

# Study Data Reviewer's Guide

SDTM Metadata Submissions Guidelines Team

Study CDISCPILLOT01

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## 1. Introduction

### 1.1 Purpose

This document provides context for tabulation datasets and terminology that benefit from additional explanation beyond the Define-XML document (define.xml). In addition, this document provides a summary of SDTM conformance findings.

### 1.2 Acronyms

Acronym	Translation
ISR	Injection Site Reaction

### 1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	3.3
Controlled Terminology	2020-12-18
Define-XML	2.1
SDTMIG-MD	1.1
Medications Dictionary	Medications were not coded
Medical Events Dictionary	Medical events were not coded

## 2. Protocol Description

### 2.1 Protocol Number and Title

Protocol Number: CDISCPIL0T01

Protocol Title: Safety and Efficacy of Zanomaline in Patients with Mild to Moderate Alzheimer's Disease.

Protocol Versions:

- Original, October 4, 2012.
- Amendment 1, December 23, 2012.

Amendment 1 changed the vital sign collections of heart rate and blood pressure to be collected in triplicate instead of single measurements. Both versions of the Vital Signs CRF

pages are included in the annotated CRF and are indicated by version numbers in the bottom right of the CRF page, as well as by bookmarks and TOC. These are discussed in [Section 3.3](#).

Exclusion criteria 12 and 31 were also updated in Amendment 1, please see [Appendix I: Inclusion/Exclusion Criteria](#) for the full text.

## 2.2 Protocol Design

Epoch		Screening		Treatment									
Visit		1	2	3	4	5	7	8	9	10	11	12 or Early Discontinuation Retrieval	13
Week		-2	(Day -1)	0	2	4	6	8	12	16	20	24	26
ARM	Zanomaline High Dose (81 mg)	Screening	Titrate (54 mg)	High (81 mg)									Titrate (54 mg)
	Zanomaline Low Dose (54 mg)	Screening	Low (54 mg)										
	Placebo	Screening	Placebo										
				Note : Early Discontinuations go to Early Discontinuation Retrieval									

This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel group study. After a two week screening EPOCH, subjects were randomized to placebo, low dose or high dose. The treatment Epoch was 26 weeks long. The LOW and PLACEBO treatment Elements were 26 weeks long, while the HIGH treatment Element was 24 weeks long, with week long titration Elements at the beginning and the end. Subjects who discontinued early returned for a visit on Week 24. Those subjects remained in the treatment Epoch.

## 2.3 Trial Design Datasets

Are Trial Design datasets included in the submission?

Yes.

### 2.3.1 TI – Trial Inclusion/Exclusion Criteria

Please see [Appendix I: Inclusion/Exclusion Criteria](#) for a complete list of IE criteria.

### 2.3.2 TS – Trial Summary

Since this is a sample submission and the drug is fictional and the trial is not listed in ClinicalTrials.gov then the UNII and ClinicalTrial.gov codes included in TS are obviously fictional but included as examples of how the values should be populated.

### 3. Subject Data Description

#### 3.1 Overview

Are the submitted data taken from an ongoing study?

No.

Were the SDTM datasets used as sources for the analysis datasets?

Yes.

Do the submission datasets include screen failures?

Yes, screen failure data is in DM, DS, IE, SE and SV.

Were any domains planned, but not submitted because no data were collected?

Yes, NV (Nervous System Findings) was not submitted as no EEGs were performed.

Also SUPPOE was planned but no OE findings were considered clinically significant so the SUPQUAL dataset was not created.

Are the submitted data a subset of collected data?

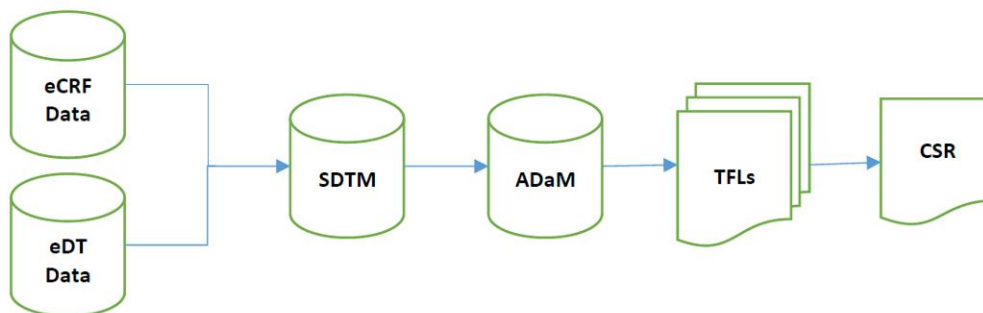
No.

Is adjudication data present?

No.

#### 3.2 Traceability Flow Diagram

As seen below, the study followed a basic data flow:



#### 3.3 Annotated CRFs

There are three different VS pages, used at different Visits. In addition to pulse and blood pressure measurements, one page also collected temperature, one collected temperature and weight, and one collected temperature, weight and height. Each of these pages were updated during the trial at the end of 2012, the updated version having the pulse and blood pressure in triplicate, with the iterations

being indicated by VSREPNUM. All versions of these CRF pages are included in the annotated CRF and have bookmarks to indicate the different versions. The versions are also indicated in the TOC. Please see Figure 1 below for sample CRF pages, with the original version on the left.

All annotations of "NOT SUBMITTED" were prompt questions which are not included as part of the SDTM data.

**Figure 1) Modified Vital Signs CRF Pages**

VITAL SIGNS	VITAL SIGNS
Vital Signs Collected? <input type="radio"/> Yes <input type="radio"/> No	Vital Signs Collected? <input type="radio"/> Yes <input type="radio"/> No
Visit <input type="text"/>	Visit <input type="text"/>
Date <input type="text"/> <input type="text"/> <input type="text"/>	Date <input type="text"/> <input type="text"/> <input type="text"/>
Weight <input type="text"/> pounds	Weight <input type="text"/> pounds
Height <input type="text"/> inches	Height <input type="text"/> inches
Temperature <input type="text"/> F	Temperature <input type="text"/> F
<b>Pulse and Blood Pressure (Supine)</b> Pulse <input type="text"/> bpm Systolic <input type="text"/> mmHg Diastolic <input type="text"/> mmHg	<b>1st Measurement (Supine)</b> Pulse <input type="text"/> bpm Systolic <input type="text"/> mmHg Diastolic <input type="text"/> mmHg
	<b>2nd Measurement (Standing)</b> Pulse <input type="text"/> bpm Systolic <input type="text"/> mmHg Diastolic <input type="text"/> mmHg
	<b>3rd Measurement (Standing)</b> Pulse <input type="text"/> bpm Systolic <input type="text"/> mmHg Diastolic <input type="text"/> mmHg

### 3.4 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	Custom	SUPP-	Related Using RELREC
<a href="#">AE – Adverse Events</a>		X				DD, DS, FA
CM – Concomitant Medications		X				
DD – Death Details		X				AE
<a href="#">DM – Demographics</a>			X		X	
DS – Disposition			X			AE
<a href="#">EC – Exposure as Collected</a>			X		X	
EX – Exposure			X			
FA – Findings About Events or Interventions		X				AE
FT – Functional Tests	X					
IE – Inclusion/Exclusion Criteria Not Met			X			
<a href="#">LB – Laboratory Test Results</a>		X				
MH – Medical History			X			
<a href="#">NV – Nervous System Findings</a>		X			X	
OE – Ophthalmic Examinations			X			
<a href="#">QSPH – Questionnaires-QSPH</a>	X					
<a href="#">QSSL – Questionnaires-QSSL</a>	X					
RS – Disease Response and Clin Classification	X					
SE – Subject Elements			X			
SV – Subject Visits			X			
VS – Vital Signs		X				

### 3.4.1 AE – Adverse Events

There are two AE CRFs, one for spontaneously reported AEs, one for Injection Site Reactions (ISRs). AETERM for the ISRs defaults to "Injection Site Reaction" while the details of the reaction, pain, induration, etc., are contained in the FA domain. RELREC is used to show the relationships between the domains.

### 3.4.2 DM – Demographics

The following variables are represented in the SUPPDM dataset. Note: RACE4 and RACE5 were not included in the data as no subject reported more than 3 races.

QNAM	Description
RACE1	Race 1
RACE2	Race 2
RACE3	Race 3
RACE4	Race 4
RACE5	Race 5

### 3.4.3 EC – Exposure as Collected

EC represents the exposure data as collected, and it contains the amount of study drug (ECDOSE) injected in "mL" (ECDOSU), as well as the strength of the solution (ECPSTRG) in "g/L" (ECPSTRGU). The strength of the solution is blinded at the time of administration, but is used, along with the dose, to calculate the total dose of study drug (EXDOSE) in EX resulting in the protocol specified unit of "mg" (EXDOSU).

The following variables are represented in the SUPPEC dataset.

QNAM	Description
ECREASOC	Reason for Occur Value

### 3.4.4 LB – Laboratory Test Results

An unsplit LB is included in the "sdtm" folder and represented in the Define-XML document as a single table. Because of the excessive file size, LB is then split by category, LBCAT, into LBCH ("Chemistry"), LBHE ("Hematology") and LBUR ("Urinalysis" and "Other"). The split datasets have been placed into the "split" sub-folder.



### 3.4.5 NV – Nervous System Findings

The criteria specified in the protocol which required an EEG to be performed did not occur, and so NV is not included in the submission. SUPPNV was also planned and is not included. Both are indicated in the Define-XML document with HasNoData attribute set to “Yes”.

The following variables are represented in the SUPPNV dataset.

QNAM	Description
NVCLSIG	Clinically Significant

### 3.4.6 QS – Questionnaires-QSPH

QS was split by sponsor decision. QSPH contains the Patient Health Questionnaire-9 data.

### 3.4.7 QS – Questionnaires-QSSL

QS was split by sponsor decision. QSSL contains the Satisfaction with Life Survey data.

## 4. Data Conformance Summary

### 4.1 Conformance Inputs

Were validation checks performed to evaluate conformance?

Yes, the XPT files along with the Define-XML document were evaluated programmatically by the SDTM MSG team. At the completion of this version of the MSG, no public validators were available to validate SDTMIG v3.3 data. Because this is a CDISC reference document rather than an actual submission, no specific tools are indicated, but the CDISC v3.3 business rules were used.

Were sponsor-defined validation rules used to evaluate conformance?

No.

Were the SDTM datasets evaluated in relation to define.xml?

Yes.

Was define.xml evaluated?

Yes, the Define-XML document was evaluated manually and programmatically by the SDTM MSG team. At the completion of this version of the MSG, no public validators were available to validate Define-XML v2.1.

## 4.2 Issues Summary

(Note: As validation tools for 3.3 were not available at the time this document was created, only a sample of checks that would have fired are included.)

Dataset	Publisher ID	Diagnostic Message	Severity	Count	Explanation
AE	CG0042	No qualifiers set to 'Y', when AE is Serious	Severe	1	Subject CDISC003 had an AE of Epistaxis on 2013-09-30 with AESER set to "Y" without any of the individual serious qualifiers set to "Y" also. The site was queried several times but the data were not updated.
LB	CG0303	Variable label ("Lab Test or Examination Short Name") not equal to IG label ("Lab Test or Examination Short Name.").	Mild	1	SDTMIG v3.3 added a period to the end of the label, this was corrected in v3.4. The correct (v3.4) version was used in the LB domain.

## 4.3 Additional Conformance Details

This section is not applicable as no additional compliance details are available.

**Appendix I: Inclusion/Exclusion Criteria**

<b>Protocol/ Amendment Version</b>	<b>Category</b>	<b>IETESTCD</b>	<b>Full Text of Criterion</b>
Original	Inclusion	INCL01	Males and postmenopausal females at least 50 years of age.
Original	Inclusion	INCL02	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 (Protocol Attachment LZZT.7).
Original	Inclusion	INCL03	MMSE score of 10 to 23.
Original	Inclusion	INCL04	Modified Hachinski Ischemic Scale score of 4. (Protocol Attachment LZZT.8).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Inclusion	INCL05	<p>CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year. The following findings are incompatible with AD.</p> <ol style="list-style-type: none"> <li>1. Large vessel strokes <ol style="list-style-type: none"> <li>a. Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory.</li> <li>b. Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts.</li> </ol> </li> </ol> <p>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.</p> <p>Only one such questionable area allowed per scan, and size is restricted to 1 cm in frontal/parietal/temporal cortices and 2 cm in occipital cortex.</p> <ol style="list-style-type: none"> <li>2. Small vessel ischemia <ol style="list-style-type: none"> <li>a. 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.</li> <li>b. 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.</li> </ol> </li> <li>3. Miscellaneous <ol style="list-style-type: none"> <li>a. Benign small extra-axial tumors (ie, meningiomas) are accepted if they do not contact or indent the brain parenchyma.</li> <li>b. Small extra-axial arachnoid cysts are accepted if they do not indent or deform the brain parenchyma.</li> </ol> </li> </ol>
Original	Inclusion	INCL06	Investigator has obtained informed consent signed by the patient (and/or legal representative) and by the caregiver.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Inclusion	INCL07	Geographic proximity to investigator's site that allows adequate follow-up.
Original	Inclusion	INCL08	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.
Original	Exclusion	EXCL09	Persons who have previously completed or withdrawn from this study or any other investigating Zanomaline TTS or the oral formulation of Zanomaline.
Original	Exclusion	EXCL10	Use of any investigational agent or approved Alzheimer's therapeutic medication within 30 days prior to enrollment into the study.
Original	Exclusion	EXCL11	Serious illness which required hospitalization within 3 months of screening.
Original	Exclusion	EXCL12	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
Original	Exclusion	EXCL13	Episode of depression meeting DSM-IV criteria within 3 months of screening.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Exclusion	EXCL14	A history within the last 5 years of the following: a) Schizophrenia b) Bipolar Disease c) Ethanol or psychoactive drug abuse or dependence.
Original	Exclusion	EXCL15	A history of syncope within the last 5 years.
Original	Exclusion	EXCL16	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
Original	Exclusion	EXCL17	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
Original	Exclusion	EXCL18	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

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Exclusion	EXCL19	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
Original	Exclusion	EXCL20	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.
Original	Exclusion	EXCL21	A history within the last 5 years of a serious genitourinary disorder, including a) Renal failure b) Uncontrolled urinary retention
Original	Exclusion	EXCL22	A history within the last 5 years of a serious rheumatologic disorder, including a) Lupus b) Temporal arteritis c) Severe rheumatoid arthritis
Original	Exclusion	EXCL23	A known history of human immunodeficiency virus (HIV) within the last 5 years.
Original	Exclusion	EXCL24	A history within the last 5 years of a serious infectious disease including a) Neurosyphilis b) Meningitis c) Encephalitis
Original	Exclusion	EXCL25	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.
Original	Exclusion	EXCL26	Visual, hearing, or communication disabilities impairing the ability to participate in the study; (for example, inability to speak or understand English, illiteracy).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Exclusion	EXCL27	Laboratory test values exceeding the 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.
Original	Exclusion	EXCL28	Central laboratory test values below reference range for folate, and vitamin B12, and outside reference range for thyroid function tests.
Original	Exclusion	EXCL29	Positive syphilis screening with confirmatory testing.
Original	Exclusion	EXCL30	Central laboratory test value above reference range for glycosylated hemoglobin (A1C) (insulin dependent diabetes mellitus patients only)



Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Exclusion	EXCL31	<p>Treatment with the following medications within 1 month prior to enrollment</p> <p>a) Anticonvulsants including but not limited to</p> <ul style="list-style-type: none"> <li>- Tegretol (carbamazepine)</li> <li>- Depakote (valproic acid)</li> </ul> <p>b) Alpha receptor blockers including but not limited to</p> <ul style="list-style-type: none"> <li>- Catapres (clonidine)</li> <li>- Aldomet (methyldopa)</li> </ul> <p>c) Calcium channel blockers that are CNS active including but not limited to</p> <ul style="list-style-type: none"> <li>- Nimotop (nimodipine)</li> </ul> <p>d) Beta blockers including but not limited to</p> <ul style="list-style-type: none"> <li>- Inderal (propranolol)</li> <li>- Tenormin (atenolol)</li> </ul> <p>e) Beta sympathomimetics (unless inhaled) including but not limited to</p> <ul style="list-style-type: none"> <li>- Proventil Repetabs , Ventolin tablets (albuterol tablets)</li> <li>- Dopamine</li> </ul> <p>f) Parasympathomimetics (cholinergics) (unless ophthalmic) including but not limited to</p> <ul style="list-style-type: none"> <li>- Urecholine (bethanechol)</li> <li>- Reglan (metoclopramide)</li> </ul> <p>g) Muscle relaxants-centrally active including but not limited to</p> <ul style="list-style-type: none"> <li>- Flexeril (cyclobenzaprine)</li> <li>- Soma (carisoprodol)</li> </ul> <p>h) Monoamine oxidase inhibitors (MAOI) including but not limited to</p> <ul style="list-style-type: none"> <li>- Nardil (phenelzine)</li> <li>- Eldepryl (selegiline)</li> <li>- Parnate (tranylcypromine)</li> </ul> <p>limited to</p> <ul style="list-style-type: none"> <li>- Theo-Dur (theophylline)</li> </ul>

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Original	Exclusion	EXCL31 (continued)	<p>m) Histamine (H2) antagonists including but not limited to</p> <ul style="list-style-type: none"> <li>- Tagamet (cimetidine)</li> <li>- Axid (nizatidine)</li> </ul> <p>n) Narcotic Analgesics including but not limited to</p> <ul style="list-style-type: none"> <li>- Darvocet-N 100 , Propacet (propoxyphene + acetaminophen)Percocet (oxycodone with acetaminophen) and Tylenol with codeine #2, #3, #4</li> </ul> <p>(acetaminophen + codeine) ARE allowed in the month prior to enrollment, but are not permitted in the 4 days prior to enrollment.</p> <p>o) Neuroleptics (antipsychotics) including but not limited to</p> <ul style="list-style-type: none"> <li>- Haldol (haloperidol)</li> <li>- Mellaril (thioridazine)</li> </ul> <p>The use of neuroleptics on an as needed basis is permitted during the month prior to enrollment, but are to be discontinued at least 7 days prior to enrollment.</p> <p>p) Antianxiety agents including but not limited to</p> <ul style="list-style-type: none"> <li>- BuSpar (buspirone)</li> <li>- Librium (chlordiazepoxide)</li> </ul> <p>Ativan (lorazepam) is allowed on an as needed basis in the month prior to enrollment, but is not permitted in the 24 hours prior to enrollment.</p> <p>q) Hypnotics/Sedatives including but not limited to</p> <ul style="list-style-type: none"> <li>- Restoril (temazepam)</li> </ul> <p>Chloral Hydrate is allowed on an as needed basis in the month prior to enrollment, but is not permitted in the 24 hours prior to enrollment.</p>
Amendment 1	Inclusion	INCL01	Males and postmenopausal females at least 50 years of age.
Amendment 1	Inclusion	INCL02	<p>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 (Protocol Attachment LZZT.7).</p>

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Inclusion	INCL03	MMSE score of 10 to 23.
Amendment 1	Inclusion	INCL04	Modified Hachinski Ischemic Scale score of £4. (Protocol Attachment LZZT.8).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Inclusion	INCL05	<p>CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year. The following findings are incompatible with AD.</p> <ol style="list-style-type: none"> <li>1. Large vessel strokes <ol style="list-style-type: none"> <li>a. Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory.</li> <li>b. Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts.</li> </ol> <p>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.</p> <p>Only one such questionable area allowed per scan, and size is restricted to 1 cm in frontal/parietal/temporal cortices and 2 cm in occipital cortex.</p> </li> <li>2. Small vessel ischemia <ol style="list-style-type: none"> <li>a. 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.</li> <li>b. 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.</li> </ol> </li> <li>3. Miscellaneous <ol style="list-style-type: none"> <li>a. Benign small extra-axial tumors (ie, meningiomas) are accepted if they do not contact or indent the brain parenchyma.</li> <li>b. Small extra-axial arachnoid cysts are accepted if they do not indent or deform the brain parenchyma.</li> </ol> </li> </ol>

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Inclusion	INCL06	Investigator has obtained informed consent signed by the patient (and/or legal representative) and by the caregiver.
Amendment 1	Inclusion	INCL07	Geographic proximity to investigator's site that allows adequate follow-up.
Amendment 1	Inclusion	INCL08	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.
Amendment 1	Exclusion	EXCL09	Persons who have previously completed or withdrawn from this study or any other investigating Zanomaline TTS or the oral formulation of Zanomaline.
Amendment 1	Exclusion	EXCL10	Use of any investigational agent or approved Alzheimer's therapeutic medication within 30 days prior to enrollment into the study.
Amendment 1	Exclusion	EXCL11	Serious illness which required hospitalization within 3 months of screening.
Amendment 1	Exclusion	EXCL12A	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.
Amendment 1	Exclusion	EXCL13	Episode of depression meeting DSM-IV criteria within 3 months of screening.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Exclusion	EXCL14	A history within the last 5 years of the following: a) Schizophrenia b) Bipolar Disease c) Ethanol or psychoactive drug abuse or dependence.
Amendment 1	Exclusion	EXCL15	A history of syncope within the last 5 years.
Amendment 1	Exclusion	EXCL16	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
Amendment 1	Exclusion	EXCL17	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
Amendment 1	Exclusion	EXCL18	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

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Exclusion	EXCL19	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
Amendment 1	Exclusion	EXCL20	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.
Amendment 1	Exclusion	EXCL21	A history within the last 5 years of a serious genitourinary disorder, including a) Renal failure b) Uncontrolled urinary retention
Amendment 1	Exclusion	EXCL22	A history within the last 5 years of a serious rheumatologic disorder, including a) Lupus b) Temporal arteritis c) Severe rheumatoid arthritis
Amendment 1	Exclusion	EXCL23	A known history of human immunodeficiency virus (HIV) within the last 5 years.
Amendment 1	Exclusion	EXCL24	A history within the last 5 years of a serious infectious disease including a) Neurosyphilis b) Meningitis c) Encephalitis
Amendment 1	Exclusion	EXCL25	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.
Amendment 1	Exclusion	EXCL26	Visual, hearing, or communication disabilities impairing the ability to participate in the study; (for example, inability to speak or understand English, illiteracy).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Exclusion	EXCL27	Laboratory test values exceeding the 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.
Amendment 1	Exclusion	EXCL28	Central laboratory test values below reference range for folate, and vitamin B12, and outside reference range for thyroid function tests.
Amendment 1	Exclusion	EXCL29	Positive syphilis screening with confirmatory testing.
Amendment 1	Exclusion	EXCL30	Central laboratory test value above reference range for glycosylated hemoglobin (A1C) (insulin dependent diabetes mellitus patients only)



Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Exclusion	EXCL31A	<p>Treatment with the following medications within 1 month prior to enrollment</p> <p>a) Anticonvulsants including but not limited to</p> <ul style="list-style-type: none"> <li>- Tegretol (carbamazepine)</li> <li>- Depakote (valproic acid)</li> </ul> <p>b) Alpha receptor blockers including but not limited to</p> <ul style="list-style-type: none"> <li>- Catapres (clonidine)</li> <li>- Aldomet (methyldopa)</li> </ul> <p>c) Calcium channel blockers that are CNS active including but not limited to</p> <ul style="list-style-type: none"> <li>- Nimotop (nimodipine)</li> </ul> <p>d) Beta blockers including but not limited to</p> <ul style="list-style-type: none"> <li>- Inderal (propranolol)</li> <li>- Tenormin (atenolol)</li> </ul> <p>e) Beta sympathomimetics (unless inhaled) including but not limited to</p> <ul style="list-style-type: none"> <li>- Proventil Repetabs , Ventolin tablets (albuterol tablets)</li> <li>- Dopamine</li> </ul> <p>f) Parasympathomimetics (cholinergics) (unless ophthalmic) including but not limited to</p> <ul style="list-style-type: none"> <li>- Urecholine (bethanechol)</li> <li>- Reglan (metoclopramide)</li> </ul> <p>g) Muscle relaxants-centrally active including but not limited to</p> <ul style="list-style-type: none"> <li>- Flexeril (cyclobenzaprine)</li> <li>- Soma (carisoprodol)</li> </ul> <p>h) Monoamine oxidase inhibitors (MAOI) including but not limited to</p> <ul style="list-style-type: none"> <li>- Nardil (phenelzine)</li> <li>- Eldepryl (selegiline)</li> <li>- Parnate (tranlycypromine)</li> </ul> <p>limited to</p> <ul style="list-style-type: none"> <li>- Theo-Dur (theophylline)</li> </ul>

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Amendment 1	Exclusion	EXCL31A (continued)	<p>m) Histamine (H2) antagonists including but not limited to</p> <ul style="list-style-type: none"> <li>- Tagamet (cimetidine)</li> <li>- Axid (nizatidine)</li> </ul> <p>n) Narcotic Analgesics including but not limited to</p> <ul style="list-style-type: none"> <li>- Darvocet-N 100 , Propacet (propoxyphene + acetaminophen)Percocet (oxycodone with acetaminophen) and Tylenol with codeine #2, #3, #4</li> </ul> <p>(acetaminophen + codeine) ARE allowed in the month prior to enrollment, but are not permitted in the 4 days prior to enrollment.</p> <p>o) Neuroleptics (antipsychotics) including but not limited to</p> <ul style="list-style-type: none"> <li>- Haldol (haloperidol)</li> <li>- Mellaril (thioridazine)</li> </ul> <p>The use of neuroleptics on an as needed basis is permitted during the month prior to enrollment, but are to be discontinued at least 7 days prior to enrollment.</p> <p>p) Antianxiety agents including but not limited to</p> <ul style="list-style-type: none"> <li>- BuSpar (buspirone)</li> <li>- Librium (chlordiazepoxide)</li> </ul> <p>Ativan (lorazepam) is allowed on an as needed basis in the month prior to enrollment, but is not permitted in the 24 hours prior to enrollment.</p> <p>q) Hypnotics/Sedatives including but not limited to</p> <ul style="list-style-type: none"> <li>- Restoril (temazepam)</li> </ul> <p>Chloral Hydrate is allowed on an as needed basis in the month prior to enrollment, but is not permitted in the 24 hours prior to enrollment.</p> <p>r) Histamine (H1) antagonists including but not limited to</p> <ul style="list-style-type: none"> <li>- Benadryl (diphenhydramine)</li> <li>- Seldane (terfenadine)</li> </ul> <p>Intermittent use of these antihistamines is permitted during the month prior to enrollment, but is not permitted in the 4 days prior to enrollment.</p>