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

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
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Amendment Scope:	Europe
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Compound Name(s):	
Trial Phase:	Phase II Trial
Short Title:	Xanomeline (LY246708)
Sponsor Name and Address:	Eli Lilly, Lilly Corporate Ctr, Indianapolis, IN, 4628, United States of America
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Note:

The table of contents is auto generated upon PDF production and only includes first level sections.

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.1.1 Primary and Secondary Objectives and Estimands

1.1.2 Overall Design

Committees

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).

1.2 Trial Schema

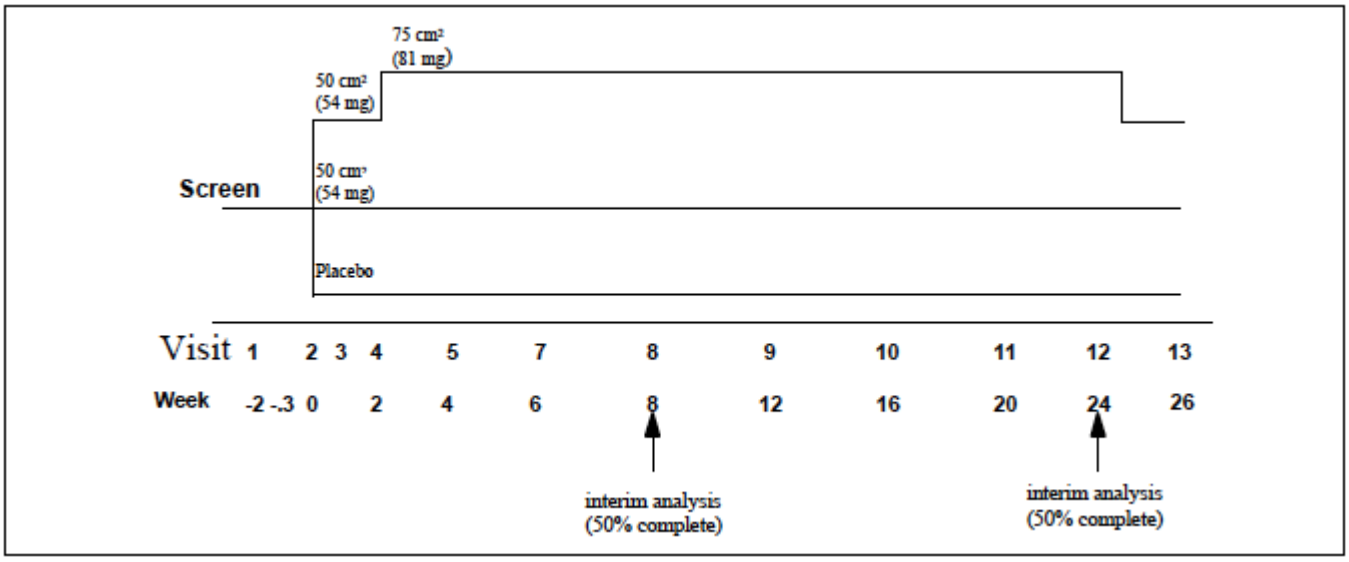

Figure LZZT.1. Illustration of study design for Protocol H2Q-MC-LZZT(c).

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 cm 2 TTS Formulation E, 54 mg xanomeline), and a high-dose xanomeline arm (75 cm 2 TTS Formulation E, 81 mg xanomeline). All patients receiving xanomeline will be started at 50 cm 2 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.

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).

1.3 Schedule of Activities

Note:

The following SoA timelines are auto generated using the detailed study design held within the USDM.

Timeline: Main Timeline, Potential subject identified

	Screening	Screening	Treatment One	Treatment One	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Two	Treatment Three	Follow Up
	Screening 1	Screening 2	Baseline	Week 2	Week 4	Week 6	Week 8	Week 8	Week 12	Week 12	Week 16	Week 16	Week 20	Week 20	Week 24	Week 26
	Screening	Pre dose	Dosing	Week 2	Week 4	Week 6	Week 8	Week 8 Home	Week 12	Week 12 Home	Week 16	Week 16 Home	Week 20	Week 20 Home	Week 24	Week 26
		-4..0 hours		-3..3 days	-3..3 days	-3..3 days	-3..3 days		-4..4 days		-4..4 days		-4..4 days		-4..4 days	-3..3 days
Informed consent	X															
Inclusion and exclusion criteria	X															
Patient number assigned	X															
Demographics	X															
Hachinski Ischemic Scale	X															
MMSE	X															
Physical examination	X															X
Medical history	X															
Habits	X															

Chest X-ray	X														
Apo E genotyping				X											
Patient randomised			X												
Vital Signs and Temperature	X	X	X	X	X	X	X		X		X		X		X	X
Ambulatory ECG placed		X													
Ambulatory ECG removed			X												
ECG	X			X	X	X	X		X		X		X		X	X
Placebo TTS test	X														
CT scan	X														
Concomitant medications	X		X	X	X	X	X		X		X		X		X	X
Hematology	X			X	X	X	X		X		X		X		X	X
Chemistry	X			X	X	X	X		X		X		X		X	X
Uninalysis	X			X					X						X	
Plasma Specimen (Xanomeline)			X	X	X	X			X				X			
Hemoglobin A1C	X[1]															

Study drug record , Medications dispensed, Medications returned			X	X	X	X	X		X		X		X		X	X
TTS Acceptability Survey																X
ADAS-Cog	X[2]		X				X				X				X	
CIBIC+	X[3]		X				X				X				X	
DAD	X[4]		X				X				X				X	
NPI-X	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Performed if patient is an insulin-dependent diabetic

[2] 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.

[3] 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.

[4] 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.

[5] 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.

Timeline: Adverse Event Timeline, Subject suffers an adverse event

	Adverse Event
Adverse events	X

Timeline: Early Termination Timeline, Subject terminates the study early

	Early Termination
Physical examination	X
Vital Signs and Temperature	X
ECG	X
Concomitant medications	X
Hematology	X
Chemistry	X
Uninalysis	X
Plasma Specimen (Xanomeline)	X
Study drug record , Medications dispensed, Medications returned	X
TTS Acceptability Survey	X
ADAS-Cog	X
CIBIC+	X
DAD	X

NPI-X	X
Check adverse events	X

Timeline: Vital Sign Blood Pressure Timeline, Automatic execution

	Supine	VS while supine	Standing	VS while standing	Standing	VS while standing
Subject supine	X					
Vital signs while supine		X				
Subject Standing			X		X	
Vital signs while standing				X		X

2 INTRODUCTION

3.1 Primary Objective(s) and Associated Estimand(s)

The primary objectives of this study are

- 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]).
- To document the safety profile of the xanomeline TTS.

3.1.1 {Primary Estimand}

3.2 Secondary Objective(s) and Associated Estimand(s)

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.
- 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.

3.3 Exploratory Objective(s)

4 TRIAL DESIGN

4.1 Description of Trial Design

Approximately 300 patients will be enrolled (see Schedule of Events for Protocol H2Q-MC-LZZT(c), Attachment LZZT.1).

Duration

SOMETHING HERE

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.

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.

4.1.1 Stakeholder Input into Design

4.2 Rationale for Trial Design

4.2.1 Rationale for Intervention Model

4.2.2 Rationale for Duration

4.2.3 Rationale for Estimands

4.2.4 Rationale for Interim Analysis

4.2.5 Rationale for Control Type

4.2.6 Rationale for Adaptive or Novel Trial Design

4.2.7 Rationale for Other Trial Design Aspects

4.3 Trial Stopping Rules

4.4 Start of Trial and End of Trial

4.5 Access to Trial Intervention After End of Trial

5 TRIAL POPULATION

5.1 Description of Trial Population and Rationale

5.2 Inclusion Criteria

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

01	Males and postmenopausal females at least 50.0 years of age.
02	Patients with Probable Mild to Moderate Alzheimer's Disease 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).
03	MMSE score of 10 to 23.
04	Hachinski Ischemic Scale score of ≤4 (Attachment LZZT.8).
05	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.

06	Investigator has obtained informed consent signed by the patient (and/or legal representative) and by the caregiver.
07	Geographic proximity to investigator's site that allows adequate follow-up.
08	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.

5.3 Exclusion Criteria

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

09	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.

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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.

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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. a) Neurosyphilis b. b) Meningitis c. 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: ↑ creatinine, ↑ total bilirubin, ↑ SGOT, ↑ SGPT, ↑ alkaline phosphatase, ↑ GGT, ↑↓ hemoglobin, ↑↓ white blood cell count, ↑↓ platelet count, ↑↓ 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 1. 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. 2. 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.

3. 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.
4. Free Thyroid Index reference range 1.1 to 4.6.

Positive syphilis screening.

29b 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%

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

a. Anticonvulsants including but not limited to

31b

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 (H2) 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 (H1) antagonists including but not limited to

Actifed® , Actifed Plus® (triprolidine) Benadryl® , Unisom® , Tylenol P.M.®	3 days
(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
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.

6.10.2 {Rescue Therapy}

6.10.3 {Other Non-investigational Intervention}

6.11 Concomitant Therapy

6.11.1 {Prohibited Concomitant Therapy}

6.11.2 {Permitted Concomitant Therapy}

7 PARTICIPANT DISCONTINUATION OF TRIAL INTERVENTION AND DISCONTINUATION OR WITHDRAWAL FROM TRIAL

11 TRIAL OVERSIGHT AND OTHER GENERAL CONSIDERATIONS

14 APPENDIX: REFERENCES