

Xanomeline (LY246708)

Note:

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Sponsor**Confidentiality****Statement:**

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

Trial Acronym: LZZT

Protocol Identifier: H2Q-MC-LZZT

Original Protocol:

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Amendment Identifier: 1

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Compound Codes(s):**Compound Name(s):**

Trial Phase: Phase II Trial

Short Title: Xanomeline (LY246708)

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

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2 INTRODUCTION

2.1 Purpose of Trial

2.2 Summary of Benefits and Risks

3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1 Primary Objectives

To determine if there is a statistically significant relationship (overall Type 1 error $\alpha=0.05$) 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

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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:

1Subjects shall be between [min_age] and [max_age]

2[StudyPopulation] as defined by the NINCDS and the ADRDA guidelines (Attachment LZZT.7)

3[Activity1] score of 10 to 23

5.4 Exclusion Criteria

Patients may be excluded in the study for **any** of the following reasons:

9Persons 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

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6.2 Rationale for Trial Intervention

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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

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15 APPENDIX: REFERENCES

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