None

Sponsor Confidentiality Statement:

M11: Enter Sponsor Confidentiality Statement
USDM: No mapping path

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

M11: Enter Full Title
USDM: StudyVersion/@titles/StudyTitle/@text

Trial Acronym: LZZT

M11: Enter trial Acronym
USDM: StudyVersion/@titles/StudyTitle/@text

Protocol Identifier: H2Q-MC-LZZT

M11: Enter Protocol Identifier
USDM: StudyIdentifier[Organization/@type/@code=C70793]/@studyIdentifier

Original Protocol:

M11: Original protocol
USDM: No mapping path

Version Number: 2

M11: Enter Version Number
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Version Date: 2006-07-01

M11: Enter Version Date
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Amendment Identifier: 1

M11: Amendment Identifier
USDM: StudyVersion/StudyAmendment/@number

Amendment Scope: Europe

M11: Amendment Scope
USDM: StudyVersion/StudyAmendment/SubjectEnrollment/@code/@standardCode/@decode

Compound Codes(s):

M11: Enter Compound Code(s)

M11: Enter Nonproprietary Name(s), Enter Proprietary Name(s)
USDM: No mapping path

Trial Phase: Phase II Trial

M11: Trial Phase
USDM: StudyVersion/@studyPhase/@standardCode/@decode

Short Title: Xanomeline (LY246708)

M11: Enter Trial Short Title
USDM: StudyVersion/@titles/StudyTitle/@text

Sponsor Name and Address: Eli Lilly, Lilly Corporate Ctr, Indianapolis IN 4628 Denmark

M11: Enter Sponsor Name, Enter Sponsor Legal Address
USDM: StudyIdentifier[Organization/@type/@code=C70793]/Organization/@name,
StudyIdentifier[Organization/@type/@code=C70793]/Organization/Address/@text

Regulatory Agency Identifier Number(s): NCT12345678

M11: EU CT Number, IDE Number, FDA IND Number, JRCT Number, NCT Number, NMPA IND Number, WHO/UTN Number, Other Regulatory Agency Identifier Number
USDM: StudyIdentifier[Organization/@type/@code=C188863|C93453]/@studyIdentifier

Spondor Approval Date: 2006-06-01

M11: Enter Approval Date or state location where information can be found
USDM: StudyVersion/GovernanceDate[@type/@code=C132352]/@dateValue

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.2 Trial Schema

1.3 Schedule of Activities

2 INTRODUCTION

2.1 Purpose of Trial

2.2 Summary of Benefits and Risks

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3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1 Primary Objectives

To determine if there is a statistically significant relationship (overall Type 1 erroralpha=0.05) between the change in both the ADAS-Cog (11) and CIBIC+ scores, and drug dose (0, 50 cm2 [54 mg], and 75 cm2 [81 mg]).	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
To document the safety profile of the xanomeline TTS.	Adverse events Vital signs (weight, standing and supine blood pressure, heart rate) Laboratory evaluations (Change from Baseline)
To assess the dose-dependent improvement in behavior. Improved scores on the Revised Neuropsychiatric Inventory (NPI-X) will indicate improvement in these areas.	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

4 TRIAL DESIGN

4.1 Description of Trial Design

4.1.1 Participant Input into Design

4.2 Rationale for Trial Design

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).

4.2.1 Rationale for Comparator

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).

4.2.2 Rationale for Adaptive or Novel Trial Design

4.2.3 Other Trial Design Considerations

4.3 Access to Trial Intervention After End of Trial

4.4 Start of Trial and End of Trial

5 TRIAL POPULATION

5.1 Selection of Trial Population

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.

5.2 Rationale for Trial Population

5.3 Inclusion Criteria

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

1 Subjects shall be between 100.0 and 50.0

2 Patients with Probable Mild to Moderate Alzheimer's Disease by the NINCDS and the ADRDA guidelines (Attachment LZZT.7)

3 MMSE score of 10 to 23

5.4 Exclusion Criteria

Patients may be excluded in 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.

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

Not applicable

5.5.3 Physical Activity

5.5.4 Other Activity

5.6 Screen Failures

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of Trial Intervention

6.2 Rationale for Trial Intervention

6.3 Dosing and Administration

6.3.1 Trial Intervention Dose Modification

6.4 Treatment of Overdose

6.5 Preparation, Handling, Storage and Accountability

6.5.1 Preparation of Trial Intervention

6.5.2 Handling and Storage of Trial Intervention

6.5.3 Accountability of Trial Intervention

6.6 Participant Assignment, Randomisation and Blinding

6.6.1 Participant Assignment

6.6.2 Randomisation

6.6.3 Blinding and Unblinding

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.

6.7 Trial Intervention Compliance

6.8 Concomitant Therapy

6.8.1 Prohibited Concomitant Therapy

6.8.2 Permitted Concomitant Therapy

6.8.3 Rescue Therapy

6.8.4 Other Therapy

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention

7.1.1 Criteria for Permanent Discontinuation of Trial Intervention

7.1.2 Temporary Discontinuation or Interruption of Trial Intervention

7.1.3 Rechallenge

7.2 Participant Withdrawal from the Trial

7.3 Lost to Follow-Up

7.4 Trial Stopping Rules

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Screening/Baseline Assessments and Procedures

8.2 Efficacy Assessments and Procedures

8.3 Safety Assessments and Procedures

8.3.1 Physical Examination

8.3.2 Vital Signs

8.3.3 Electrocardiograms

8.3.4 Clinical Laboratory Assessments

8.3.5 Suicidal Ideation and Behaviour Risk Monitoring

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions of AE and SAE

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

8.4.3 Identifying AEs and SAEs

8.4.4 Recording of AEs and SAEs

8.4.5 Follow-up of AEs and SAEs

8.4.6 Reporting of SAEs

8.4.7 Regulatory Reporting Requirements for SAEs

8.4.8 Serious and Unexpected Adverse Reaction Reporting

8.4.9 Adverse Events of Special Interest

8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

8.5 Pregnancy and Postpartum Information

8.5.1 Participants Who Become Pregnant During the Trial

8.5.2 Participants Whose Partners Become Pregnant

8.6 Medical Device Product Complaints for Drug/Device Combination Products

8.6.1 Definition of Medical Device Product Complaints

8.6.2 Recording of Medical Device Product Complaints

8.6.3 Time Period and Frequency for Collecting Medical Device Product Complaints

.

8.6.4 Follow-Up of Medical Device Product Complaints

8.6.5 Regulatory Reporting Requirements for Medical Device Product Complaints

8.7 Pharmacokinetics

8.8 Genetics

8.9 Biomarkers

8.1 Immunogenicity Assessments

8.1.1 Medical Resource Utilisation and Health Economics

9 STATISTICAL CONSIDERATIONS

9.1 Analysis Sets

9.2 Analyses Supporting Primary Objective(s)

9.2.1 Statistical Model, Hypothesis, and Method of Analysis

9.2.2 Handling of Intercurrent Events of Primary Estimand(s)

9.2.3 Handling of Missing Data

9.2.4 Sensitivity Analysis

9.2.5 Supplementary Analysis

9.3 Analysis Supporting Secondary Objective(s)

9.4 Analysis of Exploratory Objective(s)

9.5 Safety Analyses

9.6 Other Analyses

9.7 Interim Analyses

9.8 Sample Size Determination

9.9 Protocol Deviations

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

10.2 Committees

10.3 Informed Consent Process

10.4 Data Protection

10.5 Early Site Closure or Trial Termination

11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

11.2 Data Quality Assurance

11.3 Source Data

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12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS - DEFINITIONS, SEVERITY, AND CAUSALITY

12.1 Further Details and Clarifications on the AE Definition

12.2 Further Details and Clarifications on the SAE Definition

12.3 Severity

12.4 Causality

13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

13.1.2 Contraception

13.1.3 Pregnancy Testing

13.2 Clinical Laboratory Tests

13.3 Country/Region-Specific Differences

13.4 Prior Protocol Amendments

14 APPENDIX: GLOSSARY OF TERMS

15 APPENDIX: REFERENCES

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