS Cog (11) - Change from Baseline to Week 24 in Male Subjects – LOCF (Template 8)

13.   ADAS Cog (11) - Change from Baseline to Week 24 in Female Subjects – LOCF (Template 8)

14.   ADAS Cog (11) - Mean and Mean Change from Baseline over Time (Template 9)

15.   ADAS Cog (11) – Repeated Measures Analysis of Change from Baseline to Week 24 (Template 10)

16.   Mean NPI-X Total Score from Week 4 through Week 24 – Windowed (Template 11)

17.   Summary of Planned Exposure to Study Drug, as of End of Study (Template 12)

18.   Incidence of Treatment Emergent Adverse Events by Treatment Group (Template 13)

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20.   Summary Statistics for Continuous Laboratory Values (Template 15)

21.   Frequency of Normal and Abnormal (Beyond Normal Range) Laboratory Values During Treatment (Template 16)

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23.   Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit (Template 18)

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26.   Summary of Vital Signs at Baseline and End of Treatment (Template 21)

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29.   Summary of Concomitant Medications (Number of Subjects) **(Template 24)**

13.1.2.   Figures

1.   Time to First Dermatological Event by Treatment Group **(Figure 1)**

13.1.3.   General Comments for Data Displays

General programming comments: use font size 10.

Note that the templates that follow are for example only. Appropriate changes should be made to titles, as listed in Section 13.1.

13.2.   Templates for Data Displays

On following pages.

Population: All Subjects

Template 1

Summary of Populations

Population	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)	Total (N=xxx)
Intent-To-Treat (ITT)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Safety	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Efficacy	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Completer Week 24	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Complete Study	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

NOTE: N in column headers represents number of subjects entered in study (i.e., signed informed consent). The ITT population includes all subjects randomized. The Safety population includes all randomized subjects known to have taken at least one dose of randomized study drug. The Efficacy population includes all subjects in the safety population who also have at least one post-baseline ADAS-Cog and CIBIC+ assessment.

Population: Intent-to-Treat

Template 2
Summary of End of Study Data

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)	Total (N=xxx)	p-value[1]
Completion Status					
Completed Week 24	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	0.xxx
Early Termination (prior to Week 24)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Missing	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Reason for Early Termination (prior to Week 24)					
Adverse event	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	0.xxx
Death	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Lack of efficacy [2]	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	0.xxx
Lost to follow-up	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Subject decided to withdraw	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Physician decided to withdraw subject	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Protocol criteria not met	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Protocol violation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Sponsor decision	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Missing	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	

[1] Fisher's exact test.
[2] Based on either patient/caregiver perception or physician perception.

Population: Intent-to-Treat

Template 3
Summary of Demographic and Baseline Characteristics

		Placebo (N=100)	Xanomeline Low Dose (N=100)	Xanomeline High Dose (N=100)	Total (N=300)	p-value [1]
Age (y)	n	xx	xx	xx	xx	
	Mean	xx.x	xx.x	xx.x	xx.x	0.xxx
	SD	x.xx	x.xx	x.xx	x.xx	
	Median	xx.x	xx.x	xx.x	xx.x	
	Min.	xx.x	xx.x	xx.x	xx.x	
	Max.	xx.x	xx.x	xx.x	xx.x	
	<65 yrs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	0.xxx
	65-80 yrs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	>80 yrs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Sex	n	xxx	xxx	xxx	xxx	0.xxx
	Female	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	Male	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Origin	n	xxx	xxx	xxx	xxx	0.xxx
	Black	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	White	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	…					

Also summarize: MMSE, Duration of disease (cont. and as <12 months, >=12 months), Years of education, Baseline Weight, Baseline Height, Baseline BMI (cont. and as normal(<25), overweight(25-<30), obese(>=30))
[1] P-values are results of ANOVA treatment group comparisons for continuous variables and Pearson's chi-square test for categorical variables.
NOTE: Duration of disease is computed as months between date of enrollment and date of onset of the first definite symptoms of Alzheimer's disease.

Population: All Subjects
Template 4
Summary of Number of Subjects by Site

		Placebo (N=xxx)			Xanomeline Low Dose (N=xxx)			Xanomeline High Dose (N=xxx)			Total (N=xxx)		
Pooled Id	Site Id	ITT	Eff	Com	ITT	Eff	Com	ITT	Eff	Com	ITT	Eff	Com
xxxxxx	xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

Note: ITT: Number of subjects in the ITT population, Eff: Number of subjects in the Efficacy population; Com: Number of subjects completing Week 24

Population: Efficacy

Template 5
ADAS Cog (11) - Change from Baseline to Week xx - LOCF

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Week xx			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Change from Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
P-value(Dose Response) [1][2]			x.xxx
P-value(Xan - Placebo) [1][3]		x.xxx	x.xxx
Diff. of LS Means (SE)		xx.x(x.xx)	xx.x(x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
P-value(Xan High - Xan Low) [1][3]			x.xxx
Diff. of LS Means (SE)			xx.x(x.xx)
95% CI			(xx.xx;xx.xx)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site as factors, and baseline ADAS Cog (11) value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Population: Efficacy

Template 6
CIBIC+ - Summary at Week xx - LOCF

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Week xx			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
P-value(Dose Response) [1][2]			x.xxx
P-value(Xan - Placebo) [1][3]		x.xxx	x.xxx
Diff. of LS Means (SE)		xx.x(x.xx)	xx.x(x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
P-value(Xan High - Xan Low) [1][3]			x.xxx
Diff. of LS Means (SE)			xx.x(x.xx)
95% CI			(xx.xx;xx.xx)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site as factors.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Population: Completers
Template 7

ADAS Cog (11) - Change from Baseline to Week 24 – Completers at Week 24 - Observed Cases-Windowed

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Week 24			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Change from Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
P-value(Dose Response) [1][2]			x.xxx
P-value(Xan – Placebo) [1][3]		x.xxx	x.xxx
Diff. of LS Means (SE)		xx.x(x.xx)	xx.x(x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
P-value(Xan High – Xan Low) [1][3]			x.xxx
Diff. of LS Means (SE)			xx.x(x.xx)
95% CI			(xx.xx;xx.xx)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site as factors, and baseline ADAS Cog (11) value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Population: Efficacy
Template 8
ADAS Cog (11) - Change from Baseline to Week 24 in Male Subjects – LOCF

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Week 24			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Change from Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
P-value(Dose Response) [1][2]			x.xxx
P-value(Xan - Placebo) [1][3]		x.xxx	x.xxx
Diff. of LS Means (SE)		xx.x(x.xx)	xx.x(x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
P-value(Xan High – Xan Low) [1][3]			x.xxx
Diff. of LS Means (SE)			xx.x(x.xx)
95% CI			(xx.xx;xx.xx)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site as factors, and baseline ADAS Cog (11) value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Population: Efficacy

Template 9
ADAS Cog (11) – Mean and Mean Change from Baseline over Time

								Bsln	Change from Bsln					
		N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SD	Med	Min	Max
Placebo	Bsln	xxx	x.xx	x.xxx	x.xx	x.x	x.x							
	Wk 8(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 8 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
Xan Low	Bsln	xxx	x.xx	x.xxx	x.xx	x.x	x.x							
	Wk 8(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 8 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
Xan High	Bsln	xxx	x.xx	x.xxx	x.xx	x.x	x.x							
	Wk 8(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24(Windowed)	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 8 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 16 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x
	Wk 24 LOCF	xxx	x.xx	x.xxx	x.xx	x.x	x.x	x.xx (x.xxx)	xxx	x.xx	x.xxx	x.xx	x.x	x.x

Population: Efficacy
Template 10
ADAS Cog (11) – Repeated Measures Analysis of Change from Baseline to Week 24

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
LS Means (SE)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
p-value (Xan – placebo)		x.xxx	x.xxx
Diff of LS Means (SE)		xx.x (x.xx)	xx.x (x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
p-value (Xan High – Xan Low)			x.xxx
Diff of LS Means (SE)			xx.x (x.xx)
95% CI			(xx.xx;xx.xx)

Note: The change from baseline is calculated as the post-baseline score minus the baseline score. The covariates included in the MMRM model are treatment, site, time and treatment by time interaction, baseline ADAS-Cog (11) score, and baseline ADAS-Cog (11) score by time interaction.

Population: Efficacy

Template 11
Mean NPI-X Total Score from Week 4 through Week 24 - Windowed

	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Baseline			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
Mean of Weeks 4-24			
N	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (Range)	xx.x (xx;xxx)	xx.x (xx;xxx)	xx.x (xx;xxx)
P-value(Dose Response) [1][2]			x.xxx
P-value(Xan - Placebo) [1][3]		x.xxx	x.xxx
Diff. of LS Means (SE)		xx.x(x.xx)	xx.x(x.xx)
95% CI		(xx.xx;xx.xx)	(xx.xx;xx.xx)
P-value(Xan High - Xan Low) [1][3]			x.xxx
Diff. of LS Means (SE)			xx.x(x.xx)
95% CI			(xx.xx;xx.xx)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site as factors, and baseline NPI-X value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Population: Safety
Template 12
Summary of Planned Exposure to Study Drug, as of End of Study

		Completers at Week 24			Safety Population [1]		
		Placebo (N=100)	Xanomeline Low Dose (N=100)	Xanomeline High Dose (N=100)	Placebo (N=100)	Xanomeline Low Dose (N=100)	Xanomeline High Dose (N=100)
Average daily dose (mg)	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Max.	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Cumulative dose at end of study [2]	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min.	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Max.	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

[1] Includes completers and early terminations.
[2] End of Study refers to Week 26/Early Termination.

Population: Safety

Template 13
Incidence of Treatment Emergent Adverse Events by Treatment Group

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=xxx) n (%)	Total Events	Xanomeline Low Dose (N=xxx) n (%)	Total Events	Xanomeline High Dose (N=xxx) n (%)	Total Events	Placebo vs. Xan Low Dose p-value[1]	Placebo vs. Xan High Dose p-value[1]
Subjects with at least one AE	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Cardiac Disorders								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Hypertension	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Palpitation	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc..	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Infections and Infestations								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Cold, Common	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Infections	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc…	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Nervous System Disorders								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc…	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx

Note: Treatment emergent events are defined as events which start or worsen or recur on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group.
Note: Total Events represent the total number of times an event was recorded within each treatment group.

Population: Safety

Template 14
Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

SYSTEM ORGAN CLASS PREFERRED TERM	Placebo (N=xxx) n (%)	Total Events	Xanomeline Low Dose (N=xxx) n (%)	Total Events	Xanomeline High Dose (N=xxx) n (%)	Total Events	Placebo vs. Xan Low Dose p-value[1]	Placebo vs. Xan High Dose p-value[1]
Subjects with at least one AE	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Cardiac Disorders								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Hypertension	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Palpitation	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc..	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Infections and Infestations								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Cold, Common	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Infections	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc…	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
Nervous System Disorders								
At Least One Event	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx
etc…	xx (xx%)	xxx	xx (xx%)	xxx	xx (xx%)	xxx	0.xxx	0.xxx

Note: Treatment emergent events are defined as events which start or worsen or recur on or after the start of treatment.
Note: Adverse events are coded using MedDRA.
Note: Percentages are based on the number of subjects in the safety population within each treatment group.
Note: P-values are based on Fisher's Exact test for the comparison of placebo versus each active treatment group.
Note: Total Events represent the total number of times an event was recorded within each treatment group.

Population: Safety

Template 15
Summary Statistics for Continuous Laboratory Values

Hemoglobin

| | | --------Placebo--------- | | | ------Xanomeline Low------ | | | -----Xanomeline High----- |
| | | | Change from Bsln | | | | Change from Bsln | | | | Change from Bsln |
Week	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
Bsln	xxx	x.x(x.xx)		xxx	x.x(x.xx)		xxx	x.x(x.xx)	
2	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
4	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
6	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
8	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
12	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
16	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
20	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
24	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
26	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)	xxx	x.x(x.xx)	x.x(x.xx)
End [1]									

[1] Last observed value while on treatment (prior to or at Week 24).

Repeat for for each of the continuous lab tests hematology and chemistry analyte.

Population: Safety

Template 16

Frequency of Normal and Abnormal (Beyond Normal Range) Laboratory Values during Treatment

Lab Analyte	Placebo (N=xxx)			Xan. Low (N=xxx)			Xan. High (N=xxx)			p-val [1]
	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	
Hematology										
Hemoglobin	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx
Hematocrit	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx
…										
Chemistry										
Sodium	xx (xx%)	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	x.xxx
Potassium	xx (xx%)	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	x.xxx
…										

Note: The summary reflects one observation per patient with a patient categorized as low or high if any
scheduled lab assessment was considered to be abnormally low or abnormally high based on Normal Range
[1] Fisher's exact test

Population: Safety

Template 17
Frequency of Normal and Abnormal (Clinically Significant Change from Previous Visit)
Laboratory Values during Treatment

Lab Analyte	Placebo (N=xxx) Low n (%)	Normal n (%)	High n (%)	Xan. Low (N=xxx) Low n (%)	Normal n (%)	High n (%)	Xan. High (N=xxx) Low n (%)	Normal n (%)	High n (%)	p-val [1]
Hematology										
Hemoglobin	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx
Hematocrit	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	x.xxx
…										
Chemistry										
Sodium	xx (xx%)	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	x.xxx
Potassium	xx (xx%)	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	xxx	xx (xx%)	xx (xx%)	x.xxx
…										

Note: The summary reflects one observation per patient with a patient categorized as abnormal (low or high) if any scheduled lab assessment was considered to be abnormal based on change from observation taken at previous scheduled visit
[1] Fisher's exact test

Population: Safety

Template 18

Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges, by Visit

			Placebo			Xanomeline Low Dose			Xanomeline High Dose		
Lab Analyte	Week	Shift to	Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)	Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)	Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)
HEMATOLOGY											
Hemoglobin	2	n	xx	xx	xx	xx	xx	xx	xx	xx	xx
		Low	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
		Normal	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
		High	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Hemoglobin	4	n	xx	xx	xx	xx	xx	xx	xx	xx	xx
		Low	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
		Normal	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
		High	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: For each lab parameter, present weeks 2, 4, 6, 8, 12, 16, 20, 24, and 26.

Population: Safety

Template 19
Shifts of Laboratory Values During Treatment, Categorized Based on Threshold Ranges

Lab Analyte	Shift [1]	Placebo Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)	Xan. Low Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)	Xan. High Low at Baseline n (%)	Norm. at Baseline n (%)	High at Baseline n (%)	p-val [2]
HEMATOLOGY											
Hemoglobin	n	xx	xx	xx	xx	xx	xx	xx	xx	xx	x.xxx
	Low	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	Normal	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
	High	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	

 [1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).

[2] CMH test for general association, controlling for status at baseline.

Population: Safety
Template 20
Shifts of Hy's Law Values During Treatment

Shift during treatment [1]	Placebo		Xanomeline Low Dose		Xanomeline High Dose		p-val [2]
	Normal at Bsln n (%)	Abnormal at Bsln n (%)	Normal at Bsln n (%)	Abnormal at Bsln n (%)	Normal at Bsln n (%)	Abnormal at Bsln n (%)	
Transaminase 1.5 x ULN							
n	xx	xx	xx	xx	xx	xx	x.xxx
No change	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Change	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Bilirubin 2 x ULN and Transaminase 1.5 x ULN							
n	xx	xx	xx	xx	xx	xx	x.xxx
No change	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	
Change	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	

[1] A subject is counted only once for each analyte. A change will be considered shifting from normal at baseline to abnormal or from abnormal at baseline to normal at any visit during the treatment. The treatment period is defined as any planned visit after Week 0 (Visit 3), up to and including Week 24 (Visit 12).
[2] CMH test for general association, controlling for status at baseline.

Population: Safety

Template 21
Summary of Vital Signs at Baseline and End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	AFTER LYING DOWN 5 MIN.	Placebo	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
				Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
		Xan. Low	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
				Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
		Xan. High	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
				Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	AFTER STANDING 1 MIN.	Placebo	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
				Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx

…

Include:
Systolic BP	AFTER STANDING 3 MIN.
Diastolic BP	AFTER LYING DOWN 5 MIN.
(mmHg)	AFTER STANDING 1 MIN.
	AFTER STANDING 3 MIN.
Heart Rate	AFTER LYING DOWN 5 MIN.
(bpm)	AFTER STANDING 1 MIN.
	AFTER STANDING 3 MIN.

End of treatment is the last on-treatment visit (on or before the Week 24 visit).

Population: Safety
Template 22
Summary of Vital Signs Change from Baseline at End of Treatment

Measure	Position	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Systolic BP (mmHg)	AFTER LYING DOWN 5 MIN.	Placebo	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
		Xan. Low	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
		Xan. High	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	AFTER STANDING 1 MIN.	Placebo	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
				End of treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx

…

Include:
Systolic BP	AFTER STANDING 3 MIN.
Diastolic BP	AFTER LYING DOWN 5 MIN.
(mmHg)	AFTER STANDING 1 MIN.
	AFTER STANDING 3 MIN.
Heart Rate (bpm)	AFTER LYING DOWN 5 MIN.
	AFTER STANDING 1 MIN.
	AFTER STANDING 3 MIN.

End of treatment is the last on-treatment visit (on or before the Week 24 visit).

Population: Safety

Template 23
Summary of Weight Change from Baseline at End of Treatment

Measure	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Weight (kg)	Placebo	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
			Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	Xan. Low	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
			Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	Xan. High	xxx	Baseline	xxx	xx.x	xx.xx	xx.x	xx	xxx
			Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
Weight Change from Baseline	Placebo	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	Xan. Low	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx
	Xan. High	xxx	Week 24	xxx	xx.x	xx.xx	xx.x	xx	xxx
			End of Treatment	xxx	xx.x	xx.xx	xx.x	xx	xxx

End of treatment is the last on-treatment visit (on or before the Week 24 visit).

Population: All Subjects

Template 24
Summary of Concomitant Medications (Number of Subjects)

ATC Level 1 Ingredient	Placebo (N=xxx)	Xanomeline Low Dose (N=xxx)	Xanomeline High Dose (N=xxx)
Any medication	xx (xx%)	xx (xx%)	xx (xx%)
Endocrine & Metabolic			
Any medication	xx (xx%)	xx (xx%)	xx (xx%)
Fluticasone propionate	xx (xx%)	xx (xx%)	xx (xx%)
Beclomethasone dipropionate	xx (xx%)	xx (xx%)	xx (xx%)
Anti-infectives & immunologicals			
Any medication	xx (xx%)	xx (xx%)	xx (xx%)
Amoxycillin	xx (xx%)	xx (xx%)	xx (xx%)
Amoxycillin trihydrate	xx (xx%)	xx (xx%)	xx (xx%)
Clamoxyl	xx (xx%)	xx (xx%)	xx (xx%)
Cefaclor	xx (xx%)	xx (xx%)	xx (xx%)
Cefproxil	xx (xx%)	xx (xx%)	xx (xx%)
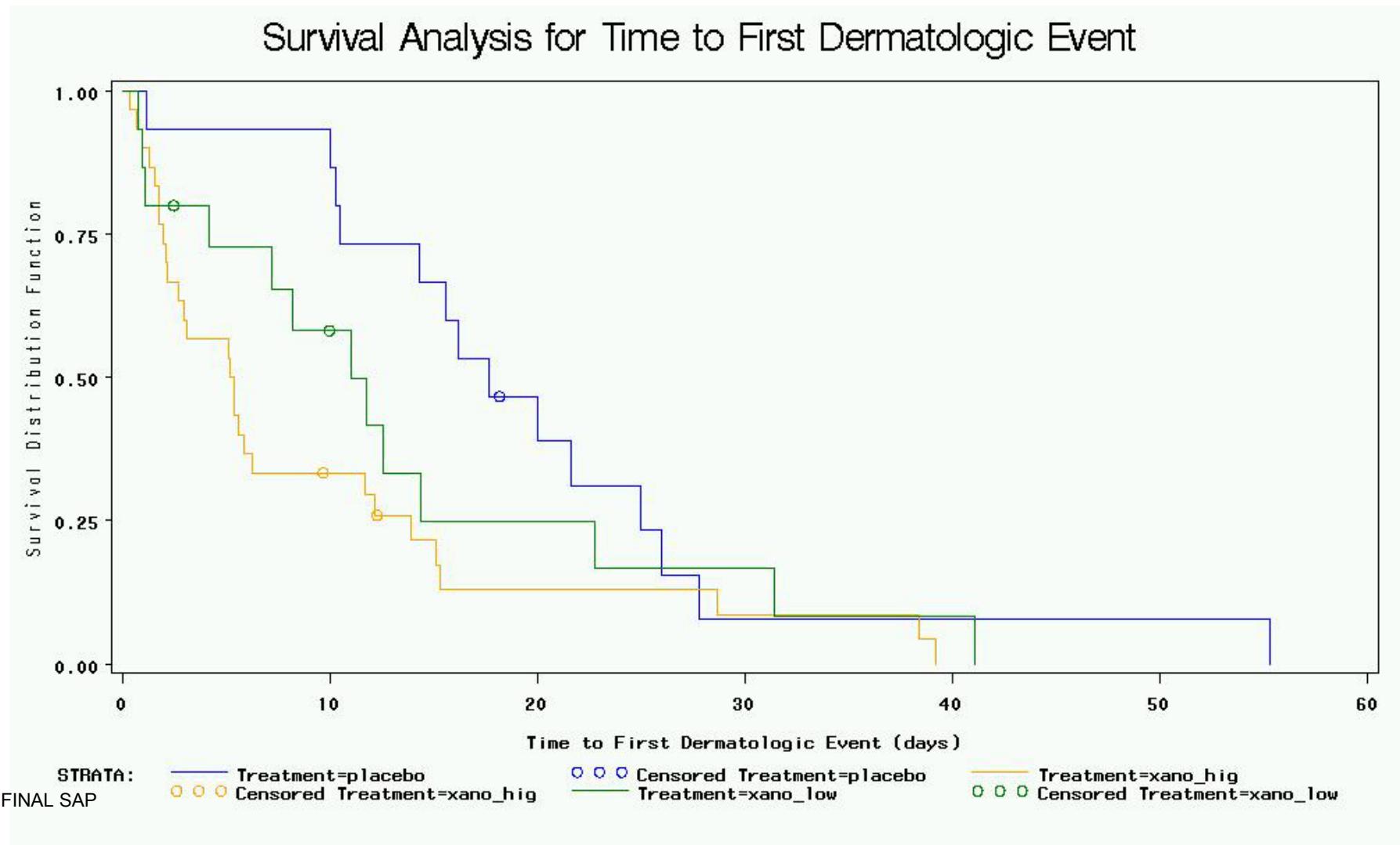
Note: A medication may be included in more than one ATC Level category and appear more than once.

Figure 1
Time to First Dermatological Event by Treatment Group

Survival Analysis for Time to First Dermatologic Event

FINAL SAP

14.   APPENDIX 1 – ADDITIONAL STATISTICAL DETAILS

14.1.   Scoring algorithms for Efficacy Endpoints

Described below are details for scoring the ADAS-Cog (11), CIBIC+, and NPI-X, and details on how to handle missing data.

14.1.1.   ADAS-Cog(11)

ADAS-Cog Scoring Methods

Item No.	Description	Score Range
ITEM01	Word Recall Task	0-10
ITEM02	Naming Objects and Fingers	0-5
ITEM03[a]	Delayed Word Recall	0-10
ITEM04	Commands	0-5
ITEM05	Constructional praxis	0-5
ITEM06	Ideational praxis	0-5
ITEM07	Orientation	0-8
ITEM08	Word recognition	0-12
ITEM09[a]	Attention/Visual Search Task	0-5 Based on number of correct answers: $>30 = 0$ $24\text{-}30 = 1$ $18\text{-}23 = 2$ $12\text{-}17 = 3$ $6\text{-}11 = 4$ $0\text{-}5 = 5$
ITEM10[a]	Maze Solution	0-5 Based on time (in seconds) and number of errors: If <2 errors then: 0-30 seconds = 0 31-60 = 1 61-90 = 2 91-120 = 3 121-239 = 4 $\geq 240 = 5$ If 2 or more errors then the score is a 5
ITEM11	Spoken Language Ability	0-5
ITEM12	Comprehension of Spoken Language	0-5

ITEM13	Word Finding Difficulty in Spontaneous Speech	0-5
ITEM14	Recall of Test Instructions	0-5
TOT01	ADAS-Cog (11)	0-70
TOT02	ADAS-Cog (14)	0-90

a   Additional items for the ADAS-Cog (14) but not part of the ADAS-Cog (11).

14.1.2.   CIBIC+

This assessment has a 7-point scale and is scored as:

    1 = Marked improvement,
    2= Moderate improvement,
    3= Minimal improvement,
    4 = No change,
    5= Minimal worsening,
    6= Moderate worsening
    7 = Marked worsening

14.1.3.   NPI-X

The primary assessment of this instrument will be for the total score, not including the sleep, appetite, and euphoria domains. This total score is computed by taking the product of the frequency and severity scores and summing them up across the domains.

    Severity:
        Range 1-3
        1 = mild, 2 = moderate, 3 = marked
    Frequency:
        Range 1-4
        1 = occasionally, 2 = often, 3 = frequently, 4 = very frequently
        Can be treated as continuous variables
    Frequency × Severity for each NPI domain
        Range 0-12

NPI-X Total (9) will be calculated as the sum of all individual domain scores (can be treated as continuous variable). If the domain is absent, then the score for the domain is 0. If the domain is not applicable then the score for the domain is set to missing. The range of NPI-X Total (9) is 0-108.

NPI-X Total (9) domains are:
- Delusions
- Hallucinations
- Agitation/Aggression
- Depression/Dysphoria
- Anxiety
- Apathy/Indifference
- Disinhibition
- Irritability/Lability
- Aberrant Motor Behavior

14.2. Handling missing item scores within efficacy data

The following applies to all totals and subtotals of ADAS-Cog(11) and NPI-X, and does not apply to CIBIC+.

Any computed total score will be treated as missing if more than 30% of the items are missing or scored "not applicable". For example, when computing ADAS-Cog(11), if 4 or more items are missing, then the total score will not be computed. When one or more items are missing (but not more than 30%), the total score will be adjusted in order to maintain the full range of the scale. For example, ADAS-Cog(11) is a 0-70 scale. If the first item, Word Recall (ranges from 0 to 10), is missing, then the remaining 10 items of the ADAS-Cog(11) will be summed and multiplied by (70 / (70-10)), or 7/6.

15.   APPENDIX 2 – DEVIATIONS FROM PROTOCOL-SPECIFIED ANALYSES

Some analyses specified in the original protocol will not be performed for the purposes of this pilot project. Where applicable, deviations are noted in the appropriate sections of this analysis plan. Otherwise, deviations from the protocol-specified analyses are described below.

15.1.   Deviations from Protocol-Specified Efficacy Analyses

The following efficacy endpoints will not be used: ADAS-Cog (14) and DAD. ANOVA and ANCOVA models for the efficacy endpoints will not assess site*treatment interaction. Furthermore, the normality assumption for the efficacy endpoints will not be investigated and consideration for rank transformations will not be done.

The protocol proposes a number of secondary analyses for the efficacy endpoints. The following secondary analyses will not be performed:

- Observed cases at each timepoint for ADAS-Cog (11) and CIBIC+.

- Average of all postrandomization NPI-X scorces including Weeks 2 and 26.

- Dichotomizing subjects for each behavior in the NPI-X instrument into those who experienced the behavior for the first time postrandomization and those who had the quotient between frequency and severity increase relative to baseline versus those who did not.

The protocol states that efficacy assessments are invalid if no study drug has been taken within 3 days prior to the assessment. This will not be considered in the pilot project. In addition, efficacy assessments occurring after the last dose of drug will be considered for windowing and for the efficacy analysis if they are collected at visit number 201.

Interim analyses will not be performed.

Covariate analyses examining the effect of Apo E on the efficacy measures will not be performed.

15.2.   Deviations from Protocol-Specified Pharmacokinetic Analyses

Pharmacokinetic analyses will not be performed.

15.3.   Deviations from Protocol-Specified Safety Analyses

ECG analyses will not be performed.

The caregiver's response about the patch will not be summarized.

No ANCOVA analyses will be performed for laboratory data. Instead, frequency tables based on the on-treatment period will include p-values.

15.4.   OMISSIONS FROM LEGACY DATA

The data reflected in the submitted datasets will not include all of the subjects in the legacy data. This is because we do not have all of the data for the remaining subjects, so chose to omit them as we have an adequate number of subjects left for the purposes of the pilot.

The lab data included many analytes. Because of the large size of the datasets, it was decided to reduce these datasets by dropping less common analytes from the datasets. This was done by comparing the lab tests performed to a list of common lab tests found on the CDISC web site. Lab tests not in this list of common tests were dropped. In addition, lab tests with character results only were dropped, to simplify the analyses provided. These include "RBC Morphology," "elliptocytosis," "basophilic stippling," and "target cells."

15.5.   Coding of Adverse Events

Due to licensing restrictions for MedDRA, all of the event terms, including verbatim text, LLT, PT, HLT, HLGT, and SOC were initially masked. Discussions with MSSO resulted in an agreement that all can be unmasked with the exception of HLT and HLGT, as long as text is what is provided and not the actual MedDRA numeric code. In the processing of providing the unmasking, it was simpler to also leave the verbatim text masked. Consequently, the SOC, PT, and LLT are real (i.e., not masked).

16. APPENDIX 3 - ANALYSES NOT PRE-SPECIFIED IN PROTOCOL

16.1. CIBIC+

At the request of the FDA reviewers, treatments will also be compared for overall differences in the CIBIC+ by using the CMH test, controlling for site. The template for this result is Ad hoc Template 1.

Population: Efficacy
Ad hoc Template 1
CIBIC+ - Categorical Analysis – LOCF

```
                                Xanomeline  Xanomeline
                     Placebo    Low Dose    High Dose
                     (N=xxx)    (N=xxx)     (N=xxx)     p-value [1]
```

Week 8
```
     N                   xx         xx          xx         x.xxx
     Marked improvement  xx (xx%)   xx (xx%)    xx (xx%)
     Moderate improvement xx (xx%)  xx (xx%)    xx (xx%)
     Minimal improvement xx (xx%)   xx (xx%)    xx (xx%)
     No Change           xx (xx%)   xx (xx%)    xx (xx%)
     Minimal worsening   xx (xx%)   xx (xx%)    xx (xx%)
     Moderate worsening  xx (xx%)   xx (xx%)    xx (xx%)
     Marked worsening    xx (xx%)   xx (xx%)    xx (xx%)
```

Week 16
```
     N                   xx         xx          xx         x.xxx
     Marked improvement  xx (xx%)   xx (xx%)    xx (xx%)
     Moderate improvement xx (xx%)  xx (xx%)    xx (xx%)
     Minimal improvement xx (xx%)   xx (xx%)    xx (xx%)
     No Change           xx (xx%)   xx (xx%)    xx (xx%)
     Minimal worsening   xx (xx%)   xx (xx%)    xx (xx%)
     Moderate worsening  xx (xx%)   xx (xx%)    xx (xx%)
     Marked worsening    xx (xx%)   xx (xx%)    xx (xx%)
```

     repeat above for week 24

[1] Overall comparison of treatments using CMH test (Pearson Chi-Square), controlling for site.

Title:

Documentation of Statistical Methods

This document contains raw statistical output for the two primary efficacy analyses and for the repeated measures analysis. In addition to the statistical output, the summary tables generated from the statistical analysis are also included. Because this document was provided in response to a request from the FDA, it was decided that this approach would allow the dates on the corresponding tables to be consistent, as well illustrate that nothing changed from the table included in the original package.

Supporting Table 14-3.01 contains the raw statistical output from the dose response analysis and the treatment comparison analysis, supporting Table 14-3.01, "Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 – LOCF."

Supporting Table 14-3.02 contains the raw statistical output from the dose response analysis and the treatment comparison analysis, supporting Table 14-3.02, "Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF."

Supporting Table 14-3.11 contains the raw statistical output from the repeated measures analysis, supporting Table 14-3.11, "ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24."

Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 24			
n	79	81	74
Mean (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.48)
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;62)
Change from Baseline			
n	79	81	74
Mean (SD)	2.5 (5.80)	2.0 (5.55)	1.5 (4.26)
Median (Range)	2.0 (-11;16)	2.0 (-11;17)	1.0 (-7;13)
p-value(Dose Response) [1][2]			0.245
p-value(Xan - Placebo) [1][3]		0.569	0.233
Diff of LS Means (SE)		-0.5 (0.82)	-1.0 (0.84)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value(Xan High - Xan Low) [1][3]			0.520
Diff of LS Means (SE)			-0.5 (0.84)
95% CI			(-2.2;1.1)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\CFB_revisions\programs\rtf_eff1__.sas   16:35 Sunday, February 4, 2007

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Dose Response Analysis (PROC GLM)

The GLM Procedure

Class Level Information

Class	Levels	Values
SITEGRP	11	701 703 704 705 708 709 710 713 716 718 900

Number of Observations Read	234
Number of Observations Used	234

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Dose Response Analysis (PROC GLM)

The GLM Procedure

Dependent Variable: CHG   Change from baseline (VAL - BASE)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	610.477907	50.873159	1.92	0.0332
Error	221	5854.045839	26.488895		
Corrected Total	233	6464.523747			

R-Square	Coeff Var	Root MSE	CHG Mean
0.094435	255.4421	5.146736	2.014834

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRTDOSE	1	42.7340434	42.7340434	1.61	0.2054
SITEGRP	10	564.7301815	56.4730182	2.13	0.0232
BASE	1	3.0136824	3.0136824	0.11	0.7362

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRTDOSE	1	36.0384965	36.0384965	1.36	0.2447
SITEGRP	10	556.3851128	55.6385113	2.10	0.0255
BASE	1	3.0136824	3.0136824	0.11	0.7362

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure

Class Level Information

Class	Levels	Values
SITEGRP	11	701 703 704 705 708 709 710 713 716 718 900
TRTPCD	3	H L P

Number of Observations Read 234
Number of Observations Used 234

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure

Dependent Variable: CHG   Change from baseline (VAL - BASE)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	612.556057	47.119697	1.77	0.0489
Error	220	5851.967689	26.599853		
Corrected Total	233	6464.523747			

R-Square	Coeff Var	Root MSE	CHG Mean
0.094757	255.9766	5.157505	2.014834

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRTPCD	2	44.1412586	22.0706293	0.83	0.4375
SITEGRP	10	565.0065822	56.5006582	2.12	0.0237
BASE	1	3.4082167	3.4082167	0.13	0.7207

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRTPCD	2	38.1166466	19.0583233	0.72	0.4896
SITEGRP	10	556.3075682	55.6307568	2.09	0.0262
BASE	1	3.4082167	3.4082167	0.13	0.7207

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure

Dependent Variable: CHG   Change from baseline (VAL - BASE)

Parameter	Estimate	Standard Error	t Value	Pr > |t|
H vs L	-0.53923124	0.83610890	-0.64	0.5196
H vs P	-1.00601360	0.84052936	-1.20	0.2326
L vs P	-0.46678236	0.81804222	-0.57	0.5688

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure
Least Squares Means

TRTPCD	CHG LSMEAN	Standard Error	Pr > |t|	LSMEAN Number
H	1.48854043	0.60334071	0.0144	1
L	2.02777167	0.57490509	0.0005	2
P	2.49455402	0.58187565	<.0001	3

Least Squares Means for effect TRTPCD
 Pr > |t| for H0: LSMean(i)=LSMean(j)

Dependent Variable: CHG

i/j	1	2	3
1		0.5196	0.2326
2	0.5196		0.5688
3	0.2326	0.5688	

TRTPCD	CHG LSMEAN	95% Confidence Limits	
H	1.488540	0.299473	2.677608
L	2.027772	0.894746	3.160798
P	2.494554	1.347790	3.641318

Supporting Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure
Least Squares Means

```
  Least Squares Means for Effect
            TRTPCD
   Difference    95% Confidence
     Between       Limits for
i j      Means LSMean(i)-LSMean(j)
1 2  -0.539231 -2.187039  1.108577
1 3  -1.006014 -2.662534  0.650506
2 3  -0.466782 -2.078985  1.145420
```

Note: To ensure overall
         protection level,
         only
         probabilities
         associated with
         pre-planned
         comparisons
         should be used.

Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Week 24			
n	79	81	74
Mean (SD)	4.3 (0.77)	4.2 (0.79)	4.3 (0.81)
Median (Range)	4.0 (2;6)	4.0 (2;6)	4.0 (3;6)
p-value(Dose Response) [1][2]			0.960
p-value(Xan - Placebo) [1][3]		0.489	0.799
Diff of LS Means (SE)		-0.1 (0.13)	0.0 (0.13)
95% CI		(-0.3;0.2)	(-0.2;0.3)
p-value(Xan High - Xan Low) [1][3]			0.349
Diff of LS Means (SE)			0.1 (0.13)
95% CI			(-0.1;0.4)

[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable.
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.
Source: C:\cdisc_pilot\CFB_revisions\programs\rtf_eff1__.sas   16:35 Sunday, February 4, 2007

Population: Efficacy
Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Dose Response Analysis (PROC GLM)

The GLM Procedure

Class Level Information

Class	Levels	Values
SITEGRP	11	701 703 704 705 708 709 710 713 716 718 900

Number of Observations Read	234
Number of Observations Used	234

Population: Efficacy
Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Dose Response Analysis (PROC GLM)

The GLM Procedure

Dependent Variable: VAL   Numeric value of PARAM

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	11	5.1478277	0.4679843	0.74	0.6995
Error	222	140.4248218	0.6325442		
Corrected Total	233	145.5726496			

R-Square	Coeff Var	Root MSE	VAL Mean
0.035363	18.64794	0.795327	4.264957

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRTDOSE	1	0.00018271	0.00018271	0.00	0.9865
SITEGRP	10	5.14764502	0.51476450	0.81	0.6156

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRTDOSE	1	0.00162106	0.00162106	0.00	0.9597
SITEGRP	10	5.14764502	0.51476450	0.81	0.6156

Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure

Class Level Information

Class	Levels	Values
SITEGRP	11	701 703 704 705 708 709 710 713 716 718 900
TRTPCD	3	H L P

Number of Observations Read	234
Number of Observations Used	234

Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure

Dependent Variable: VAL   Numeric value of PARAM

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	12	5.7499995	0.4791666	0.76	0.6938
Error	221	139.8226501	0.6326817		
Corrected Total	233	145.5726496			

R-Square	Coeff Var	Root MSE	VAL Mean
0.039499	18.64996	0.795413	4.264957

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRTPCD	2	0.83041367	0.41520683	0.66	0.5198
SITEGRP	10	4.91958584	0.49195858	0.78	0.6504

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TRTPCD	2	0.60379285	0.30189642	0.48	0.6212
SITEGRP	10	4.91958584	0.49195858	0.78	0.6504

Parameter	Estimate	Standard Error	t Value	Pr > |t|
H vs L	0.12036016	0.12827843	0.94	0.3491
H vs P	0.03287808	0.12904679	0.25	0.7991
L vs P	-0.08748208	0.12615923	-0.69	0.4888

Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure
Least Squares Means

TRTPCD VAL	LSMEAN	Standard Error	Pr > |t|	LSMEAN Number
H	4.31772026	0.09264306	<.0001	1
L	4.19736010	0.08855333	<.0001	2
P	4.28484218	0.08966746	<.0001	3

Least Squares Means for effect TRTPCD
Pr > \|t\| for H0: LSMean(i)=LSMean(j)

Dependent Variable: VAL

i/j	1	2	3
1		0.3491	0.7991
2	0.3491		0.4888
3	0.7991	0.4888	

TRTPCD VAL	LSMEAN	95% Confidence Limits	
H	4.317720	4.135143	4.500297
L	4.197360	4.022843	4.371877
P	4.284842	4.108129	4.461555

Supporting Table 14-3.02
Primary Endpoint Analysis: CIBIC+ - Summary at Week 24 - LOCF
SAS Output from Treatment Comparison Analysis (PROC GLM)

The GLM Procedure
Least Squares Means

		Least Squares Means for Effect TRTPCD Difference Between Means LSMean(i)-LSMean(j)	95% Confidence Limits for	
i	j			
1	2	0.120360	-0.132445	0.373166
1	3	0.032878	-0.221442	0.287198
2	3	-0.087482	-0.336111	0.161147

Note: To ensure overall
protection level,
only
probabilities
associated with
pre-planned
comparisons
should be used.

Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
LS Means (SE)	1.6 (0.49)	1.5 (0.52)	1.1 (0.56)
p-value(Xan - Placebo)		0.955	0.556
Diff of LS Means (SE)		-0.0 (0.70)	-0.4 (0.72)
95% CI		(-1.4;1.3)	(-1.9;1.0)
p-value(Xan High - Xan Low)			0.606
Diff of LS Means (SE)			-0.4 (0.75)
95% CI			(-1.9;1.1)

Note: The change from baseline is calculated as the post-baseline score minus the baseline score. The covariates included in the MMRM model are treatment, site group, time and treatment by time interaction, baseline ADAS-Cog (11) score, and baseline ADAS-Cog (11) score by time interaction.
Source: C:\cdisc_pilot\CFB_revisions\programs\rtf_eff_mmrm_.sas   15:51 Thursday, February 8, 2007

Supporting Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24
SAS Output from PROC MIXED

The Mixed Procedure

Model Information

Data Set	WORK.EFF
Dependent Variable	CHG
Covariance Structure	Unstructured
Subject Effect	USUBJID
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
USUBJID	234	not printed
SITEGRP	11	701 703 704 705 708 709 710 713 716 718 900
AWEEK	3	8 16 24
TRTPN	3	0 1 2

Dimensions

Covariance Parameters	6
Columns in X	31
Columns in Z	0
Subjects	234
Max Obs Per Subject	3

Supporting Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24
SAS Output from PROC MIXED

The Mixed Procedure

Number of Observations

Number of Observations Read	539
Number of Observations Used	539
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	3202.34096801	
1	2	3087.84605725	0.00000281
2	1	3087.84303515	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	USUBJID	16.8209
UN(2,1)	USUBJID	11.2056
UN(2,2)	USUBJID	28.2581
UN(3,1)	USUBJID	11.8853
UN(3,2)	USUBJID	14.4451
UN(3,3)	USUBJID	31.3944

Supporting Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24
SAS Output from PROC MIXED

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	3087.8
AIC (smaller is better)	3099.8
AICC (smaller is better)	3100.0
BIC (smaller is better)	3120.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
5	114.50	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TRTPN	2	200	0.20	0.8184
SITEGRP	10	218	2.32	0.0129
AWEEK	2	159	0.71	0.4918
AWEEK*TRTPN	4	187	1.25	0.2926
BASE	1	213	0.00	0.9510
BASE*AWEEK	2	158	0.34	0.7137

Supporting Table 14-3.11
ADAS Cog (11) - Repeated Measures Analysis of Change from Baseline to Week 24
SAS Output from PROC MIXED

The Mixed Procedure

Least Squares Means

Effect	ADaM Planned Arm Code, Numeric	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	0	1.5535	0.4930	180	3.15	0.0019	0.05	0.5808	2.5263
TRTPN	1	1.5136	0.5236	211	2.89	0.0042	0.05	0.4815	2.5457
TRTPN	2	1.1270	0.5552	215	2.03	0.0436	0.05	0.03263	2.2213

Differences of Least Squares Means

Effect	ADaM Planned Arm Code, Numeric	ADaM Planned Arm Code, Numeric	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTPN	0	1	0.03993	0.7002	195	0.06	0.9546	0.05	-1.3410	1.4209
TRTPN	0	2	0.4266	0.7237	196	0.59	0.5562	0.05	-1.0007	1.8539
TRTPN	1	2	0.3867	0.7481	212	0.52	0.6058	0.05	-1.0881	1.8614

Appendix 10.   Documentation of Laboratory Standards

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 11. Publications Based on the Study

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 12.   Publications Referenced in This Report

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 13.   Subject Data Listings

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.

Appendix 14.   Case Report Forms for Selected Subjects

Due to the nature of this CDISC Pilot Project, this appendix is not included in this study report.