

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

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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:> 2

Amendment Number: 1

Amendment Scope:

Compound Number(s):

Compound Name(s):

Trial Phase: Phase II Trial

Acronym: H2Q-MC-LZZT

Short Title: Xanomeline (LY246708)

Sponsor Name and Address: Eli Lilly
Lilly Corporate Ctr, Indianapolis, -, IN, 4628, United States of America

I 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

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

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 Subjects shall be between 50 years and 100 years

5.4 Exclusion Criteria

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

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

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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

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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

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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

II GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

11.2 Data Quality Assurance

11.3 Source Data

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

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13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

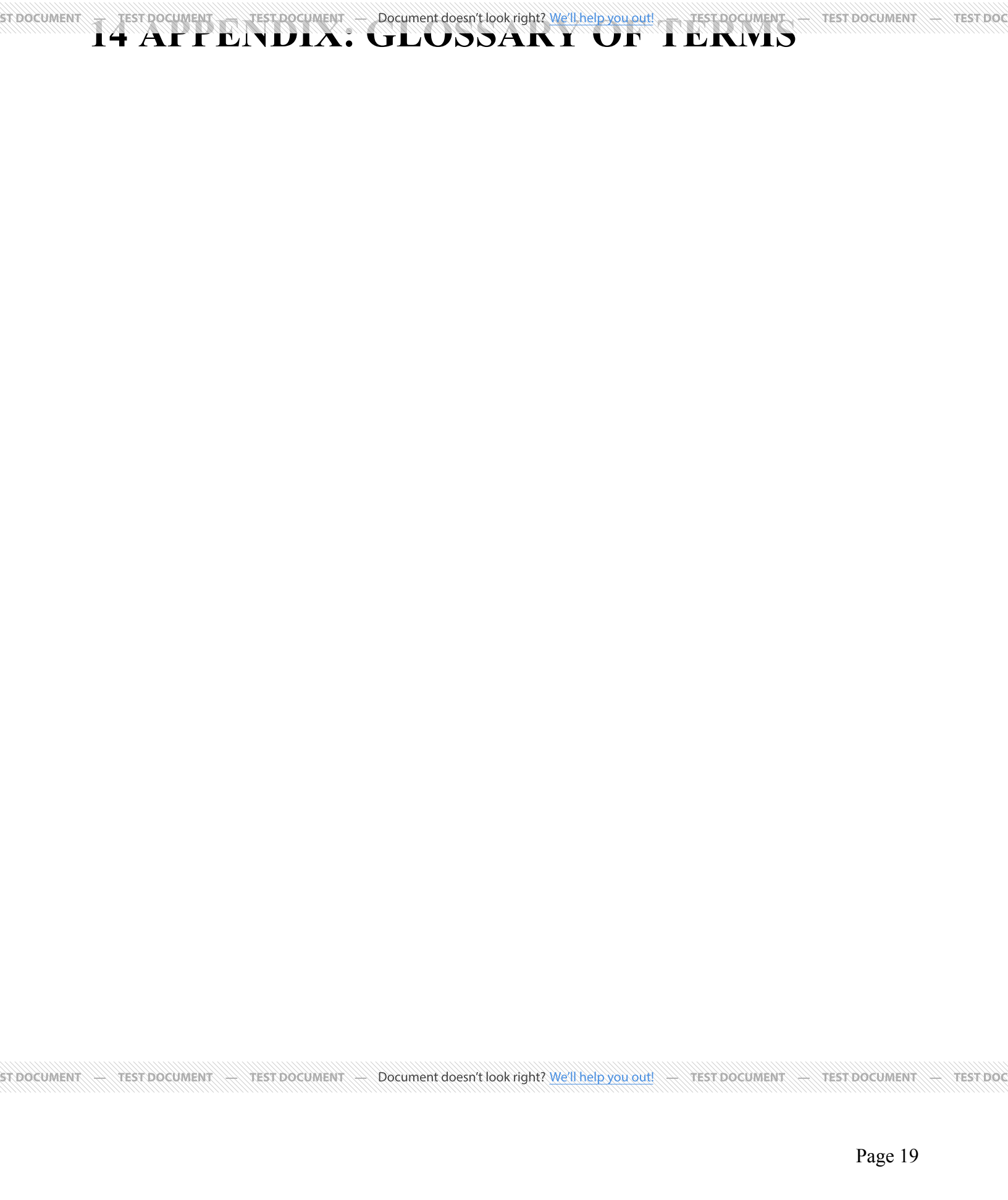
13.1.2 Contraception

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