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

0 TITLE PAGE

Protocol Full Title:	Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease
Protocol Number:	H2Q-MC-LZZT
Version:	***** Failed to translate reference, attribute not found *****
Amendment Number:	***** Failed to translate reference, attribute not found *****
Amendment Scope:	***** Failed to translate reference, attribute not found *****
Compound Number(s):	***** Failed to translate reference, attribute not found *****
Compound Name(s):	***** Failed to translate reference, attribute not found *****
Trial Phase:	Phase II Trial
Acronym:	H2Q-MC-LZZT
Short Title:	Xanomeline (LY246708)
Sponsor Name and Address:	***** Failed to translate reference, attribute not found *****

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.2 Trial Schema

1.3 Schedule of Activities

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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

Primary Objective	Primary Endpoint
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 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)

4 TRIAL DESIGN

4.1 Description of Trial Design

4.1.1 Participant Input into Design

4.2 Rationale for Trial Design

4.2.1 Rationale for Comparator

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

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

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.

5.4 Exclusion Criteria

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

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

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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

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15 APPENDIX: REFERENCES

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