CLINICAL STUDY PROTOCOL

An Open-Label, Extension Study of the Effects of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Alzheimer's Disease or Behavioral Variant Frontotemporal Dementia

STUDY CODE: TRx-237-020

STUDY PHASE: 3

VERSION 3.0 DATED 24 MARCH 2016

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VERSION 2.1 DATED 22 JUNE 2015

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VERSION 1.0 DATED 25 APRIL 2014

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1 PROTOCOL APPROVAL, RESPONSIBLE PERSONNEL, AND INVESTIGATOR SIGNATURES

1.1 Protocol Approval

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Signature Date

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1.3 Investigator Signature Sheet

By signing below, I agree to the conditions relating to this study as set out in this protocol (TRx-237-020 dated 24 March 2016).

I agree to conduct this study according to Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

I fully understand that any changes instituted by me without previous discussion with TauRx or their designated representative constitute a violation of the protocol.

I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the subject.

I will ensure that the drugs supplied by TauRx will be used only for administration to subjects enrolled in this study and for no other purpose.

Study Site Principal Investigator's Name, Title, Address and Contact Information:

_____
_____
_____
_____
_____
_____

Signature: _____ Date: _____

SYNOPSIS

Name of Sponsor / Company: **TauRx Therapeutics Ltd (TauRx)**	
Name of Finished Product: **Leuco-methylthioninium bis(hydromethanesulfonate) (LMTM, TRx0237) Tablets, 100 mg**	
Name of Active Ingredient: **Methylthioninium (MT)**	
Number and Title of Study: TRx-237-020: An Open-Label, Extension Study of the Effects of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Alzheimer's Disease or Behavioral Variant Frontotemporal Dementia	
Study Site(s): Approximately 170 sites in North America, Europe, Asia, and Australia	
Study Duration: The study will continue until alternate options for access to treatment are available, *i.e.*, commercialization or, depending on country, on a Named Patient or compassionate basis or *via* a Managed Access Program.	**Phase of Development:** Phase 3
Objectives: The primary objectives of this open-label extension study are to provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the long-term safety and tolerability of leuco-methylthioninium bis(hydromethanesulfonate) given in flexible doses of up to 300 mg/day, or in those countries where limited by a Competent Authority (CA) or Ethics Committee (EC), 200 mg/day.	
Study Design: This is a multicenter, flexible dose, open-label extension study. Appropriateness of continued treatment will be re-evaluated every 12 months on the basis of benefit and safety/tolerability; informed consent must be obtained for each subsequent extension. For subjects who do not re-enroll for a subsequent extension of treatment, identified end of treatment evaluations will be performed at the final on-treatment visit (*e.g.*, Visit 6). If a subject discontinues prematurely, an early termination visit should be conducted at which time all assessments identified for Visit 6 should be performed. For subjects who cease to take LMTM, a post-treatment follow-up visit 4 weeks after the last dose of study drug is to be scheduled, regardless of the reason for discontinuation. The trial will be monitored for safety by a Data Safety Monitoring Board (DSMB) throughout its duration.	
Number of Subjects: It is anticipated that approximately 1050 to 1400 subjects may enroll if all eligible subjects elect to continue treatment beyond the double-blind study in which they participated (assuming 60 to 80% of subjects in each double-blind study complete).	
Subject Population: ***Inclusion Criteria*** 1. Subjects with a diagnosis according to NIA/AA criteria of all cause dementia and probable Alzheimer's disease (AD) at enrollment and who completed participation in one of the following three TauRx studies (inclusive of the 4-week post-treatment follow-up visit): TRx-237-005, TRx-237-008, or TRx-237-015[1]. OR Subjects with a diagnosis of probable bvFTD according to the International Consensus Criteria for behavioral variant frontotemporal dementia (bvFTD) at enrollment and who completed participation in TauRx study TRx-237-007 through Visit 9 (Week 52). Treatment will not be made available to subjects who have withdrawn from the double-blind study of prior participation prior to completion.	

[1] Subjects who participated in Study TRx-237-015 and did not consent to extended treatment for up to 15 months as per Protocol Version 3.0 (extended from 12 months as per the original study protocol) may be enrolled into this open-label extension study following completion of the 12-month double-blind treatment period and 4-week post-treatment follow-up visit for Study TRx-237-015.

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Name of Active Ingredient: **Methylthioninium (MT)**

2. Females of child-bearing potential must continue to use adequate contraception (or, if in Italy, agree to avoid pregnancy) defined as follows:
   - barrier method (such as condom, diaphragm or cervical/vault cap) with spermicidal foam, gel, film, cream, or suppository; intrauterine device (IUD) or system; oral or long-acting injected or implanted hormonal contraceptives for at least 3 months prior to Baseline; or vasectomized partner (with the appropriate post-vasectomy documentation of the absence of spermatozoa in the ejaculate); or true abstinence (when this is in line with the preferred and usual lifestyle of the subject)
   - subjects must agree to continue to maintain adequate contraception throughout participation in the study
3. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) consistent with national law and IRB/EC approval, is/are able to read, understand, and provide written informed consent in the designated language of the study site
   - In Germany and the Netherlands, subjects must be able to provide their own written informed consent (see Section 13)
4. Has an identified adult caregiver who meets the following criteria:
   - Either lives with the subject or sees the subject on average for ≥ 1 hour/day ≥ 3 days/week, and in the investigator's opinion, the extent of contact is sufficient to provide meaningful assessment of changes in subject behavior and function over time and provide information on safety and tolerability
   - Is willing to provide written informed consent for his/her own participation
   - Is able to read, understand, and speak the designated language at the study site
   - Agrees to accompany the subject to each study visit
   - Is able to verify daily compliance with study drug
5. Able to comply with the study procedures in the view of the investigator

Exclusion Criteria

1. History of swallowing difficulties (note: study drug should be swallowed whole and MUST NOT be broken crushed, chewed or dissolved in fluids prior to ingestion)
2. Pregnant or breastfeeding
3. Clinically significant laboratory, pulse co-oximetry, electrocardiogram, or imaging abnormality (in original study) or emergent intercurrent illness that, in the judgment of the principal investigator, could result in the risk of participation outweighing the potential benefit
4. Current participation in, or intent to enroll in, a clinical trial of a drug, biologic, device, or medical food
5. In Germany, subjects who meet the following criteria are to be excluded:
   - Subjects who reside in a continuous care or assisted living facility if mandated by an order issued by either the judicial or the administrative authorities
   - Subjects whose willingness to participate in the clinical trial may be unduly influenced by the expectation (regardless of whether justified) of benefits associated with participation, or of a retaliatory response from family, caregivers, or treating personnel in case of refusal to participate

Dose/Route/ Regimen:
The initial dose in this study is LMTM 200 mg/day (one 100-mg tablet given twice daily [*b.i.d.*]). Thereafter, dosing is flexible up to a maximum of 300 mg/day (or in those countries where limited by a CA or EC, 200 mg/day). The dose may be increased (at Visit 3 or at any subsequent dispensing visit as determined by the investigator during the treatment period) or decreased (at any time at or after Visit 2) in one step of 100 mg higher or lower as needed in response to safety assessments and benefit as judged by the investigator. Interruption(s) of dosing (for up to 30 days

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on a given occasion) may also be allowed at any time if the investigator determines this is indicated, *e.g.*, tolerability concerns or laboratory abnormalities. In the event of continued poor tolerance or the need for a dose interruption (for safety reasons) of more than 30 days on a given occasion, subjects should be withdrawn from treatment. LMTM tablets are available in the 100-mg strength only (expressed as MT base equivalents). Study drug shall be dispensed at 3 monthly intervals. Study drug preferably should be taken twice daily, in the morning and evening. Once daily dosing or three times per day dosing are also acceptable; no more than 200 mg is to be administered at one time and the dose shall not exceed a maximum of 300 mg/day (or 200 mg/day in countries limited by a CA or EC). Tablets may be taken with or without meals. Subjects will be instructed to take each dose of study medication with water. Tablets are not to be broken, crushed or chewed or dissolved in fluids prior to ingestion.
Methodology: The final designated visit in the double-blind study in which the subject previously participated will serve as Baseline (designated Visit 1) for this open-label extension study. If the Baseline visit does not coincide with the final double-blind visit, selected assessments will be repeated (see Assessments). Subjects may continue participation at the same site at which they participated in the originating double-blind study or transfer to a geographically close investigational site (that also participated in the same study). Eligibility for continued open-label treatment is to be determined by the original investigator and, if applicable, a referral to a new site made. The new investigator will have access to the subject's prior study eCRFs and is to confirm eligibility; Baseline testing can be repeated as necessary in the judgment of the new investigator. The first on-treatment visit will occur approximately 2 weeks (± 3 days) after Visit 1 (designated Visit 2). Thereafter, on-treatment visits are to occur approximately every 13 weeks (± 14 days) relative to Baseline (*e.g.*, after approximately 13, 26, 39, 52 weeks, *etc.*) or upon early termination. Safety assessments will be performed at each visit. In the intervening time, caregivers will be contacted by telephone at approximately 6 weeks after Baseline. In the event of tolerability problems, subjects and/or caregivers will be asked to contact the investigator and an unscheduled visit will be arranged to assess the subject. Safety assessments will be performed at the final off-treatment follow-up visit (approximately 4 weeks after the last dose of study drug) for subjects who discontinue prematurely or who do not wish to proceed to an additional extension phase. Resource utilization and quality of life will be evaluated at Baseline (if not available from the prior study of participation or within the required time frame as detailed below) and approximately every 6 months thereafter (or upon early termination). The Mini-Mental State Examination (MMSE) will be performed at Baseline (if not available from within the prior 42 days in the previous study of participation) and approximately every 6 months thereafter (or upon early termination). The MMSE scores will be used to inform the evaluation for possible serotonin toxicity (to be included in the targeted physical and neurological examinations).

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Name of Active Ingredient: **Methylthioninium (MT)**

Assessments:

Baseline:

Following the signing of informed consent and review of inclusion and exclusion criteria, the following Baseline assessments are to be performed in order to confirm continued eligibility for the study:

- If the Baseline visit does not coincide with the final double-blind study visit, intervening medical history, adverse events (AEs), and concomitant medication use are to be recorded; serum pregnancy testing in women of childbearing potential is to be performed.
- If the final double-blind study visit occurred more than 42 days prior, additional safety assessments are to be repeated, including seated blood pressure and pulse, body weight, clinical laboratory tests, 12-lead ECG testing, and targeted physical and neurological examinations (including an assessment for signs and symptoms of serotonin toxicity).

Baseline assessments may be repeated (also within 42 days) as determined by the new investigator for subjects transferring to a new site.

Safety and Tolerability:

At each post-Baseline visit (unless otherwise noted), whether or not subjects are on study medication, all AEs, concomitant medications, vital signs, clinical laboratory findings, ECGs, and targeted physical and neurological examinations will be assessed (unless otherwise noted) according to the following:

- AE recording.
- Concomitant medication use.
- Seated blood pressure and pulse (after the subject has been at rest in a seated position for approximately 5 minutes, with pulse recorded over 60 seconds).
- Body weight.
- Standard clinical laboratory testing, including hematology and serum chemistry.
- A serum pregnancy test (women of childbearing potential).
- A 12-lead ECG obtained in triplicate (approximately every 6 months).
- Targeted physical and neurological assessments (including an assessment for signs and symptoms of serotonin toxicity).

Post-treatment safety assessments will be conducted at a follow-up visit, to be scheduled to occur approximately 4 weeks after the last dose of study drug for all subjects who cease to take LMTM (regardless of the reason for discontinuation).

Resource Utilization and Quality of Life:

The following scales will be evaluated at Baseline and approximately every 6 months thereafter (or upon early termination):

- The Resource Utilization in Dementia – short version (RUD-Lite) (to be performed at Baseline if not available from within the prior 42 days in the previous study of participation).
- The EuroQol – 5 Dimension – 5 Level version (EQ-5D-5L) (applied to the subject and to the caregiver on behalf of the subject).

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Statistical Analysis:

The Safety Population will include all subjects who are documented to have taken at least one dose of study drug. Subjects dispensed study medication who subsequently are lost to follow up without any contact are not included in the Safety Population but will be included in the study disposition tabulation and listings. With the exception of study disposition, all tables and listings will be generated on the basis of the Safety Population.

Baseline Characteristics, Dosing, and Study Disposition: Tabular summaries of demographics and baseline characteristics will be prepared based on data collected at the Baseline visit for the original study of participation and at baseline for the open-label extension study. Tabular summaries of concomitant medication use (ongoing at start of study and newly initiated) will be restricted to the open-label extension study.

Tabular summaries will be prepared of study disposition and drug exposure during the open-label extension study (dose and duration as well as the proportions of subjects with dose interruptions and/or dose reductions).

Safety and Tolerability: Tabular summaries and listings will include: AEs coded using the MedDRA version adopted at the start of the double-blind study in which the subject previously participated (Version 15.0 or later); vital signs (blood pressure, pulse, and body weight); laboratory tests; ECGs; targeted physical and neurological examinations; and signs and symptoms of possible serotonin toxicity). Additional safety evaluations, if any, performed to evaluate changes in medical history will be listed (*e.g.*, pulse co-oximetry).

In addition to by-subject listings of all safety data, individuals with laboratory abnormalities, ECG abnormalities, or vital sign measurements that meet pre-specified criteria for possible clinical significance will be listed separately, taking into consideration their results from the original double-blind study of participation. The numbers of subjects for each parameter will be tabulated (by visit and overall).

For health economics and quality of life measures, the individual items and overall scores for the RUD-Lite and the EQ-5D-5L will be summarized descriptively by visit. Results will be listed by subject. A summary of the planned analyses is provided in the statistical analysis section of this protocol; a detailed description of the planned analyses, as well as intended sensitivity analyses, will be provided in the Statistical Analysis Plan.

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

Abbreviation	Definition
β-hCG	beta subunit of human chorionic gonadotropin
5-HTP	5-hydroxytryptophan
AA	Alzheimer's Association
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's Disease
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AMG	Arzneimittelgesetz (German Drug Law)
ARIA	amyloid related imaging abnormalities
AST	aspartate transaminase
ATC	Anatomical Therapeutic Classification
b.i.d.	twice daily
bpm	beats per minute
bvFTD	behavioral variant Frontotemporal Dementia
°C	Degrees Celsius
CA	Competent Authority
CCA	cost consequence analysis
CFR	Code of Federal Regulations (United States)
CK	creatine kinase
CNS	Central Nervous System
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CUA	cost utility analysis
CV	curriculum vitae
CYP	Cytochrome P450
DES	Discrete Event Simulations
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol – 5 Dimension – 5 Level
EU	European Union

Abbreviation	Definition
FDA	Food and Drug Administration (United States)
g, kg, mg	gram, kilogram, milligram
GCP	Guidelines for Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability Accountabilty Act
ICER	incremental cost effectiveness ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
IWRS	interactive web response system
L, dL, mL	liter, deciliter, milliliter
LDH	lactate dehydrogenase
LMT	leuco-methylthioninium
LMTB	leuco-methylthioninium-dihydrobromide
LMTM	leuco-methylthioninium bis(hydromethanesulfonate)
MAO A	monoamine oxidase A
MAO B	monoamine oxidase B
MAPT	microtubule-associated protein tau
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mmHg	millimeters of mercury
mmol	millimole
MRI	magnetic resonance imaging
MMSE	Mini-Mental State Examination
msec	millisecond(s)
MT	Methylthioninium
MTC	methylthioninium chloride
NDA	New Drug Application
NIA	National Institute on Aging
P-gp	P-glycoprotein
PE	physical examination

Abbreviation	Definition
QA	quality assurance
QALY	quality adjusted life years
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RUD-Lite	Resource Utilization in Dementia – short version
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States of America
WBC	white blood cell
WCT	Worldwide Clinical Trials
WHO	World Health Organization

2 BACKGROUND

Methylthioninium (MT) is proposed for treatment of Alzheimer's disease (AD) and other dementias that involve pathology of the microtubule associated protein tau, and with potential for benefit in other progressive neurodegenerative diseases characterized by pathological protein aggregation. The investigational product LMTM (also referred to as leuco-methylthioninium dihydromesylate and LMT.2MSOH, as well as by its code name, TRx0237) is a crystalline form of the reduced form of the active MT moiety. Chemically, the drug is named *N,N,N',N'*-tetramethyl-10*H*-phenothiazine-3,7-diaminium bis(methanesulfonate). It is provided as a solid oral immediate-release dosage form. As a dihydromethanesulfonate salt (also known as dimesylate), LMTM stabilizes the reduced form of the MT moiety in the solid state.

AD is a severe irreversible neurodegenerative disease resulting in complete loss of mental faculties. In AD, the microtubule associated protein tau is redistributed exponentially into paired helical filaments forming neurofibrillary tangles which correlate with pyramidal cell destruction (Wischik *et al*., 1997). There is a robust clinico-pathological correlation between tau pathology, tau aggregation, and clinical measures of dementia (Bierer *et al*., 1995; Mukaetova-Ladinska *et al*., 2000). These relationships are maintained from the earliest detectable stages of dementia and progress in parallel with clinical deterioration.

Behavioral variant frontotemporal dementia (bvFTD) is one of the other dementias under investigation. It is a rare, progressive neurodegenerative disease characterized by progressive deterioration of behavior and language, associated with atrophy of the frontal and temporal lobes. Recent developments in molecular genetics and molecular neuropathology have confirmed that the diverse histopathological appearances can actually be understood at the molecular level to be based on deposition within various types of brain cells of aggregated forms of either Tau protein or TDP-43 protein. It is estimated that about half of bvFTD subjects have underlying pathology related to the protein Tau (Hodges *et al*., 2004; Shi *et al*.; 2005), with approximately 10% having tau gene (MAPT) mutations (Rademakers *et al.,* 2004). MT has the potential to provide therapeutic benefit as it is postulated to dissolve neurotoxic aggregates composed of microtubule associated protein Tau and TDP-43 in the brain as well as to prevent further formation.

Details regarding nonclinical and clinical findings from completed studies with LMTM, LMTB, and MTC are described in the Investigator's Brochure.

Double-blind, placebo-controlled trials of LMTM are ongoing in subjects with AD (TRx-237-005 and TRx-237-015) and bvFTD (TRx-237-007). These allow for 12 to 18 months of double-blind treatment at doses of 150 to 250 mg/day (or placebo), depending on the study. At completion of the study in Studies TRx-237-005 and TRx-237-015, subjects are to return for a 4-week post-treatment visit before entering this open-label extension study. Given the nature of the patient population in Study TRx-237-007, subjects are not required to return for a 4-week post-treatment visit prior to entering this open-label extension study (subjects are only required to return for the post-treatment visit if they discontinue participation early or complete treatment but do not enter this extension study). As of 30 September 2015 (data available at the time of the

Development Safety Update Report #4 cut-off date of 14 October 2015), 1902 subjects with AD or bvFTD have been randomized to receive study drug (LMTM or matching placebo) in the ongoing double-blind Phase 3 studies.

A double-blind, placebo-controlled, Phase 2 study was also conducted (TRx-237-008), however, this study was terminated early for administrative reasons; 9 subjects were randomized. These subjects are also eligible for the open-label extension study.

The intent of this extension study is to provide LMTM treatment to those subjects in whom the benefit is judged to outweigh the risk, and to assess the longer-term safety and tolerability of LMTM given in doses of up to 300 mg/day, or in those countries where limited by a Competent Authority (CA) or Ethics Committee (EC), 200 mg/day. Treatment with LMTM in this study will either be *de novo* in subjects having been randomized to placebo or will be a continuation of treatment, albeit not necessarily at the same dose, to those subjects having been previously randomized to LMTM.

LMTM 150 mg/day is the lowest dose to which a subject participating in the Phase 2 or Phase 3 studies may be randomized. However, 200 mg/day has been chosen as the initial dose for continuation of treatment in this open-label extension study as it is intermediate to the doses previously used. This dose has been chosen because 250 mg/day was the active treatment in Study TRx-237-008 and is the active treatment for half of the subjects receiving LMTM in Study TRx-237-015, and 200 mg/day is the active treatment in Studies TRx-237-005 and TRx-237-007. Subjects previously randomized to placebo will receive LMTM for the first time at this dose. All subjects with AD will have undergone at least a 3-week period off-treatment prior to entry into this study; as prior treatment assignment will be blinded, this provides a standardized approach for treating all subjects. Dose interruptions are allowed at any time (to a maximum of 30 days on a given occasion) and dose adjustments are flexible to a minimum of 100 mg/day and a maximum of 300 mg/day (or 200 mg/day in those countries where limited by a CA or EC), to be based on safety and tolerability and benefit as judged by the investigator. As the acceptable risk/benefit balance will vary from subject to subject, the selection of dose is left to the discretion of the investigator, together with the subject and caregiver(s), based on judgment of the risk/benefit balance in any given subject.

Because some subjects will receive LMTM for the first time in this study, the initial safety assessments will be made after 2 weeks. Thereafter, safety assessments will be made approximately every 3 months. Investigators are encouraged to continue with their routine clinical assessment of subjects consistent with good clinical practice to evaluate continued benefit from study participation.

Safety assessments are guided by the accruing safety information in the ongoing double-blind studies. The majority of the safety evaluations made in the double-blind studies will continue; specifically, intervening medical history, adverse events, and concomitant medication use will be assessed and recorded; seated blood pressure and pulse as well as body weight will be measured; clinical laboratory testing will be performed, including serum pregnancy testing in women of childbearing potential; 12-lead electrocardiograms (ECGs) will be monitored; and targeted physical and neurological examinations will be performed. The rationale for not mandating routine pulse co-oximetry measurement,

assessment of the potential for suicide or self-harm, and magnetic resonance imaging (MRI) for amyloid related imaging abnormalities (ARIA) is given below:

- Routine pulse co-oximetry has been included in all studies performed to date. As of 17 August 2015, 6 subjects (< 1%) in the ongoing Phase 3 trials have had a methemoglobin value >3.5% (the pre-specified threshold for possible clinical significance); all were isolated values, the highest of which was 8%. Relevant laboratory-related adverse events of special interest (AESIs) have been reported in only 5 subjects (< 1%): positive Heinz bodies (without other evidence of hemolytic anemia, considered a false positive due to a prolonged delay in preparing the slides for testing); hemolytic anemia (Heinz body negative, recovered with treatment interruption); and 3 reports of isolated increased methemoglobin. Pulse co-oximeters will not be routinely provided to sites and no specific monitoring is mandated in this open-label extension study protocol.
- The Columbia-Suicide Severity Rating Scale (C-SSRS), which queries five aspects of suicidal ideation, is evaluated at each visit in the primary double-blind study of participation. While not validated for use in patients with dementia, the scale has been used in other studies of CNS-active medications and provides a systematic means of collecting data in dementing syndromes for future potential regulatory use. As of 17 August 2015, 69 unique subjects across the ongoing double-blind Phase 3 studies have reported experiencing suicidal thoughts. There were 64 subjects with an on-treatment affirmative C-SSRS score (regardless of pre-treatment score) and 5 subjects with suicidal ideation recorded as an adverse event that was not identified *via* the C-SSRS. The majority of cases represented a general "wish to be dead". Such feelings are not uncommon in these patient populations. This scale will continue to be used in the double-blind Phase 3 studies but not in the open-label extension study as any emergent change is likely to be attributable to the evolution of the underlying disease. At entry into the extension study, subjects receiving active medication will already have been followed for approximately 12 to 19 months for drug-induced change.
- As of 30 September 2015, ARIA has been reported for 12 of 1902 subjects, representing 0.6% of subjects, comparable to or lower than the incidence reported for subjects randomized to placebo in four recently published large Phase 3 studies (two studies per publication) of humanized anti-amyloid-beta monoclonal antibodies, solanezumab and bapineuzumab (Doody *et al*., 2014; Salloway *et al*., 2014). Thus, the frequency of ARIA is not considered to represent a safety signal and MRI monitoring for ARIA will not be undertaken in this open-label extension study.

Electronic Case Report Forms (eCRFs) will be available for recording results of additional safety evaluations should these be warranted in the opinion of the investigator to further evaluate a change in a subject's status (*e.g.*, pulse co-oximetry).

The need for additional safety monitoring for any given subject is to be judged by the investigator based on historical information for the subject from the respective originating double-blind study and/or repeat of selected baseline testing as well as ongoing review of safety measurements made during this open-label extension study.

The formal efficacy rating scales used in the double-blind studies will not be continued given the open-label design of this extension study; however, resource utilization and quality of life will be evaluated approximately every 6 months.

3 OBJECTIVES

The primary objectives of this open-label extension study are to provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the long-term safety and tolerability of LMTM given in flexible doses of up to 300 mg/day (or in those countries where limited by a CA or EC, 200 mg/day).

4 STUDY DESIGN

4.1 General Description

This study is a multicenter, open-label extension study of LMTM in subjects with mild to moderate AD or bvFTD at the time they first enrolled in a double-blind trial.

Participation in this study will be offered to any subject who completed participation in a TauRx-sponsored Phase 2 or Phase 3 double-blind study, *i.e.*, Studies TRx-237-005, TRx-237-007, TRx-237-008, or TRx-237-015. Only AD subjects who have completed the full double-blind period of the originating studies (including the 1-month post-treatment follow-up), or bvFTD subjects who completed the full double-blind treatment period through Visit 9 in TRx-237-007, will be eligible for inclusion in this open-label extension study (see Section 6.2.1 for guidance regarding study drug dosing for bvFTD subjects entering this extension study).

Subjects may enter this study at the final designated visit in the double-blind study, provided subjects and caregivers have had sufficient time to consider the study prior to giving consent, or at any subsequent time. Subjects may continue participation at the same site at which they participated in the originating double-blind study or transfer to a geographically close investigational site (that also participated in the same study). Eligibility for continued open-label treatment is to be determined by the original investigator and, if applicable, a referral to a new site made. The new investigator will have access to the subject's prior study eCRFs and is to confirm eligibility (see Section 5); Baseline testing can be repeated as necessary in the judgment of the new investigator. The initial visit will be designated Visit 1.

The initial LMTM dose is 200 mg/day (one 100-mg tablet twice daily [*b.i.d.*]). The dose may be increased (at Visit 3 or at any subsequent dispensing visit as determined by the investigator during the treatment period) to a maximum of 300 mg/day (or in those countries where limited by a CA or EC, 200 mg/day) in response to benefit as judged by the investigator. Alternatively, the dose may be interrupted at any time (for up to 30 days on a given occasion) or decreased to a minimum of 100 mg/day (at any time at or after Visit 2) as needed in response to safety assessments (see Section 6.2.2). The recommended decrement or increment of dose adjustment is 100 mg/day. The study drug will be dispensed in 13-week (± 2-week) supplies.

The first on-treatment visit will occur approximately 2 weeks after Visit 1 (designated Visit 2) for the initial post-treatment safety assessment. Thereafter, subjects will be seen in the clinic at approximately every 13 weeks (relative to Baseline). Required assessments will be performed at all visits as described in the Schedule of Assessments in Section 4.4 and, for further detail, in Section 7; additional optional safety assessments are also described. Caregivers will be contacted by telephone at the mid-point between Visits 2 and 3; they will also be asked to contact the investigator in response to any safety concern. An unscheduled visit will be arranged to assess the subject as needed.

Resource utilization and quality of life will be evaluated as described in Section 8.

Continued participation will be re-evaluated approximately every 12 months on the basis of safety, tolerability, and continued benefit as judged by the investigator. Subjects deemed eligible for continued treatment (and/or their caregivers) must provide informed consent for re-enrollment. Subjects for whom consent is not provided consistent with national requirements and IRB/EC approval will be discontinued.

For subjects who cease to take LMTM, a post-treatment follow-up visit 4 weeks after the last dose of study drug is to be scheduled, regardless of the reason for discontinuation. Subjects who fail to complete the initial 12-month extension period will not be eligible to continue to receive treatment during any subsequent extension period.

A schematic representation of the first 12 months of the study is provided in Figure 4-1.

Figure 4-1 Schematic Representation of Study (First 12 Months)

	← Open-Label Treatment → LMTM 200 mg/day initial dose and flexible dosing thereafter (to max. 300 mg/day and min. 100 mg/day [a]) (52 weeks)							← Follow up → (4 weeks after last dose)
	First dose of open-label treatment ↓						Last dose [b] ↓	Follow up Visit [c] ↓
Visit	↑ **1**	↑ **2** [a]	**(T)** [d]	↑ **3** [a]	↑ **4**	↑ **5**	↑ **6**	↑ **--**
Week	**0**	**2**	**6**	**13**	**26**	**39**	**52**	**56**
Day (± days)	**1**	**15 (3)**	**43 (14)**	**92 (14)**	**183 (14)**	**274 (14)**	**365 (14)**	**393 (14)**

[a] In those countries where limited by a CA or EC, the maximum allowable dose is 200 mg/day. The dose may be increased (at Visit 3 or at any subsequent dispensing visit as determined by the investigator during the treatment period) or decreased (at any time at or after Visit 2) on the basis of safety; the dose may be interrupted at any time (for up to 30 days on a given occasion). See Section 6.2.2 for more details regarding dose reduction or interruption due to safety and tolerability.

[b] For subjects who do not re-enroll for a subsequent extension of treatment, identified end of treatment evaluations will be performed at the final on-treatment visit (Visit 6). If a subject discontinues prematurely, an early termination visit should be conducted at which time all assessments identified for Visit 6 should be performed. Continued participation will be re-evaluated approximately every 12 months on the basis of safety and continued benefit; informed consent for continued treatment must be provided. The same visit schedule (with the exception of the initial 2-week visit) will be followed for each 12-month treatment period; scheduled visits will be numbered in an ascending fashion.

[c] All subjects who discontinue treatment or who do not wish to proceed to the subsequent extension phase will be seen for a post-treatment follow-up visit 4 weeks after the last dose of study drug.

[d] A telephone contact (T) will occur between the scheduled Weeks 2 and 13 study visits (at approximately Week 6).

4.2 Population

Subjects enrolled into this study will either have a diagnosis according to the National Institute on Aging / Alzheimer's Association (NIA/AA) criteria of all cause dementia and probable Alzheimer's disease or a diagnosis of probable bvFTD according to the International Consensus Criteria for bvFTD (Rascovsky *et al.*, 2007).

Subjects must have completed participation for the full double-blind period in a TauRx-sponsored Phase 2 or 3 double-blind clinical trial in AD (TRx-237-005 [19 months], TRx-237-008 [2 months], or TRx-237-015 [16 months[2]], including the 4-week off-treatment follow-up visit) or for the full double-blind period of 12 months (through Visit 9) in TRx-237-007. Subjects who have withdrawn from the original study, or who have had any treatment interruption longer than 30 days making them ineligible to continue in the original study, will not be eligible to participate in the extension study. In the opinion of the principal investigator, there should be a reasonable expectation of continued benefit and that safety and tolerability findings would not pose an unacceptable risk; see Section 2 for a discussion regarding judgment of the risk/benefit balance in any given subject as well as appropriate safety monitoring in this open-label extension study. The study will be open only to approximately 170 participating sites in North America, Asia, Australia, and Europe. If all eligible subjects elect to continue treatment (assuming 60 to 80% completion), it is anticipated that as many as approximately 1050 to 1400 subjects may enroll.

4.3 Duration

The study will continue until alternate options for access to treatment are available*, i.e.*, commercialization or, depending on country, on a Named Patient or compassionate basis, or availability *via* a Managed Access Program. (See Section 5.4 for a discussion of other reasons for study termination.)

4.4 Schedule of Assessments

Baseline safety assessments may be made at the final designated visit of the prior TauRx study in which the subject was enrolled. For purposes of the open-label extension, these will be designated as Baseline (Visit 1, Day 1). If Visit 1 does not coincide with the final designated visit of the previous double-blind study of participation, medical history, concomitant medication use, and adverse events should be updated; serum pregnancy testing should be performed in women of childbearing potential. If more than 42 days have elapsed since that final visit, additional baseline safety assessments must be repeated. The additional safety assessments include clinical laboratory testing (*e.g.*, hematology and serum chemistry panels), seated blood pressure and pulse, body weight, 12-lead ECG testing, and targeted physical and neurological examinations (including serotonin toxicity assessments). Baseline assessments may be repeated (also within 42 days) as determined by the new investigator for subjects transferring to a different site.

[2] Subjects who participated in Study TRx-237-015 and did not consent to extended treatment for up to 15 months as per Protocol Version 3.0 (extended from 12 months as per the original study protocol) may be enrolled into this open-label extension study following completion of the 12-month double-blind treatment period and 4-week post-treatment follow-up visit for Study TRx-237-015.

During the first year, post-Baseline study visits will occur at approximately 2 weeks (Visit 2), 13 weeks (Visit 3), 26 weeks (Visit 4), 39 weeks (Visit 5), and 52 weeks (Visit 6) after Baseline. Caregivers will be contacted by telephone at approximately 6 weeks after Baseline (the intervening time between Visits 2 and 3).

The majority of the safety assessments (described further in Section 7) will be repeated at each visit, *i.e.*, approximately 2 weeks post-Baseline and at visits occurring approximately every 3 months (13 weeks) relative to Baseline. These assessments include adverse event and concomitant medication recording, seated blood pressure and pulse, body weight, clinical laboratory testing (*e.g.*, hematology and serum chemistry panels), serum pregnancy testing in women of childbearing potential, and targeted physical and neurological examinations. The 12-lead ECGs will be obtained approximately every 6 months (26 weeks) relative to Baseline. Throughout the assessments for safety, the investigator is to be cognizant of the potential for serotonin toxicity, taking the MMSE into consideration as well.

The EQ-5D-5L, applied to the subject and to the caregiver on behalf of the subject, will be evaluated at Baseline (as it is not used in the Phase 3 studies of prior participation). The RUD-Lite will be also be evaluated at Baseline if not available from within the prior 42 days. These evaluations will be repeated approximately every 6 months (26 weeks) relative to Baseline.

The same aforementioned 13-week and 26-week schedules of in-clinic assessments will be maintained for continued treatment beyond the first 12 months (if there is re-consent at Visit 6), with no requirement for the Week 2 visit or Week 6 telephone contact in the second or any subsequent year of participation. Continued treatment will be restricted to those subjects for whom continued benefit is expected by the investigator to outweigh risk and informed consent is provided.

For subjects who do not re-enroll for a subsequent extension of treatment, identified end of treatment evaluations will be performed at the final on-treatment visit (*e.g.*, Visit 6). If a subject discontinues prematurely, an early termination visit should be conducted at which time all assessments identified for Visit 6 should be performed.

Post-treatment safety assessments will be conducted at a follow-up visit, to be scheduled to occur approximately 4 weeks after the last dose of study drug for all subjects who cease to take LMTM (regardless of the reason for discontinuation).

A schedule of assessments is shown in Table 4-1. Assessments are listed by visit in Appendix A: Assessments by Visit.

Table 4-1 Schedule of Assessments

Visit Name	Baseline [a]	First 12 Month Open-Label Extension [b]					Follow-up [c]
Overall Visit Number:	1	2	3	4	5	6	
Months Relative to Baseline Day:	--	--	3	6	9	12	13
Weeks Relative to Baseline Day:	--	2	13	26	39	52	56
(Allowable Time Window in days):	--	(± 3)	(± 14)	(± 14)	(± 14)	(± 14)	(± 14)
Informed Consent (Subject and Caregiver) (M)	X					X [d]	
Inclusion/Exclusion Criteria Review (M)	X						
Concomitant Medication Recording/Review (M)	X*	X	X	X	X	X	X
Adverse Events / Medical History Review (M)	X*	X	X	X	X	X	X
Study Drug Dispensing	X		X	X	X	X [d]	
Study Drug Compliance Assessment [e]		X	X	X	X	X	
Blood Samples for Laboratory Tests	X*	X	X	X	X	X	X
Serum Pregnancy Test (women of childbearing potential)	X*	X	X	X	X	X	X
Seated Blood Pressure and Pulse	X*	X	X	X	X	X	X
Temperature and Respiratory Rate	X*	X	X	X	X	X	X
Body Weight	X*	X	X	X	X	X	X
12-Lead Electrocardiogram [f]	X*			X		X	X
Physical and Neurological Examination (M) [g]	X*	X	X	X	X	X	X
MMSE [h]	X*			X		X	X
RUD-Lite	X*			X		X	
EQ-5D-5L [i]	X			X		X	

Notes: (M) = requires medical assessor

[a] Unless otherwise indicated, the safety assessments completed at the final designated visit of the prior TauRx double-blind study in which the subject was enrolled will serve as Baseline (Day 1) for this extension study and are not required to be repeated. If the final visit does not coincide with the open-label Baseline visit, changes in medical history, adverse events, and concomitant medication use are to be recorded, and serum pregnancy testing in women of childbearing potential performed. If it occurred more than 42 days prior, the assessments indicated by an asterisk (*) are to be repeated. Baseline assessments may be repeated (also within 42 days) as determined by the new investigator for subjects transferring to a different site.

[b] Study visits during the treatment period are to occur within stipulated time windows. If a visit is delayed, the next visit should occur earlier to return to the schedule. After the Day 1 visit (Visit 1), a documented telephone contact will occur between the scheduled Visit 2 and 3 study visits, scheduled to occur at approximately Week 6 (± 14 days) and will include AE and concomitant medication review. Subjects who complete 52 weeks of treatment (Visit 6, 10, *etc*.) will be offered an opportunity to continue with open-label treatment if, in the opinion of the principal investigator, the potential benefit continues to outweigh the risk; informed consent must be obtained at each re-enrollment for any subsequent 12-month treatment extension. The same schedule will be followed in subjects who enter subsequent 12-month extension phases, *i.e*., safety visits approximately every 13 weeks (with no requirement for the Week 2 visit or Week 6 telephone contact in any subsequent year of participation), as well as resource utilization and quality of life assessments approximately every 6 months; visits will be numbered in an ascending fashion. For subjects who do not re-enroll for a subsequent extension of treatment, identified end of treatment evaluations will be performed at the final on-treatment visit (Visit 6); if a subject discontinues prematurely, an early termination visit should be conducted at which time all assessments identified for Visit 6 should be performed.

[c] An off-treatment follow-up visit is to be scheduled (approximately 4 weeks after the last dose of study drug) for all subjects who cease to take LMTM (regardless of the reason for discontinuation).

[d] For subjects who wish to proceed to an additional extension phase, informed consent will be obtained at Visit 6 for continued participation. If informed consent is obtained, study drug dispensing will also occur at Visit 6.

[e] Compliance with study drug will be assessed by questioning the subject and caregiver at Visit 2; thereafter, compliance will also be assessed by counting returned tablets (in addition to questioning the subject and caregiver).

[f] A 12-lead ECG of at least 10 seconds in duration will be obtained in triplicate (taken within a period of 5 minutes) and evaluated by a centralized ECG reading facility approximately every 6 months and at the 4-week follow-up visit (if applicable).

[g] Targeted physical and neurological examinations are to be performed at each visit (or upon early termination), including the 4-week follow-up visit if applicable; these targeted examinations will include assessments for signs and symptoms indicative of potential serotonin toxicity (see Section 7.1.3.2 for guidance on assessment).

[h] The MMSE will be performed approximately every 6 months and at the 4-week follow-up visit (if applicable) to inform the evaluation for possible serotonin toxicity (to be included in the targeted physical and neurological examinations).

[i] There will be two applications of the EQ-5D-5L at each visit: one version will be completed by the subject and a second copy of this version will be completed by the caregiver (see Section 8.3 for further detail).

4.5 Assignment of Treatment

This is not applicable to this open-label study as all subjects will receive LMTM. Treatment assignment from the prior double-blind clinical study will be recorded in listings; however, this information will remain unknown to the subject and caregiver as well as to the investigator and study site personnel until the blind for the respective double-blind trial has been broken.

Subjects will be assigned a study identification number with the first three digits for the study (020), the next two letters for the country, the next three digits for the site, and the last two digits for the sequential order of enrollment at a given site.

4.6 Study Treatment

The initial LMTM dose for all subjects will be 200 mg/day. Thereafter, dosing will be flexible (in 100-mg decrements or increments). The dose may be increased (at Visit 3 or at any subsequent dispensing visit as determined by the investigator during the treatment period) or decreased (at any time at or after Visit 2) in response to benefit as judged by the investigator and safety and tolerability. The maximum allowable dose is 300 mg/day (or in those countries where limited by a Competent Authority or Ethics Committee, 200 mg/day). The dose may also be interrupted at any time as needed (for up to 30 days at any one time).

Study drug and regimens, including dose interruptions and modifications in response to adverse events, are further described in Section 6.

4.7 Concomitant Medication

Current medications (and medications used since the last double-blind visit in the prior study of participation) will be recorded using the eCRF mapped from the originating double-blind study of prior participation. "Medication" is used to encompass prescription and over-the-counter drugs or biologics, vitamins used in supra-pharmacologic doses, alternative pharmacotherapies for dementia, medical foods, and for women, forms of contraception. At each scheduled or unscheduled visit, and at each telephone contact, any changes to existing concomitant medications and any new concomitant medications will be reviewed and recorded.

It is desirable, but not mandatory, that concomitant medications identified at Baseline be maintained at a constant dose for the duration of the study if clinically indicated. The investigator should evaluate any changes in the dose of existing concomitant medications and/or initiation of new concomitant medications, and the medical monitor should be contacted to discuss any concerns as needed. The date of commencement, dose, and date of any change of dose of concomitant medications are to be recorded in the eCRF.

4.7.1 Dementia Medication

Subjects are allowed to take an AChEI and/or memantine, a medical food (*e.g.,* Axona, Souvenaid) or a stable dose of alternative pharmacotherapy for dementia (*e.g.*, Vitamin E, folate [in doses up to 5 mg/day; doses of approximately 1 mg/day in the management of

folate deficiency are acceptable], a specific neurocognitive vitamin formulation [such as NeuroVits comprising 20 mg Vitamin B_6, 1 mg Vitamin B_{12}, 0.8 mg folate], ginkgo biloba, hormone replacement therapy, treatments related to coconut oil, or circumin). Ideally, the dosage and time of dosing should remain unchanged during participation in the study. There are no restrictions for other non-pharmacological treatments during the treatment period.

Results suggest that MT may inhibit cytochrome P450 3A4 (CYP3A4), an enzyme system that is involved in the metabolism of two of the AChEIs allowed in the study, donepezil and galantamine. Because drug-drug interaction studies have not been performed with these drugs, it is not known whether systemic exposure to either of these drugs will increase or by how much. Therefore, subjects receiving these drugs should be monitored and if adverse events suggest an increase in systemic exposure, dose adjustment of donepezil or galantamine may be considered. If any change in dose occurs for whatever reason, the subject may continue on study drug unless it is judged to pose a risk to the subject.

4.7.2 Drugs with Serotonergic Potential

The oxidized form of MT (MT^+) is an inhibitor of MAO A and B *in vitro*, and the investigator should be aware of the potential for drug interaction resulting in serotonin syndrome (toxicity). Recent (within five to seven plasma half-lives) or current treatment with medications identified by FDA in an October 2011 Safety Alert (augmented to include drugs not approved in the United States) should be undertaken only if the potential benefit is judged to outweigh the risk. Refer to the Investigator's Brochure for a list (not exhaustive) of such medications and their plasma half-lives (majority taken from U.S. approved product labeling). It should be noted that some of these are available without prescription and their use should also be recorded in the eCRF.

Drugs with serotonergic potential may be initiated after Visit 3 (Week 13) provided potential benefit is judged by the investigator to outweigh risk. The subject's general practitioner will be informed of the potential risk.

Guidance for monitoring subjects for potential serotonin toxicity, to be undertaken whether or not a subject is on serotonergic drugs, is described in Section 7.1.3.2.

Note, dietary supplements containing tryptophan or its metabolite 5-hydroxytryptophan (5-HTP) are considered serotonergic concomitant medications as 5-HTP is a precursor in the biosynthesis of serotonin. Tryptophan is a naturally-occurring protein, however, eating foods containing tryptophan does not significantly increase 5-HTP levels; thus, avoiding dietary sources of tryptophan is not necessary.

In the event of any question, the medical monitor should be consulted.

4.7.3 CYP and P-gp Substrates

Results of a recently completed drug-drug interaction study indicate that MT is a weak inhibitor of CYP3A4, CYP2C8, and CYP2C19 enzymes (see the Investigator's Brochure for examples of drugs metabolized by these enzymes). The extent to which this occurs within a given individual or with a given drug is not known, especially for those drugs with multiple metabolic pathways. Therefore, subjects on drugs known to be

metabolized by one or more of these enzymes (especially those that have a narrow therapeutic index) should be closely monitored for adverse events that could suggest an increase in systemic exposure. Dose adjustment of the concomitant medication may be warranted.

LMTM is also a weak inducer of CYP2B6 and the P-glycoprotein (P-gp) transporter (see the Investigator's Brochure for examples of substrates). Coadministration of LMTM with digoxin, a P-gp substrate, was shown to result in decreased concentrations of digoxin. Therefore, it is advisable to obtain a baseline digoxin level in subjects on this drug and to monitor digoxin levels periodically while on study. Any such results obtained from the local laboratory should be entered into the eCRF (together with the time of the prior dose of digoxin and the time of the sample).

4.7.4 Drugs Used to Manage Behavioral Disturbance

Subjects may be treated with antipsychotics (other than clozapine or olanzapine). Should treatment be initiated during this open-label extension, the reason(s) should be clearly documented by indicating one or more of the following reasons: delusions, hallucinations, agitation/aggression, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavior, or appetite/eating change.

"As-needed" use of antipsychotics is to be avoided if possible, but such use does not preclude further participation. Similarly, regular or occasional use of benzodiazepines to manage distress, agitation, *etc.* does not preclude further participation.

4.7.5 Other Medications

Anxiolytics and/or sedatives/hypnotics may be used as sedation for claustrophobia or agitation. Regular or occasional benzodiazepines, chloral hydrate, low dose trazodone[3] (50 mg) or zolpidem may be used as needed at bedtime for sleep.

Unless otherwise prohibited, concomitant medications (preferably at stable doses) considered appropriate by the subject's physician are allowable but should be kept to the minimum possible as clinically indicated. If there are questions about whether or not a medication is permitted in the study, the medical monitor should be consulted.

4.7.6 Dietary Tyramine

Historically, MAO inhibitors as a class have been reported to be associated with hypertensive crises caused by ingestion of foods containing high amounts of tyramine (known as a tyramine or "cheese" reaction). While there is a theoretical potential for a tyramine reaction with MT, there have been no reports to date in subjects taking part in TauRx-sponsored studies, even though there have been no dietary restrictions in these studies. Nonetheless, as a precaution, subjects and their caregivers should be advised about this potential while taking LMTM (see the Investigator's Brochure for examples of tyramine-rich foods and beverages, such as air-dried, aged or fermented meats and

[3] If trazodone is used in this way, steps must be implemented for monitoring signs and symptoms indicative of potential serotonin toxicity.□

cheeses, fava bean pods, non-pasteurized beers, sauerkraut, and most soybean products). They should also be advised to seek medical care immediately in the event of signs or symptoms of hypertensive crisis (sudden onset of severe headache, nausea, stiff neck, tachycardia or palpitations, profuse sweating, and/or confusion) or other sudden or unusual symptoms following ingestion of tyramine-rich foods or beverages.

4.7.7 Contraceptive Measures

As a precautionary measure, women of childbearing potential (*i.e.*, not documented to be post-menopausal for at least 1 year or not having undergone hysterectomy or bilateral salpingectomy or oophorectomy for at least 6 months minimum) must use adequate contraception with the exception of female subjects in Italy. Examples of adequate contraception include bilateral tubal ligation or occlusion at least 6 months prior to Baseline; use of a barrier method (condom, diaphragm or cervical/vault cap) with spermicidal foam, gel, film, cream, or suppository; intrauterine device (IUD) or system; oral or long acting injected or implanted hormonal contraceptives for at least 3 months prior to Baseline; or sexual activity restricted to a vasectomized partner (with the appropriate post-vasectomy documentation of the absence of spermatozoa in the ejaculate). Abstinence is only acceptable as true abstinence when this is in line with the subject's preferred and usual lifestyle; periodic abstinence (*e.g.*, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of birth control. Subjects must be competent to use adequate contraception and must agree to continue to maintain adequate contraceptive measures throughout study participation and until the final off-treatment visit. In Italy, subjects must accept to avoid a pregnancy throughout participation in the study. Women of childbearing potential should be encouraged to return to the clinic in the event of a delayed menstrual period to rule out possible pregnancy.

Males should practice abstinence or use acceptable birth control with any female sexual partner of childbearing potential. The risk of drug secretion through the ejaculate is not fully studied. To ensure that the fetus is not exposed to MT through vaginal absorption, male subjects (including men who have had vasectomies) whose partners are pregnant should use condoms for the duration of the study and for an additional 4 days after cessation of study treatment. The investigator must provide appropriate counsel to male subjects regarding this issue.

4.7.8 Folate and Vitamin B_{12}

Folate and Vitamin B_{12} are necessary for the production and function of red blood cells. Given the risk of anemia with the use of MT, it is important that subjects not become deficient in folate and/or Vitamin B_{12} while on study. Chronic hemolytic anemia depletes folate stores, and it is general medical practice to place all hematology patients with risk of chronic hemolytic anemia on prophylactic folate replacement, with a recommended dose of 1 mg by mouth, per day.

4.8 Data and Safety Monitoring Board / Independent Data Monitoring Committee

Safety will be overseen by a DSMB throughout the duration of study conduct. At any time, the DSMB may recommend that dosing be modified or enrollment stopped due to safety concerns; the DSMB may also request to receive additional data for individual subjects in response to identified safety concerns.

Routine meetings are to be scheduled as determined by the DSMB. *Ad hoc* meetings will be convened if needed in response to safety concerns. This DSMB will also be assessing data from other clinical studies sponsored by TauRx with the same active moiety. The DSMB Charter will describe the composition of the DSMB and safety monitoring details, as well as the frequency of meetings needed as the study progresses.

5 SELECTION OF SUBJECTS AND CRITERIA FOR WITHDRAWAL

To be eligible for enrollment in this extension study, a subject must meet all of the inclusion and exclusion criteria listed below.

5.1 Inclusion Criteria

1. Subjects with a diagnosis according to NIA/AA criteria of all cause dementia and probable Alzheimer's disease at enrollment and who completed participation in one of the following three TauRx studies (inclusive of the 4-week post-treatment follow-up visit): TRx-237-005, TRx-237-008, or TRx-237-015[4].

   OR

   Subjects with a diagnosis of probable bvFTD according to the International Consensus Criteria for bvFTD at enrollment and who completed participation in TauRx study TRx-237-007 through Visit 9 (Week 52).

   Treatment will not be made available to subjects who have withdrawn from the double-blind study of prior participation prior to completion.

2. Females of childbearing potential must continue to use adequate contraception defined as follows (or, if in Italy, agree to avoid pregnancy):
   - Barrier method (such as condom, diaphragm or cervical/vault cap) with spermicidal foam, gel, film, cream, or suppository
   - Intrauterine device [IUD] or system
   - Oral or long-acting injected or implanted hormonal contraceptives for at least 3 months prior to Baseline

[4] Subjects who participated in Study TRx-237-015 and did not consent to extended treatment for up to 15 months as per Protocol Version 3.0 (extended from 12 months as per the original study protocol) may be enrolled into this open-label extension study following completion of the 12-month double-blind treatment period and 4-week post-treatment follow-up visit for Study TRx-237-015.

- Vasectomized partner (with the appropriate post-vasectomy documentation of the absence of spermatozoa in the ejaculate)
- True abstinence (when this is in line with the preferred and usual lifestyle of the subject)

Subjects must agree to continue to maintain adequate contraception throughout participation in the study.

3. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) consistent with national law and IRB/EC approval, is/are able to read, understand, and provide written informed consent in the designated language of the study site
   - In Germany and the Netherlands, subjects must be able to provide their own written informed consent (see Section 13)
4. Has an identified adult caregiver who meets the following criteria:
   - Either lives with the subject or sees the subject on average for ≥ 1 hour/day ≥ 3 days/week, and in the investigator's opinion, the extent of contact is sufficient to provide meaningful assessment of changes in subject behavior and function over time and provide information on safety and tolerability
   - Is willing to provide written informed consent for his/her own participation
   - Is able to read, understand, and speak the designated language at the study site
   - Agrees to accompany the subject to each study visit
   - Is able to verify daily compliance with study drug
5. Able to comply with the study procedures in the view of the investigator

5.2 Exclusion Criteria

1. History of swallowing difficulties (note: study drug should be swallowed whole and MUST NOT be broken, crushed or chewed or dissolved in fluids prior to ingestion)
2. Pregnant or breastfeeding
3. Clinically significant laboratory, pulse co-oximetry, electrocardiogram, or imaging abnormality (in originating study) or emergent intercurrent illness that, in the judgment of the principal investigator, could result in the risk of participation outweighing the potential benefit
4. Current participation in, or intent to enroll in, a clinical trial of a drug, biologic, device, or medical food
5. In Germany, subjects who meet the following criteria are to be excluded:
   - Subjects who reside in a continuous care or assisted living facility if mandated by an order issued by either the judicial or the administrative authorities

- Subjects whose willingness to participate in the clinical trial may be unduly influenced by the expectation (regardless of whether justified) of benefits associated with participation, or of a retaliatory response from family, caregivers, or treating personnel in case of refusal to participate

5.3 Discontinuation/Withdrawal

For a discussion of reasons for dose adjustment or permanent discontinuation of study medication on the basis of safety, see Section 6.2.3. These include clinically evident hemolytic anemia (Section 6.2.3.1), serotonin syndrome (Section 6.2.3.2), prolongation of the QT interval on ECG and decrease in renal function (Section 6.2.3.3).

Subjects may discontinue study drug and withdraw (drop out) from the study at any time for any reason. The caregiver may also withdraw his or her consent at any time for any reason. If a caregiver withdraws his or her consent, the subject must then also be withdrawn if alternative arrangements are not available (*e.g.*, an alternate caregiver). Furthermore, the investigator also has the right to discontinue trial medication if he or she judges that treatment is no longer appropriate, the subject's clinical condition is worsening, or for an adverse event.

At the completion of each 12-month period of open-label treatment, the principal investigator must determine whether or not continued treatment is warranted on the basis of continued benefit and safety and tolerability profile. If eligible, the subject and/or caregiver must give informed consent for continued participation. In Germany and the Netherlands, continuation of treatment is not permitted if the subject is unable to give consent.

If study drug is discontinued or the subject/caregiver elect(s) not to re-enroll in a subsequent open-label treatment phase, the reason should be recorded as one of the following:

- AE
- Death
- Lack of efficacy (including progressive disease or worsening of cognitive capacity; in Germany, this includes loss of the ability to give consent if the legal representative or caregiver is not available or does not agree to continued participation)
- Lost to follow up
- Withdrawal by subject or legal representative (or caregiver), including specific reasons wherever possible
- Protocol deviation
- Non-compliance with study drug
- Pregnancy
- Study terminated by Sponsor
- Physician decision, including specific reason(s) wherever possible

- Other (specify)

If the reason for discontinuation of study drug is an AE, the principal event(s) associated with discontinuation must be specified and recorded. In this case, reasonable effort must be made to clearly document the outcome. If the reason for premature discontinuation is an SAE, this must be documented and an SAE form must be completed (also see Sections 7.1.4 and 7.1.5).

For subjects who withdraw from the study for reasons other than death, or subject or caregiver consent withdrawn (or refusal to continue participation), an early termination visit should be scheduled as soon as possible after the last dose of study drug and identified end of treatment evaluations performed. For subjects who withdraw consent or when a caregiver withdraws consent without available alternate caregiver, the investigator should request that the subject have any clinically indicated safety assessments performed and the reason for withdrawal of consent given.

5.4 Termination of the Study

The Sponsor reserves the right to terminate the study for duly justified reasons in accordance with national laws (*e.g.*, in Germany: §40, section 1 of the Arzneimittelgesetz [AMG]). These reasons include in particular:

- Administrative reasons: *e.g.*, financial reasons
- Interest of subject welfare: *e.g.*, new information or events that result in an unfavorable risk-benefit profile.

6 TREATMENTS ADMINISTERED

Study drug tablets are formulated as blue film-coated oval tablets. Only one strength of LMTM will be provided as follows:

- LMTM tablet containing 100 mg (expressed as MT base equivalent)

The active and inactive ingredients are described below.

6.1 Treatment

6.1.1 Active Ingredient

The active ingredient is methylthioninium (MT), provided as leuco-methylthioninium bis(hydromethanesulfonate) (LMTM, TRx0237). The chemical name is *N,N,N',N'*-tetramethyl-10*H*-phenothiazine-3,7-diaminium bis(methanesulfonate).

The potential for LMTM to cause urinary and/or fecal coloration should be explained to the subject and caregiver and will be described in the informed consent form (ICF). If a subject is known to have incontinence, such coloration could adversely affect compliance with study drug unless adequate precautions are taken (*e.g.*, use of incontinence pads). Even with the latter, discoloration in the context of incontinence may prove unacceptable to the subject/caregiver, and subjects should be entered into the study only after careful discussion of this possibility with them. Staining of underclothes and other fabrics is

difficult to remove using standard washing products; therefore, subjects and caregivers should be informed about available techniques for washing stained clothing (see the Investigator's Brochure). The possibility of such staining should be clearly discussed with subjects and their caregivers.

6.1.2 Inactive Ingredients

Tablets also contain the following inactive compendial excipients: mannitol, crospovidone, microcrystalline cellulose, and magnesium stearate.

The film coat of study drug tablets contains polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide, Macrogol PEG 3350, lecithin (soya), as well as non-compendial FD&C blue #2 (indigo carmine aluminum lake).

6.2 Study Regimens

All LMTM doses cited represent doses expressed as MT base equivalents.

Subjects will be instructed to take each dose of study medication with water (see Section 6.4 for discussion of study drug dispensing). Tablets may be taken with or without meals.

Subjects and caregivers will be instructed that study drug should be swallowed whole and MUST NOT be broken, crushed, or chewed or dissolved in fluids prior to ingestion. Subjects and caregivers should be warned that if the product is not swallowed immediately and is allowed to dissolve in the mouth, it will cause discoloration of teeth and oral mucosa.

The study supplies are further described in Section 6.3.

6.2.1 Initial Dose

The initial daily study drug regimen to which all subjects will be assigned is summarized in Table 6-2, including the number of tablets and LMTM doses.

Table 6-2 Initial Daily Study Drug Regimen: Tablets and LMTM Dose

Treatment	Tablet Contents (amount of MT)	Number of Tablets			Dose of MT		
		AM	*PM*	Daily Total	*AM*	*PM*	Daily Total
LMTM 200 mg/day	100 mg	1	1	2	100 mg	100 mg	200 mg

AM = morning; *PM* = evening

As the bvFTD subjects from Study TRx-237-007 are not required to return for a 4-week post-treatment visit prior to entering this open-label extension study, these subjects may choose to enroll in this extension study at Visit 9 of Study TRx-237-007 (*i.e.*, on the same day that they receive the last dose of study drug in the prior study). These subjects are to continue taking study drug (under the Study TRx-237-007 protocol) at the usual

designated time, and the first dose of study drug under this open-label extension study protocol will be instructed based on the last dose received under the prior study. Subjects from Study TRx-237-007 who are taking a reduced dose (*i.e.*, 100 mg/day) should continue taking this reduced regimen upon entering this extension study.

6.2.2 Flexible Dosing

After Week 2 (Visit 2), dosing is flexible. The dose may be increased (at Visit 3 or at any subsequent dispensing visit as determined by the investigator during the treatment period) or decreased (at any time at or after Visit 2) on the basis of benefit in the judgment of the investigator and safety and tolerability. Dose increments/decrements of 100 mg/day are recommended, with once daily dosing also allowed. The maximum allowable dose is 300 mg/day (or in those countries where limited by a CA or EC, 200 mg/day); no more than 200 mg is to be administered at a single time. The maximum dose (if 300 mg/day) may also be given as 100 mg three times daily.

Interruption(s) of study drug administration and resumption of dosing at the same or at a reduced dose is allowed at any time if the investigator determines this is indicated, provided the duration of any single interruption is ≤ 30 days. If there is an interruption for safety reasons[5] longer than 30 days on a given occasion, treatment should be discontinued. The investigator should contact the medical monitor to discuss any interruptions and dose reductions. If after allowable interruptions, the subject does not tolerate re-introduction of the study drug or a clinically significant laboratory abnormality recurs, then study drug should be discontinued.

Guidance with respect to dose modifications in response to selected adverse events or clinical laboratory abnormalities are described further below.

All dose changes, including escalations, interruptions, decreases (and subsequent increases), should be recorded in the eCRF together with the corresponding date. The reason for each dose interruption and each dose reduction also should be recorded in the eCRF. The medical monitor should be informed of any dose decreases or interruptions.

6.2.3 Dose Adjustment for Selected Adverse Events / Test Abnormalities

In this open-label extension study, the adverse events of special interest (AESIs) are signs and symptoms consistent with hemolytic anemia and serotonin syndrome (toxicity). Potential interruption or discontinuation of study drug in response to these events is discussed below. Further guidance on monitoring subjects is given in Section 7.1.3.

6.2.3.1 Hemolytic Anemia

When there are clinical symptoms and/or laboratory signs of hemolytic anemia, dosing should be discontinued. Clinical symptoms are described in Section 7.1.3.1 and laboratory signs are described in Section 7.3.2. Follow-up laboratory monitoring is also

[5] Administrative reasons (or other reasons not related to safety) are not to be considered safety reasons warranting treatment discontinuation.

described in Section 7.3.2. The medical monitor should be contacted to discuss whether or not resumption of dosing is indicated or for any other questions.

6.2.3.2 Serotonin Syndrome

Subjects are to be monitored at each visit by a medically qualified person for signs and symptoms indicative of potential serotonin toxicity, especially when initiating LMTM in this study or any medication with serotonergic potential. At each post-Baseline visit, subjects are to be evaluated by targeted physical and neurological examination and measurement of temperature, respiratory rate, blood pressure, and pulse (see Section 7.1.3.2 for guidance on assessment). Should serotonin syndrome (toxicity) be suspected clinically, treatment should be immediately discontinued. The event should be reported as an AESI and the medical monitor should be contacted for further guidance on subject management.

6.2.3.3 Other Safety Reasons Requiring Dose Adjustment

Treatment should be discontinued if the following treatment-emergent change occurs on ECG (based on the means of the three recordings) without other explanatory cause:

- QTcF interval > 500 msec: repeat ECGs should be obtained, in triplicate, within 2 weeks; if confirmed by the mean of the repeat ECGs, study drug should be discontinued pending further evaluation.

Other clinically significant changes in the ECG should be discussed with the medical monitor.

If renal concerns arise and the calculated creatinine clearance is < 30 mL/min, study drug should be discontinued.

6.3 Packaging, Labeling, and Storage

The open-label study drug will be packaged, labeled, and distributed to study sites by a designated vendor.

Study drug supplied to subjects will be packaged in 35-count 60-mL white HDPE bottles containing a 2-g desiccant bag and induction-sealed. The number of bottles dispensed is to be adequate to ensure sufficient supplies until the next scheduled study visit (with 2-week overage).

Study drug package labels will be in compliance with applicable regulatory requirements and will include the statement “Keep out of reach of children”, the cautionary statement “Caution: New Drug – Limited by Federal (United States) law to investigational use” and/or “For clinical trial use only” as appropriate, as well as any other locally mandated statements. Labels will also be translated into the local language.

At a minimum, labels will also include the following information: the name and address of the sponsor, the study code, a unique identifier, and appropriate contact information. In those jurisdictions where required, a re-test or expiry date will be included.

At the study site, study drug must be stored securely (*e.g.*, locked area, pharmacy) and at a temperature not more than 30°C. The temperature at which study drug is stored at the study site will be recorded daily using a centralized temperature monitoring system if this

is available. If not, study drug storage temperature will be recorded each working day using a maximum-minimum thermometer. While closed, the packaging protects the study drug from light and moisture; study drug should be ingested immediately after removal from the package.

Subjects and caregivers should also be provided with information about required storage conditions. Study drug should remain in the package as dispensed until it is ingested by the subject, and should not be placed in an alternate pill box including commonly-used weekly pill organizers.

6.4 Dispensing

All dosing will be on an outpatient basis. Study drug will be first dispensed to subjects/caregivers on Day 1 (Baseline, Visit 1); enough study drug will be dispensed to last the subject until Visit 3.

Thereafter, study drug will be dispensed at Week 13 (Visit 3) and at each subsequent study visit so long as the subject will continue on study drug. The supplies dispensed to a subject at each of these times will be sufficient to allow for intake of the necessary number of tablets for the scheduled number of days, with additional supplies as overage in the event of a delay in the visit. Subjects should bring all study medication, including the overage supply, with them to the Week 13 visit (Visit 3) and to each study visit thereafter during the treatment period for compliance assessment.

Subjects and caregivers will be provided with information about storage conditions and taking study drug, including instructions indicating that study drug must be used only as described in this protocol. They will be informed that subjects are to take each dose of study medication with water and that the tablets may be taken with or without meals. They will also be informed that tablets should be swallowed whole and not broken, crushed, or chewed or dissolved in fluids prior to ingestion (see Section 6.2). In the event of interruption or dose reduction or increase, the subjects and caregivers will be provided with updated dosing instructions.

6.5 Compliance

Subject compliance with prescribed dose of study drug will be assessed by questioning the subject and caregiver at the Week 2 visit (Visit 2) and at each study visit thereafter during the treatment period.

At the Week 13 visit (Visit 3) and at each study visit thereafter during the treatment period, the subject/caregiver will bring all unused study drug to the study site. The number of tablets (all tablets remaining in the bottle plus any tablets that have been removed from the bottle) will be counted and recorded by study site staff. Empty bottles and packaging should also be returned by the subject/caregiver to the study site. At each post-Baseline visit beginning with the Week 13 visit (Visit 3), the number of tablets dispensed to the subject/caregiver will also be recorded.

Any apparent discrepancies between the number of tablets taken and the number of tablets which should have been taken since the last visit will be discussed with the subject and caregiver. Compliance data obtained at Visit 2 and each study visit thereafter, including dates of any dose deviations and/or interruptions, and any other pertinent

information, will be recorded in the source documentation and on the appropriate field of the eCRF based on the investigator determination.

If during participation in the study a subject's compliance is determined to be < 80% or > 120% (taking into consideration allowable reductions/increases determined and recorded by the investigator in the number of tablets taken, or dose interruptions), the subject and caregiver should be reeducated about taking study drug properly and the clinical research associate should be informed promptly. If compliance problems are recurrent, the investigator should inform the clinical research associate and contact the medical monitor to determine the course of action.

6.6 Accountability

The investigator or designee will keep a record of all study drug received, and of all study drug dispensed to and returned by subjects.

The investigator will ensure that the supplied study drug will be used only for administration to subjects enrolled in this study and for no other purpose.

The study drug accountability record will be checked by a study monitor at monitoring visits.

All unused and returned study drug will be either returned to the Sponsor or designee or disposed of after study completion according to provided instructions.

7 ASSESSMENT OF SAFETY

Safety will be assessed over time by means of adverse events (AEs) and concomitant medication recording; clinical laboratory tests of blood (*e.g.*, hematology and chemistry panels); vital sign measurements; 12-lead ECGs; and targeted physical and neurological examinations.

Assessments to be performed in the clinic are described in the subsections that follow. At an intervening time between Visit 2 and Visit 3 (approximately 6 weeks after Baseline), caregivers of subjects are to be contacted by telephone. An unscheduled visit is to take place if needed in response to a safety concern.

7.1 Adverse Events

An AE is any unfavorable or unintended sign, symptom, or disease, whether or not considered related to the study treatment. This also includes events resulting from medication error or inappropriate use. Recording of new AEs and changes to ongoing AEs will begin at the time the ICF is signed using the eCRF mapped from the double-blind study of original participation. AEs will be ascertained by asking the subject (and caregiver) how the subject has been since the last visit. A clinical abnormality or laboratory test value abnormality that the investigator deems to be clinically significant should be recorded as an AE.

Every attempt should be made to describe the AE in terms of a diagnosis. Once a clear diagnosis has been made, individual signs and symptoms shall not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they

should be reported as separate events. Events and signs/symptoms leading up to a diagnosis should be retained. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All AEs must be fully recorded in the source documents and in the eCRF, regardless of whether or not the event is considered related to study drug.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) or pregnancy requiring immediate notification (see Sections 7.1.4 and 7.1.5).

Follow-up of an AE, even after the final dose of study drug, is required if the AE or its sequelae persist. Follow-up is required, including beyond the scheduled final off-treatment visit if needed, until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For each AE, information recorded will include the following: the date when the AE started, the date when the AE stopped (or whether it remained ongoing), the intensity of the AE (see Section 7.1.1), the relationship of the AE to study drug (see Section 7.1.2), action taken with regard to study drug (none, dose reduction, interrupted, or discontinued), other drug therapy (no change, new medication, altered medication, or both of the latter), outcome, and whether or not the AE was considered an SAE (see Section 7.1.4).

7.1.1 Intensity

The intensity (severity) of each AE will be assessed by the investigator and graded as mild, moderate, or severe, as follows:

- Mild: An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An AE that prevents normal everyday activities

7.1.2 Relationship to Study Drug

The investigator will make a judgment considering whether or not, in his or her opinion, each AE is related to the study drug according to classifications described here. However, even if the investigator feels that there is no relationship to the study drug, the AE should be reported nevertheless. For each AE, the relationship or association (causality) of the AE to study drug will be assessed by the investigator and characterized as not related, unlikely related, possibly related, or related as follows:

- Not related: If there is a confirmed cause of the AE (other medical condition, other therapy) which does not involve the study drug
- Unlikely related: If the temporal association between the AE and the study drug is such that the AE is not likely to be related to the study drug

- Possibly related: If the AE shows a reasonable temporal association to study drug administration but could be due to the subject's clinical state or other therapies administered
- Related: If the AE shows a reasonable temporal association to study drug administration and cannot be explained by the known characteristics of the subject's clinical state

7.1.3 Adverse Events of Special Interest

The following adverse events are of special interest because additional steps are to be taken by the investigator to assess and manage them. The medical monitor shall be informed (either directly by the laboratory or the site, depending on the nature of the event). AESIs include:

- Signs or symptoms consistent with hemolytic anemia (see Section 7.1.3.1)
- A case clinically judged to possibly represent serotonin syndrome (see Section 7.1.3.2)

See Section 6.2.3 for additional details regarding dose interruption, reduction, or discontinuation in response to these AESIs.

Each AESI should be recorded as for any other adverse event.

7.1.3.1 Hemolytic Anemia

The subject should be evaluated at each visit for possible clinical symptoms associated with hemolytic anemia, in conjunction with review of hematology results. Should hemolytic anemia be suspected, follow-up testing should be performed as described in Section 7.3.2. The medical monitor should be contacted to discuss whether or not resumption of dosing is indicated or for any other questions.

The signs and symptoms of anemia include:

- Cyanosis, headache, anxiety, exercise intolerance, fatigue, confusion, dizziness, tachypnea, palpitation, dysrhythmia, seizures, and coma

Signs of possible hemolytic anemia include:

- Decrease by 20% from Baseline in RBC count and/or hemoglobin
- Abnormal RBCs in peripheral blood smear
- Elevation of reticulocyte count to above laboratory normal range
- Increase in LDH or indirect bilirubin, or low haptoglobin

7.1.3.2 Serotonin Syndrome (Toxicity)

Subjects are to be monitored for signs and symptoms indicative of potential serotonin toxicity, especially when initiating LMTM in this study or any medication with serotonergic potential. At each post-Baseline visit, subjects are to be evaluated by a medically qualified person by targeted physical and neurological examination and measurement of temperature, respiratory rate, blood pressure, and pulse. Results of the MMSE should also be taken into consideration. The evaluation should focus on detecting

signs and symptoms of serotonin syndrome (or serotonin toxicity) that include mental changes (confusion, hyperactivity, memory problems not attributed to underlying condition), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever. A further guide is provided below.

Table 7-1 Overview of Monitoring and Management of Serotonin Syndrome (Toxicity)

Signs and Symptoms of Serotonin Toxicity	Monitoring at Each Clinic Visit	Action
Any one of the following: Autonomic findings (temperature ≥38 ºC, diaphoresis, shivering, tachypnea/dyspnea, diarrhea, hypertension or hypotension) Neuromuscular changes (tremor; hyperreflexia; spontaneous, inducible, or ocular clonus; muscle rigidity[1]; hypertonia; dizziness; incoordination; or mydriasis) Other central nervous system changes (agitation/akathisia, elevated mood, insomnia)	Oral (sublingual) temperature[2] Seated blood pressure and pulse Targeted PE and neurological examination, focused on the following: deep-tendon reflexes, clonus, and muscle rigidity; size and reactivity of pupils; dryness of oral mucosa; intensity of bowel sounds; skin color; and presence or absence of diaphoresis MMSE (Baseline[3], Weeks 26, 52, at the 4-week follow-up visit, and as needed to respond to changes)	Discontinue study drug Appropriate medical management to be undertaken Report to Medical Monitor as AESI

[1] Muscle rigidity can overwhelm other neuromuscular findings and mask the diagnosis
[2] Oral (sublingual) temperature measurements are preferable; aural temperature is an acceptable alternative (use of alternate measurement is to be noted in the eCRF)
[3] MMSE to be rated at Baseline if not available from within the prior 42 days in the previous study of participation

Should serotonin syndrome (toxicity) be suspected clinically, "serotonin toxicity" should be recorded as the adverse event rather than the individual signs or symptoms. These should be indicated by answering "yes" or "no" to each of the signs and/or symptoms indicated on the form provided in the eCRF. These signs and symptoms, based on physical and neurological examination, include the following: abnormal conscious level (delirium), agitation or akathisia, elevated mood, insomnia, myoclonus, tremor, mydriasis, nystagmus, clonus, hyperreflexia, hypertonia (rigidity), dizziness, incoordination, shivering, diaphoresis (sweating), diarrhea, pyrexia (fever), tachycardia, tachypnea or dyspnea, hypertension or hypotension. An "other" field should also be included in the eCRF to indicate any additional findings.

7.1.4 Serious Adverse Events

An SAE is defined as any event that:

- Results in death (including suicide)
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing inpatient hospitalization

- Planned admissions for respite care are not to be considered an SAE (the medical monitor should be contacted for confirmation regarding whether or not an admission for respite care should be considered planned or unplanned). Unplanned admissions for respite care will constitute an SAE unless it is as a result of caregiver needs that are independent of the subject's condition.
- An admission or prolongation of existing hospitalization because the subject does not want to be discharged, or because the caregiver is unable or unwilling to care for the subject, is not to be considered an SAE.
- Admissions to a hospital that were planned or anticipated before the start of the study for an unrelated pre-existing medical condition are not to be considered an SAE.

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other medically significant events that require immediate medical or surgical intervention.

Medical and scientific judgment should be exercised in deciding whether an event is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definitions above.

All SAEs must be reported on the eCRF. An assessment should be made by the investigator of whether the event is study-drug related, *i.e.*, is 'causally' related to the study drug.

7.1.5 Pregnancy

Pregnancy is to be considered an immediately reportable event. This includes pregnancy of a female subject or a female sexual partner of a male subject.

Subjects who become pregnant during the clinical study should discontinue study drug immediately and contact the investigator.

Subjects should be instructed to notify the investigator of a pregnancy either during the treatment period of the study or within 3 months after the last dose of study drug. Whenever possible, a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to the Sponsor after delivery.

Although the pregnancy is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy should be followed through delivery for the observation of any SAE. Therefore, regardless of whether or not a pregnancy is actually considered an SAE, a pregnancy form should be completed for all pregnancies.

Pregnancies should initially be reported in the Pregnancy Notification Form, Part I and sent by e-mail to the following address:

drugsafety@wwctrials.com.

When the outcome of the pregnancy is known, site personnel will complete the Pregnancy Notification Form, Part II and e-mail it to the following address:

drugsafety@wwctrials.com.

All data related to pregnancy, pregnancy outcome, and SAE associated with pregnancy will be recorded in a safety database maintained by personnel responsible for pharmacovigilance at Worldwide Clinical Trials.

7.1.6 Reporting Requirements and Timeframes

The requirements for reporting SAEs and pregnancies are described below. A Safety Management Plan will be implemented to further describe and document the process for safety reporting.

7.1.6.1 Investigator Reporting of SAEs and Pregnancy to Sponsor

If any of the adverse events are SAEs as defined by this protocol (see Section 7.1.4) or a pregnancy (see Section 7.1.5), special procedures will be followed. All such events will be reported to the Sponsor designee, Worldwide Clinical Trials, immediately (and not exceeding 24 hours following knowledge of the event) and followed by follow-up reports as soon as possible, whether or not the events are deemed study drug-related.

Serious Adverse Events must be reported by entering the SAE information in the AE/SAE section of the Electronic Data Capture (EDC) system. The information provided in the EDC system should be as complete as possible, but must contain the following minimum fields:

- Subject number
- Brief description of the SAE (diagnosis or signs/symptoms)
- Serious criteria
- Causality assessment
- Assessment of the intensity of the event

WCT Drug Safety will receive notification of the initial SAE *via* an e-mail alert generated from the EDC system. In the event of any temporary disruption of the EDC system, an alternative SAE reporting mechanism will be available to site personnel; in this instance, a paper SAE Report Form will be available. Site personnel will complete the paper SAE report form, scan and e-mail it within 24 hours to the following address:

drugsafety@wwctrials.com

Site personnel must complete the AE/SAE section with the SAE information as soon as the EDC system becomes available. Serious adverse events that are ongoing should be followed until resolved or stabilized to a level acceptable to the investigator.

The investigator is obliged to provide additional information as requested by the medical monitor. In general, this will include a description of the event in sufficient detail to

allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a subject death, a summary of available autopsy findings, if performed, must be submitted as soon as possible to the contract research organization. However, any supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The investigator should ensure that information reported is accurate and consistent.

Information not available at the time of the initial report (*e.g.,* an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented on a follow-up form. All follow-up information must be reported in the same timelines as initial information.

Any SAEs considered related to the study drug and discovered by the investigator at any interval after the study must also be reported to the Sponsor within 24 hours following knowledge of the event.

7.1.6.2 Sponsor Reporting of SUSARs to Regulatory Authorities

Suspected, unexpected serious adverse reactions (SUSARs) are adverse events that are believed to be related to an investigational medicinal product and are both unexpected (*i.e.*, the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. As stated in the EU 'CT-3' Communication from the Commission (2011/C 172/01) and the US Code of Federal Regulations (21 CFR 312.32), for there to be a reasonable possibility of a causal relationship between the event and study drug there must be facts (evidence) or arguments to suggest a causal relationship. Final assessment of expectedness for purposes of regulatory reporting is the responsibility of the Sponsor.

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of the decision as soon as possible. Requirements for SUSAR reporting are described below. All SUSAR reporting will adhere to European Directives 2001/20/EC, 21 CFR 312.32 of the U.S. Code of Federal Regulations, Health Canada Food and Drug Regulation C.05.014, and other regions as applicable.

7.1.6.2.1 Unblinding Treatment Allocation

As this is an open-label study, treatment allocation in this study is by default unblinded for all SUSAR reporting to the pertinent regulatory authorities. The onset of a possible SUSAR relative to the prior treatment history is an important aspect of the assessments. Therefore, should treatment assignment in the previous double-blind study of participation (*i.e.*, Studies TRx-237-005, TRx-237-007, TRx-237-008, and TRx-237-015) not yet be unblinded, the treatment assignment for a given subject will be made available for assessment of the SUSAR and will be included in the reporting of the event to a regulatory authority (as of implementation of Amendment 3.0).

When an event may be a SUSAR, the blind should be broken only for that specific subject. The blind should be maintained for individuals responsible for the ongoing conduct of the study (*e.g.*, management, monitors and investigators) and those

responsible for data analysis and interpretation of results at the conclusion of the study (*e.g.*, biometrics personnel).

Unblinded information should only be accessible to those who need to be involved in the safety reporting to pertinent regulatory authorities, independent ethics committees/independent review boards (IECs/IRBs) and DSMBs, or individuals performing ongoing safety evaluations during the study.

7.1.6.2.2 Fatal or Life-threatening SUSARs

It is the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the pertinent regulatory authorities as soon as possible, but no later than 7 calendar days (or earlier if locally mandated). These will be reported to the DSMB in parallel.

7.1.6.2.3 Other SUSARs

It is the responsibility of the Sponsor to report other SUSARs to the pertinent regulatory authorities as soon as possible, but no later than 15 calendar days (or earlier if locally mandated). These will be reported to the DSMB in parallel.

7.1.6.3 Reporting to IECs/IRBs

The IEC/IRB will be notified of any SUSARs according to local regulations and within the designated timeframe.

The investigator (or prospectively agreed to designee) is required to notify the IEC/IRB of any fatal SUSAR as soon as possible but no later than 7 calendar days after he/she first became aware of the reaction (or earlier if locally mandated).

The investigator (or prospectively agreed to designee) is required to notify the IEC/IRB of any other SUSAR as soon as possible but no later than 15 calendar days after he/she first became aware of the reaction (or earlier if locally mandated).

7.2 Urgent Safety Measures

The Sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of the clinical study against any immediate hazard to their health or safety.

The Sponsor and the Medical Monitor or designated deputy will be notified of any urgent safety measures taken by the investigator or qualified designee and advised of their responsibility to notify the licensing authority. The investigator or qualified designee will notify the IEC/IRB.

If these measures are taken, the Sponsor or investigator shall immediately give written notice to the pertinent regulatory authorities consistent with the regional/national requirements and IEC/IRB of the measures taken and the circumstances giving rise to those measures. In any event, the written notice shall be no later than 7 days from the date the measures are taken.

7.3 Clinical Laboratory Tests

Scheduled blood samples for hematology and chemistry panels will be obtained at each visit during the study, including Baseline (if not available within the prior 42 days), after 2 weeks, and approximately every 13 weeks (relative to Baseline) thereafter (or upon early termination). Laboratory testing will be repeated at the 4-week post-treatment follow-up visit if applicable.

A trained and authorized person will collect blood samples from the subject by venipuncture from a suitable vein.

Kits with supplies for the collection of blood samples will be provided to each study site before the study initiation visit. The kits will be labeled to identify the clinical study, and will include specimen labels, pre-printed laboratory requisition forms, all supplies needed for specimen collection and shipping, instructions for collection and preparation of specimens, and pre-printed forms to expedite shipment.

A protocol-specific laboratory manual will be provided to each study site. The laboratory manual will include contact details, lists of the contents of collection kits, shipment schedule of collection kits, and detailed guidelines and recommendations for completing laboratory requisition and for specimen collection, preparation, storage, and transportation.

A central laboratory will process all scheduled laboratory blood samples unless otherwise noted. Data will be transferred electronically for inclusion in the database. Investigators are to enter the results of any testing performed at local laboratories (and the corresponding normal ranges) into the eCRF.

7.3.1 Serum Chemistry

The blood volume for each chemistry panel will be approximately 3.5 mL. Blood samples collected for serum chemistry panels are to be destroyed approximately 1 week after testing has been completed. The chemistry panel will include the following analytes:

Sodium	Gamma-glutamyl transpeptidase (GGT)
Potassium	Alanine transaminase (ALT)
Calcium	Aspartate transaminase (AST)
Albumin	Glucose (random, not fasted)
Total protein	Creatinine[2]
Urea nitrogen, urea[1]	Phosphorus
Total and direct (conjugated) bilirubin (indirect bilirubin calculated as the difference)	Uric acid
Alkaline phosphatase	Chloride
Lactate dehydrogenase (LDH)	Creatine kinase (CK)

[1] The analytical method measures urea in serum. In the Covance CLS database, the test is named either Urea Nitrogen or Urea, depending on whether the results are expressed in conventional or SI units, respectively. Urea Nitrogen is reported in mg/dL while Urea is reported in mmol/L per SI unit convention.

[2] Creatinine clearance is to be estimated by the central laboratory using the Cockcroft-Gault equation.

7.3.2 Hematology

The blood volume for each hematology panel will be approximately 2.0 mL. Blood samples collected for hematology panels are to be destroyed approximately 3 days after testing has been completed. The hematology panel will include the following analytes:

Hematocrit	White blood cells (WBC) and absolute and percent differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils); any abnormal cells will be noted
Hemoglobin	
Mean corpuscular hemoglobin (MCH)	
Mean corpuscular hemoglobin concentration (MCHC)	
Red blood cells (RBC) and any immature forms	Platelet count
RBC morphology	Mean cell volume (MCV)
Reticulocyte count and percent	

If the investigator is concerned on the basis of significant hematological abnormalities that Heinz bodies may be present, a blood sample may be sent to the local laboratory for assessment and screening of Heinz bodies. The percent of erythrocytes with Heinz bodies should be reported based on a suitably prepared slide; blood samples should be as fresh as possible at the time of slide preparation. If Heinz bodies are present, study medication must be stopped (see Section 6.2.3.1) and another blood sample should be obtained within 1 week. Hematological indices should continue to be monitored until this resolves.

7.3.3 Other Laboratory Tests

A serum pregnancy test for qualitative testing for the beta subunit of human chorionic gonadotropin (β-hCG) will be obtained for all women of childbearing potential at Baseline (if the Baseline visit does not coincide with the final double-blind study visit) and each subsequent study visit (or upon early termination). In the event of a borderline result, testing will be repeated and if the result is still borderline, quantitative testing for β-hCG will be performed.

7.3.4 Review of Laboratory Results

Laboratory results from each study visit will be assessed in a timely manner. The investigator or an authorized physician sub-investigator must interpret the laboratory findings and confirm their review.

The clinical significance of all laboratory values which are outside the laboratory normal reference range should be noted and commented upon by the investigator.

Abnormal values which are considered by the investigator to be clinically significant, taking the age of the subject into account, should be documented as an AE, unless

accounted for by a pre-existing medical condition detailed in the subject's medical history. The diagnosis associated with a clinically significant laboratory abnormality generally should be recorded as the underlying abnormality or diagnosis (*e.g.*, renal insufficiency) if there is sufficient overall information to permit a diagnosis to be made by the investigator. Otherwise, the observed deviation in the laboratory result should be recorded (*e.g.*, elevated creatinine).

The investigator must review and assess laboratory results for clinically significant abnormalities. If any of these suggest hemolytic anemia, treatment interruption should be considered (see Section 6.2.3.1).

Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE may be obtained from the central laboratory. If a local laboratory needs to be used in some circumstances, the data and corresponding normal ranges will be recorded in the eCRF, entered directly from a laboratory slip. When clinically indicated, the medical monitor should be informed in such circumstances. In particular, if a clinically significant abnormal result is observed that is not resolved by the following visit, repeated tests should be performed until resolution of the abnormality.

7.4 Vital Sign Measurements

In the clinic, measurements of the vital signs described below will be made by a trained and authorized person. These will be made at Baseline (if not available from within the prior 42 days) and every subsequent visit thereafter (or upon early termination), including the 4-week post-treatment follow-up visit if applicable.

7.4.1 Blood Pressure and Pulse

Blood pressure and pulse should be measured with the subject in a seated position for at least 5 minutes. A manual or automated sphygmomanometer will be used to measure systolic and diastolic blood pressure, with results recorded in mmHg. Pulse rate will be measured in the radial artery for 60 seconds and will be recorded as beats/minute. If possible, blood pressure and pulse rate preferably should be measured in the same arm at each visit.

7.4.2 Temperature and Respiratory Rate

Temperature and respiratory rate will be measured for evaluation in the assessment for signs and symptoms indicative of potential serotonin toxicity. Oral (sublingual) temperature measurements are preferable; aural temperature is an acceptable alternative (this alternate means of measuring temperature is to be recorded in the eCRF).

7.4.3 Weight

Body weight will be recorded at Baseline (if not available from within the prior 42 days) and every subsequent visit thereafter (or upon early termination), including the 4-week post-treatment follow-up visit if applicable. Weight will be measured while the subject is clothed with shoes off and recorded in kilograms (kg).

7.5 Electrocardiography

A 12-lead ECG of at least 10 seconds in duration will be obtained in triplicate (taken within a period of 5 minutes) at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination), including the 4-week post-treatment follow-up visit if applicable. Recordings will be evaluated by a centralized ECG reading facility. Interval data (including QT and corrected QT intervals), ventricular rate, and overall interpretation are to be reported for every ECG. The interval data and ventricular rate are to be noted in the eCRF as averages of the three readings (with the exception of values that are not evaluable and reported as zero, in which case the average will exclude this zero value and note in the eCRF the average of values > 0).

A local cardiology consult should be sought if the investigator deems it necessary. For evaluation of subjects with left bundle branch block, a cardiology consult is strongly recommended.

7.6 Physical and Neurological Examinations

Targeted examinations (as described below) are to be performed at Baseline (if not available from within the prior 42 days) and every subsequent visit thereafter (or upon early termination), including the 4-week post-treatment follow-up visit if applicable. In the event of an abnormality, subjects should continue to be followed until resolution or stabilization.

The targeted examinations are to be focused on, but not limited to, evaluating subjects for potential serotonin toxicity (see Section 7.1.3.2 for guidance on assessment) and also as clinically indicated (*e.g.*, targeted to any changes in medical history, in the event of an AE that requires such follow up, or any reported change in the subject's physical condition). At a minimum (in addition to assessments for serotonin toxicity), they are to include evaluation of deep tendon reflexes, clonus, and muscle rigidity; size and reactivity of pupils; dryness of oral mucosa; intensity of bowel sounds; skin color; and presence or absence of diaphoresis.

Additional targeted examinations may be performed as clinically indicated (*e.g.*, in the event of an AE that requires such follow up or any reported change in the subject’s physical condition).

Findings will be documented in the subject's medical record and in the eCRF.

8 OTHER ASSESSMENTS

8.1 Mini-Mental State Examination (MMSE)

The MMSE (Folstein *et al*., 1975) was originally developed to differentiate between psychiatric patients with functional and organic conditions, to quantify the level of cognitive impairment, and to monitor changes over time. The MMSE subsequently has become a widely used and extensively validated cognitive test demonstrating satisfactory reliability, validity, and change sensitivity under a wide variety of conditions (Tombaugh and McIntyre, 1992).

Over a 12-month period, Alzheimer's disease patients might typically show a decline in MMSE score of 2-4 points (Schneider, 2001).

The utility of the MMSE as a means of assessing treatment response in Alzheimer's disease has been questioned (Bowie *et al*., 1999), but its status as a clinical outcome measure has been supported by the UK National Institute for Clinical Excellence guidance (NICE, 2001). Furthermore, the MMSE has demonstrated an ability to detect change in clinical studies with AChEIs (Birks and Harvey, 2004).

In an epidemiological study (Mukaetova-Ladinska *et al*., 2000), pre-mortem MMSE scores have been correlated with post-mortem Braak stage (based on the spread of tau pathology through the brain). MMSE is also sensitive to decline in bvFTD (Knopman *et al.*, 2008).

The MMSE will be performed at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination) and at the 4-week follow-up visit (if applicable) by raters deemed appropriate and delegated by the principal investigator. For each individual subject, the MMSE questionnaire to be utilized in this study will be the same version utilized for the subject in the respective originating double-blind study (to maintain longitudinal consistency per subject). The MMSE scores will be used to inform the evaluation for possible serotonin toxicity (to be included in the targeted physical and neurological examinations).

8.2 Resource Utilization in Dementia Questionnaire (RUD Lite)

The RUD was developed as a comprehensive instrument to measure resource use by patients in a clinical trial setting, which in a further step can be calculated into costs (Wimo *et al*., 1998; Wimo *et al*., 2003; Jonsson, 2007). The RUD Lite is a shorter version of the RUD (Wimo and Winblad, 2003). The RUD and RUD Lite assess both formal and informal resource use, making it possible to calculate costs from a societal perspective. The RUD is administered as an interview with the caregiver. The validity and reliability of the RUD instrument has been investigated both in residential care and community care settings by comparing responses to the RUD questions with actual observations of care-giving time (Jonsson, 2007; Wimo and Nordberg, 2007).

The following dimensions are captured on the subjects' part: accommodation/long term care, respite care, hospital care, social service, and home nursing care. In addition, the following aspects are covered from the caregiver perspective: caregiving time for the subject and work status.

The RUD Lite will be performed at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination).

8.3 EuroQol – 5 Dimension – 5 Level Instrument (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group to describe and value health-related quality of life. It has been utilized in a global Phase 3 study in patients with AD (using the EQ-5D Proxy version completed by caregivers)[6]. The

[6] https://clinicaltrials.gov/ct2/show/NCT00762411

instrument comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated by the subject and caregiver on a 5-point scale as having "no problems" (a score of "1"), "slight problems" (a score of "2"), "moderate problems" (a score of "3"), "severe problems" (a score of "4"), and "extreme problems" (a score of "5") based on descriptive examples; the scores are not intended to be summed. Present overall state of health is also to be rated on a vertical visual analogue scale (approximately 20 cm in length) from 0 to 100 (the higher the number the better the quality of life).

The EQ-5D-5L will be performed at Baseline and approximately every 6 months thereafter (or upon early termination). There will be two applications of the self-reported EQ-5D-5L at each visit: one version will be completed by the subject and a second copy of this version will be completed by the caregiver.

For application to the subject, the rater should explain to the subject what is required and how to complete the scale. If the rater deems that the subject can then complete without further assistance, the subject should then proceed to complete the scale without further assistance from the rater. If a subject cannot complete the scale, the rater will be permitted to read the questions and options for response and report the subject's responses. There should be no assistance from the caregiver.

For application to the caregiver on behalf of the subject, the rater should guide the caregiver in completing the scale as though the caregiver is responding for the subject, giving what the caregiver believes to be an accurate response to each question. If the caregiver cannot complete the scale, the rater will be permitted to read the questions and options for response and report the caregiver's responses.

It is important to ensure that the subject and caregiver each complete the EQ-5D-5L independently (although the subject and caregiver may each be assisted by a rater), with the assessments not influenced by knowledge of the other's responses. If independence cannot be assured, the order of administration of the EQ-5D-5L is subject first, followed by the caregiver.

9 STATISTICAL PLAN

A statistical analysis plan (SAP) will be written and finalized prior to database lock. A detailed description of the planned statistical analyses will be provided in the SAP; changes from analyses described in this protocol will be documented in the final study report. The database will be locked after review of data is complete, all queries are resolved, and all decisions made about the inclusion or exclusion of any spurious data and the handling of unused or missing data.

For purposes of safety reporting and regulatory submissions, one or more interim reports may be prepared prior to study termination.

9.1 Efficacy Endpoints

Not applicable to this open-label extension study.

9.2 Sample Size Calculations

Not applicable to this open-label extension study.

9.3 Statistical Analysis

9.3.1 Analysis Populations

The Safety Population will include all subjects who take at least one dose of study drug. Subjects dispensed study medication who subsequently are lost to follow up without any contact are not included in the Safety Population but will be included in the study disposition tabulation and listings. With the exception of study disposition, all tables and listings will be generated on the basis of the Safety Population.

9.3.2 General Considerations

Results will be summarized descriptively; no inferential statistics are planned. Tabulations will be on the basis of all subjects pooled and also with subjects categorized separately by diagnosis and also by study of original participation. Data from the prior study will be mapped into the open-label database.

For purposes of calculations of change from baseline, Baseline (Visit 1) for the open-label study will be used. Depending on the parameter, the data may have been acquired during the double-blind study of prior participation.

For purposes of data tabulations, target visit windows will be assigned in the SAP.

Listings of by-subject data will be organized by subject number.

9.3.3 Health Economic Analysis

A summary of the planned analyses is provided below; a detailed description of the planned analyses, as well as intended sensitivity analyses, will be provided in the SAP.

In order to investigate the pharmacoeconomic impact of LMTM, two approaches will be used:

- a cost consequence analysis (CCA), and
- a cost utility analysis (CUA).

With a cost consequence analysis, a broad set of relevant outcomes (here the primary and secondary outcomes) can be tabulated and discussed in relation to costs (Mauskopf *et al*., 1998). Costs and outcomes are presented separately.

In the cost utility analysis, the incremental cost effectiveness ratio (ICER) is analyzed. As an outcome, the gained quality adjusted life years (QALY) derived from the EQ5D instrument will be used.

Both pharmacoeconomic approaches mentioned above include a risk of getting non-significant effects regarding costs, as clinical trials evaluating efficacy are typically

underpowered with respect to pharmacoeconomic results and long-term effects cannot be assessed due to time constraints in the clinical trials. Therefore, a modeling approach will complement the analysis.

9.3.3.1 Resource Use

The Resource Utilization in Dementia instrument (RUD) is a comprehensive and validated instrument collecting data on resource use in trials, with the aim to calculate costs from a societal viewpoint. The RUD Lite questionnaire, a short version of RUD mainly discarding the resource use by the caregivers, is employed in this study. All subjects for whom RUD Lite data was collected for at least one time point will be included in the summaries.

Together with costs of institutional care, the value of informal care is the heaviest cost driver in dementia care. Three components of caregiver time will be included in the analysis:

- time spent on toilet visits, eating, dressing, grooming, walking and bathing;
- time spent on shopping, food preparation, housekeeping, laundry, transportation, taking medication and managing financial matters; and
- time spent on supervising the subject.

Each component of caregiver time will be calculated as the hours of care on a typical day multiplied by days spent on providing these services. The caregiver time will be summarized for each treatment group by visit and with AChEI and/or memantine status at randomization, severity, and geographic region.

Caregiver work status, whether the subject was admitted to a hospital, whether the subject received services in a hospital emergency room, whether the subject visited any health care professional, and whether the subject received any nursing services will be summarized likewise.

Caregiver relationship with subject and the subject's living accommodations will be summarized descriptively.

9.3.3.2 Unit Costs

Costs will be calculated as the multiplication of the amount of units of resource use and the unit cost for this particular resource. Unit costs for each unit will be collected for each country (if unit cost data are not available for each trial country, then unit cost data for the dominant country only will be used). An average wage will be used as a proxy for the opportunity cost of informal care. Caregiver time for retired carers will be given a value of 35% of caregivers of working age (Johannesson *et al*., 1991).

9.3.3.3 Statistical Analysis

In order to statistically support the descriptive analysis, regression models will be employed. Generalized linear models assuming gamma distributed dependent variables will be used accounting for the skewness of resource use and cost data. Bootstrapping methods will complement the analysis by providing estimates for the confidence intervals (Ramsey *et al*., 2005) in the univariate analyses.

If there is a substantial amount of missing data on resource use (> 20%), multiple imputation approaches will be tested.

9.3.3.4 Economic Modelling

As the long term cost-effectiveness of LMTM beyond the trial periods is of great interest, economic evaluations based on various modeling techniques will be used. These models most often have a CUA design in which the relation between costs and outcomes is expressed as the ICER. The QALY concept is the most frequently used outcome. External data for disease progression and mortality as well as data on resource use and costs beyond the trial period are used as inputs. From the trial, data on efficacy are used as an empirical core for the model. Within trial data on resource use and costs as well as the EQ5D data calibrates the external sources in the model. Often-used modeling techniques such as Markov models (Sonnenberg and Leventhal in Wimo *et al*., 1998) and Discrete Event Simulations (DES) (Guo *et al*., 2014) will be tested.

9.4 Baseline Characteristics and Concomitant Medications

Tabular summaries of demographics and baseline characteristics will be prepared based on data collected at the Baseline visit for the original study of participation and at baseline for the open-label extension study. Tabular summaries of concomitant medication use (ongoing at start of study and newly initiated) will be restricted to the open-label extension study. All data, including study eligibility, will be listed.

Concomitant medications and recently used medications (anti-dementia and psychiatric drugs used within the prior 3 months) will be coded using the most current version of the World Health Organization (WHO) drug dictionary. Tabulations will be prepared of all drugs used concomitantly (relative to the first dose of study drug in the open-label extension study) based on WHO Anatomical Therapeutic Classification (ATC) level 1 term, ATC level 3 term, and Preferred Term (generic name) with frequency and percentage of subjects using each concomitant medication. Concomitant medications are to be listed with these elements as well as the verbatim drug name.

9.5 Study Drug Exposure

Total duration of exposure and mean daily dose per subject over the treatment period in the open-label study will be summarized descriptively. The proportion of subjects with dose interruptions and/or dose reductions will be summarized descriptively.

9.6 Safety Analysis

The analysis of safety will include summaries of AEs, laboratory tests, vital signs, ECGs, and physical and neurological examinations (including serotonin toxicity assessments).

9.6.1 Adverse Events

Adverse events will be coded to System Organ Class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version adopted at the start of the double-blind study in which the subject previously participated (Version 15.0 or later).

Adverse events will be regarded as treatment-emergent (TEAE) if they start on or after the first dose of study drug administration in the open-label study or if they were present prior to the first date of study drug administration and increased in severity or relationship to study drug while on study treatment. Those that resolved prior to the first dose or were ongoing at the same intensity and relationship will be regarded as pre-treatment AEs and not summarized.

Tabular summaries are described below, with the number and percentage of subjects reporting each type of event presented. If a subject reports the same preferred term more than once, it is counted only once within that category. Further, for a given tabulation, the preferred term will only be counted once in its worst severity, greatest relationship to treatment, and worst action taken.

Pre-study AEs, those present at the time of the first dose of study drug administration, will be presented separately.

An overall summary table of TEAEs will be produced showing the number and percent of subjects with the following: TEAE, severe intensity TEAE, TEAE related to study drug, AESIs, serious TEAE, TEAE with outcome of death, and TEAE leading to interruption, dose reduction, or discontinuation from the study. In addition, the summary table will include the number of TEAEs, severe TEAEs, TEAEs related to study drug, and serious TEAEs.

Separate summaries of incidences (number and percentage of subjects) of all individual TEAEs and the subsets of drug-related TEAEs, TEAEs that are severe in intensity, serious TEAEs, and TEAEs leading to change in dose will be provided.

The subset of TEAEs that have an onset more than 7 days after the last dose of study drug will be considered post-treatment. An overall summary table of the number and percent of subjects with post-treatment AEs will be prepared.

All AEs will be presented in a data listing. In addition, listings also will be provided for SAEs, AEs leading to death, AEs leading to discontinuation of study drug, AEs leading to dose reduction and/or interruption, and any other AEs that are of special interest (to be defined prior to database lock).

9.6.2 Laboratory Tests

Descriptive statistics will be based on central laboratory results as described below. Laboratory results that are obtained from laboratories other than the central laboratory will not be included in tabular summaries. They will, however, be listed separately. Normal ranges will be provided by the central laboratory and each local laboratory used for testing parameters other than Heinz bodies.

Categorical laboratory parameters will be summarized for each target visit using counts and percent of subjects in each result category. Continuous laboratory parameters will be summarized for each target visit using descriptive statistics for both the original values and the change from Baseline. For each analyte, Baseline values will be restricted to those subjects in the Safety Population for whom there is at least one post-Baseline value.

Selected parameters for which normal ranges differ may additionally be summarized by gender, age, and country (or region).

Box and whisker plots will be presented for selected parameters including hemoglobin, reticulocytes, neutrophils, and liver function tests.

Shift tables will be provided cross tabulating the number of subjects who are low, normal, or high at Baseline (with respect to the normal range) against results at each target week.

Potentially clinically significant ranges will be defined in the SAP for selected parameters, and the number and percent of subjects meeting these criteria summarized. Tabular summaries will be based on those subjects who meet criteria at Baseline and those in whom the values represent a treatment-emergent worsening.

Listings of laboratory parameters will be presented. Listings will flag results above and below the normal range as well as those that meet criteria for being potentially clinically significant (whether or not a treatment-emergent worsening). Separate listings for each hematology and chemistry parameter will show results that meet criteria for being potentially clinically significant. In addition, for subjects who have one or more result that meets criteria, all laboratory results will be displayed.

9.6.3 Vital Signs and Weight

Blood pressure, pulse, temperature, respiratory rate, and weight will be summarized for each target visit using descriptive statistics for both the original values and the change from Baseline.

Potentially clinically significant vital sign changes will be defined, and the number and percent of subjects meeting these criteria will be summarized.

Listings of vital sign measurements will be presented. Listings will flag results that meet criteria as being potentially clinically significant. Separate listings for each vital sign parameter will show results that meet criteria for being potentially clinically significant. In addition, for subjects who have one or more result that meets criteria, all corresponding vital sign results will be displayed.

9.6.4 Electrocardiogram

ECG results will be provided by the central ECG reader. Tabular summaries and analyses are to be based on the central ECG data. Machine-read ECG results and interpretations are to be recorded in the eCRF and included in a separate listing; this also applies to any subsequent local interpretations if used to make dosing or patient management decisions.

ECG interval data will be summarized based on the average of the triplicate measures. All other study visit ECG data (interpretations or means of triplicate measurements if

performed for clinical reasons) will be summarized separately. ECG interval and ventricular rate data will be summarized using descriptive statistics for both the original values and the change from Baseline. Windows for each target visit will be used (additional details provided in the SAP). Parameters to be analyzed include heart rate (HR) and PR, QRS, QT, and corrected QT (using Fridericia's and Bazett's corrections), and RR intervals. Counts and percent of subjects in each result category will be tabulated. Overall interpretations of abnormality(ies) will also be tabulated, with subjects categorized by whether or not they have treatment-emergent abnormalities.

Subjects are also to be categorized and enumerated on the basis of QTc interval and change from Baseline as follows:

- QTcB/F outliers (in categories of > 450 to ≤ 480, > 480 to ≤ 500, > 500 msec)
- Change in QTcB/F outliers (in categories of > 30 to ≤ 60, > 60 to < 90, ≥ 90 msec)

All HR, interval data, and interpretations will be listed. Any new finding after Baseline will be categorized into diagnostic groups: rhythm, conduction, hypertrophy, arrhythmia, ischemia, infarction, other.

9.6.5 Physical and Neurological Examinations and Serotonin Syndrome (Toxicity)

Physical and neurological examination results obtained at Baseline (Visit 1) will be summarized by body system. Evaluation at subsequent visits will be summarized in a treatment-emergent fashion. Summaries will present the number and percentage of subjects with normal and abnormal observations by body system/parameter evaluated. By-subject listings will detail the abnormality(ies). Ratings for signs and symptoms of serotonin syndrome (toxicity) will also be summarized. For each target visit, the number of subjects for whom "yes" is answered for any of the signs and/or symptoms will be tabulated. A by-subject listing of results will also be prepared.

9.6.6 Health Economics and Quality of Life Measure

The individual items and overall scores for the RUD-Lite and EQ-5D-5L will be summarized descriptively by visit. Results will be listed by subject. A summary of the planned analyses is provided in Section 9.3.3; a detailed description of the planned analyses, as well as intended sensitivity analyses, will be provided in the SAP.

10 REGULATORY

Investigators and all other parties involved in the conduct of the study are responsible for ensuring that the study is conducted at their sites in accordance with the approved protocol, the principles of the most current applicable version of the Declaration of Helsinki (in the European Union, the study shall be conducted in accordance with the 1996 version as per Directive 2005/28/EC), the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) (CPMP/ICH/135/95, July 1996), and with applicable country and local regulatory requirements and laws.

The Sponsor will be responsible for ensuring that the relevant approval is obtained from the local regulatory authority prior to the start of the study. The relevant documents will be provided to the investigator. The Sponsor or designee will forward any protocol amendments to the regulatory authority and will ensure that SAEs are reported, and progress reports and details of any serious protocol violations are provided as required.

The regulatory authority will be informed should the study be terminated early.

11 APPROVAL OF THE PROTOCOL AND AMENDMENTS

Following authorization by the Sponsor, the final protocol and all related documents (*e.g.,* information sheets and ICFs) will be submitted to the IEC/IRB.

The Sponsor will be responsible for ensuring that regulatory and IEC/IRB approvals are obtained prior to the start of the study. The relevant documents will be provided to the investigator.

Neither the investigator nor the Sponsor will modify this protocol. If modification is necessary, either party must first obtain the concurrence of the other. The party initiating a modification will confirm it in writing, and the investigator will be responsible for informing the IEC/IRB. In case of a substantial amendment, prior approval of the IEC/IRB is required.

The Sponsor or designee is responsible for submission of a protocol amendment to the regulatory authority. In the event of a substantial amendment, prior approval is required.

12 SERIOUS BREACHES

The investigator and all other parties involved in the conduct of this study will comply with the protocol and ICH GCP. All deviations will be reported to the study monitor.

It is the responsibility of the Sponsor to notify the licensing authority of any serious breach which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

All serious breaches will be notified to the pertinent regulatory authorities according to the relevant national regulatory requirement. The reporting will be *via* the Sponsor in accordance with the Sponsor Standard Operating Procedures.

13 INFORMED CONSENT

It is the responsibility of the investigator or a medically trained, medically qualified sub-investigator to obtain informed consent from each subject participating in this study, or his/her representative who is permitted to provide consent in accordance with local legislation. Where required by local law, the person who informs the subject must be a physician.

Subjects and/or their legal representative(s) must give written (signed and personally dated) informed consent prior to study entry and before any study specific procedures are undertaken; in Germany (as per §40, section 1 of the German Drug Law [AMG]) and in

the Netherlands, the subject must be able to provide his or her own written informed consent. The identified caregiver(s) for each subject also must provide written consent to his/her own participation as outlined below. Where there is a change of caregiver, the new caregiver must provide written informed consent.

Potential subjects will be assessed for whether they have capacity to understand the ICF and give consent.

Where possible, fully informed consent will be obtained from the subject. However, subjects entering this study may lack the necessary mental capacity to give fully informed consent. If the potential subject is unable to comprehend the ICF, then one or more legally acceptable representatives will be required to sign the ICF as required by national law. In this situation, and provided that it is permitted by local legislation, the subject's agreement to participate in the study will still be obtained to his/her best level of understanding and recruitment will not proceed if the subject refuses or shows significant distress.

Informed consent can be obtained only after the aims, methods, anticipated benefits, and known potential hazards of the study have been explained to and discussed with the potential subject and caregiver by the investigator. A subject information sheet, providing a written summary of all relevant information, will be given to the potential subject and caregiver prior to written informed consent being obtained. The caregiver will also be given an information sheet. The information sheet will make clear that access to the subject's medical records will be required. It is the responsibility of the investigator to ensure that the potential subject and/or caregiver are aware of this. The investigator will explain to the potential subject and caregiver that they are at liberty to refuse to take part in the study or, should they decide to participate, they may withdraw from the study at any time. Such a decision should not, in any way, impinge on the future management of the subject. The potential subject and caregiver will be allowed as much time as they need to decide whether or not to participate in the study and will be provided with a contact point where further information about the study may be obtained.

The study is multinational and includes sites in the European Union and the United States of America, two geographic regions that maintain descriptions of clinical studies on the internet. As required by the U.S. Food and Drug Administration, the ICF must contain the following text: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time." Consistent with European Union law, the ICF also indicates that information will be on https://www.clinicaltrialsregister.eu. Information regarding other national registries will also be included in the ICF, where applicable.

For subjects transferring to a geographically close investigational site, informed consent should be accompanied by a signed Authorization for Transfer of Subject Medical Records prior to transferring a subject's medical data to the new site.

Continued participation will be re-evaluated approximately every 12 months on the basis of safety, tolerability, and continued benefit as judged by the investigator. Subjects deemed eligible for continued treatment (and/or their caregivers) must provide informed

consent for re-enrollment. The same 13-week and 26-week schedules of assessments (as described in Section 4.4) will be maintained for continued treatment beyond the first 12 months (including re-consent at Visit 6). Subjects for whom consent is not provided consistent with national requirements and IRB/EC approval will be discontinued.

14 INVESTIGATOR RESPONSIBILITIES

The primary responsibility of all investigators participating in the study is for the well-being and interests of their subjects, including subjects enrolled in this study. The investigator has overall responsibility for the conduct of the trial at his/her study site and may delegate specific duties to appropriately trained members of his/her research team or to other hospital staff, *e.g.*, the pharmacy. Any delegation must be clearly documented in a study site specific delegation list.

The investigator is responsible for the following:

- Performing the study in accordance with ICH GCP
- Ensuring that adequate time and appropriate resources are available to perform the study as described in this protocol
- Ensuring that all persons assisting with the trial are adequately qualified, trained, and informed about the protocol, trial-related duties, and functions
- Maintaining a list of sub-investigators and other appropriately qualified persons to whom duties have been delegated
- Signing an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol
- Maintaining adequate control of study drug and appropriate records of drug disposition
- Maintaining adequate records of each subject's participation

Where local laws require it, national regulatory requirements with regard to the inclusion of subjects who are unable to consent will be followed by the investigators. In particular, in Germany, the risk threshold and degree of burden/distress will be monitored constantly by the investigators in accordance with §41, section 3 of the German Drug Law (AMG).

The Sponsor and the appointed DSMB will constantly evaluate the risk threshold of this particular study by assessing the safety profile according to Sections 4.8 and 7, as well as assessing the safety profile of other ongoing studies with the same active moiety. Any changes in the risk profile during the course of the study will be communicated to the investigators. In addition, the investigators will review adverse events at each visit in accordance with the schedule of assessments (see Table 4-1), and have the right to reduce the dose, interrupt or discontinue study drug for safety reasons as described in Sections 5.3 and 6.2.2.

The burden/distress associated with participation in this study is addressed in the patient information leaflet. During the study, the investigators should obtain information from the subjects in order to adequately monitor the degree of burden/distress. Subjects are

advised that they have the right to discontinue study drug and withdraw from the study at any time for any reason and should inform the investigators accordingly in order to assist the investigators with monitoring activities.

15 CONFIDENTIALITY AND DATA PROTECTION

All study-related documentation is confidential, whether obtained by the investigator or provided by the Sponsor or their representative.

The investigator must ensure the anonymity of subjects in the trial is maintained on eCRFs, samples, specimens, and other documents leaving the study site and submitted to the Sponsor or its designees. Subjects must NOT be identified by name, but by an identification code (usually trial number). For all subjects (including subjects who were screened but not enrolled), the investigator must keep a separate log of subject codes, names, and addresses.

To conform to the requirements of EU Directive 95/46/EC, subjects will be explicitly asked to consent to transmission of their data outside the European Economic Area. In the United States, data will be protected consistent with the Health Insurance Portability Accountabilty Act (HIPAA).

Confidentiality of the records identifying the subject will be maintained. Representatives of the Sponsor such as monitor(s) or auditor(s), IRB/IEC, and pertinent regulatory authorities will be permitted direct access to these records and other source data/documents as appropriate.

Details of access to the subjects' data will be fully described within the subject information sheet. The consequence of the subject's withdrawal of consent with regards to the use of data will also be described.

16 QUALITY ASSURANCE AND CLINICAL MONITORING

Standard operating procedures (SOPs) will be adhered to for all activities relevant to the quality of the study, including protocol compliance, data collection, quality control, and data analyses and reporting.

All aspects of the study will be subject to a Quality Assurance (QA) audit plan. QA audits will be conducted on critical phases during the clinical and reporting phases of the study. These audits will be carried out by quality assurance personnel, independent of the staff involved in the study, according to relevant SOPs.

Clinical monitoring will be performed by trained clinical research personnel. Detailed expected on-site and remote monitoring activity will be described in a clinical monitoring plan, which will be modified on an ongoing basis to ensure subject safety and data integrity.

The investigator (or his/her designated deputy) agrees to cooperate with the monitor and other clinical research personnel to ensure that any problems detected in the course of these monitoring visits are quickly resolved.

Audits of study sites and/or trial processes may be carried out at any stage.

17 DOCUMENTATION

The protocol, its amendments, and any other required documents must be submitted for appropriate regulatory review and approval.

The investigator at each study site must generate and maintain adequate records (medical records, source documents, and eCRFs) to enable the conduct of this study to be fully documented.

Initially, data will be collected on source documents which will then be transcribed to the eCRF. The eCRF may serve as the primary collection medium for any data (to be agreed with the investigator and documented in the Source Data Verification Agreement). Each enrolled subject must have an eCRF completed and this must be reviewed and approved by the investigator.

The documents specified by ICH GCP (*e.g.*, copies of protocols, CRF pages, original copies of test results, reports, drug dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept on file by the investigator for a minimum of 15 years or for the period of time specified by local law for the preservation of hospital patient documents, whichever is the longest. No study documents should be destroyed without prior written agreement between the Sponsor and the investigator. Should the site wish to assign the study records to another party, or move them to another location, the Sponsor must be informed.

A record must be kept of all subjects consenting for the study and subsequently excluded. The reason for non-participation in the study should be recorded.

Documents that must be provided before or at site initiation include (but are not limited to) the following:

- Protocol and amendments (if applicable) signed and dated by applicable Sponsor representatives, as well as by the investigator
- Regulatory approval (or in absence of document, evidence that study may proceed)
- Signed and dated IEC approval
- Approved subject information sheet, ICF, and advertisement for recruitment (if any)
- eCRFs
- Confidentiality agreement(s)
- Financial disclosure
- Study drug/shipping records
- Authorized signature log/delegation list
- Signed Form FDA 1572

- Signed *curricula vitae* (CV) for personnel who have signed the authorized delegation log (including principal investigator, all sub-investigators, and designated assistants)
- Investigator Brochure with signed and dated Investigator Brochure receipt
- Signed and dated clinical trial agreement
- Research and development (or institution) approval, if applicable
- Signed and dated indemnity/insurance statement (if applicable)
- Laboratory reference ranges and accreditation for all applicable laboratories (central and local, as applicable)
- Pharmacy agreement (if any)
- Instructions for handling investigational product
- Sample label
- SAE forms

18 PUBLICATION

Since this is a multiple site study, the community of investigators and delegated individual investigators shall not publish any partial results before the end of the study or before the analysis and publication of the results of the entire study.

The investigator and/or institution shall have the right to publish, display, or otherwise communicate orally, in writing, or electronically (hereafter a "publication") the results of their work conducted under this protocol after 12 months from NDA or equivalent filing, or earlier only with explicit consent of the Sponsor in advance and in writing.

Sites and/or investigators must provide the Sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication, and agree to delay the publication if, in the Sponsor's reasonable view, the publication may prejudice the Sponsor's intellectual property. The Sponsor will make every reasonable effort to consider and release each proposed abstract or publication within 60 days of submission. The investigator and/or site will include where possible comments made by the Sponsor. Authorship will be determined by mutual agreement. Access to data will be in accordance with authorship.

19 INDEMNITY, INSURANCE AND COMPENSATION

A clinical trials insurance and product liability insurance policy will be in place to cover the conduct of this study.

20 ADMINISTRATIVE AND FINANCIAL AGREEMENT

Agreed costs for each participating study site will be met by the Sponsor. For each study site, an agreement will be prepared and signed off by the relevant authority on behalf of the institution (*e.g.*, National Health Service Trust, University) and by the Sponsor or its designee before the initiation of the trial. Each investigator and sub-investigator must also sign a Form FDA 3455 or its equivalent to disclose any financial arrangements or interests.

21 STUDY ADMINISTRATION

This trial will be conducted in compliance with ICH GCP and other applicable regulatory requirements.

Contract Research Organizations and/or independent contract personnel will be contracted to manage and monitor the trial, to provide services for data management and statistical analysis, to provide regulatory advice and services, to handle the reporting of Serious Adverse Events, to provide services for laboratory analysis, to package and distribute the clinical trial supplies, and to provide quality assurance support and services.

Calibration certification for the following equipment used to generate study data will be confirmed: pharmacy temperature loggers and ECG machines.

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23 APPENDICES

23.1 Appendix A: Assessments by Visit

Before participation in this extension study may begin, the subject and caregiver will each be provided with an information sheet and both will be given as much time as needed to decide whether or not to participate in this study. Subjects and caregivers must re-consent to continue participation annually (approximately Weeks 52, 104, *etc.*).

Baseline Visit (Visit 1, Day 1)

For potential subjects, the safety and efficacy assessments completed at the final designated visit of the prior TauRx study in which they were enrolled will serve as Baseline assessments for this extension study (unless otherwise noted). If the final visit occurred more than 42 days prior, assessments are to be repeated as specified below.

Subjects may continue participation at the same site at which they participated in the originating double-blind study or transfer to a geographically close investigational site (that also participated in the same study). Eligibility for continued open-label treatment is to be determined by the original investigator and, if applicable, a referral to a new site made. The new investigator will have access to the subject's prior study eCRFs and is to confirm eligibility. Baseline assessments may be repeated (also within 42 days) as determined by the new investigator for subjects transferring to a new site.

Screening / Baseline Assessments

The following assessments will be obtained, performed or measured at Baseline to confirm eligibility for enrollment prior to dosing or, in the case of the EQ-5D-5L, to provide a Baseline assessment (as this scale is not used in the prior double-blind studies):

- Written Informed Consent for participation in the study from the subject (or legally acceptable representative) and from the identified caregiver(s) (before any study related procedures may be performed)
- Inclusion and exclusion criteria review (to confirm eligibility)
- EQ-5D-5L (applied to the subject and to the caregiver on behalf of the subject)

In addition to the assessments listed above, the following assessments are to be performed if Baseline (Visit 1) does not coincide with the final designated visit in the prior double-blind study (Visit 11 in TRx-237-005, Visit 9 or Visit 10 in TRx-237-007, Visit 7 in TRx-237-008, or Visit 10 in TRx-237-015):

- Adverse events review (after signing of the Informed Consent)
- Medical history
- Prior and concomitant medication review
    - Details of current and recent medication (since last study visit), including dose changes
- Blood sample for serum pregnancy test in women of childbearing potential only

In addition to the assessments listed above, the following assessments are to be performed if Baseline (Visit 1) is not within 42 days of the final designated visit in the prior double-blind study (Visit 11 in TRx-237-005, Visit 9 or Visit 10 in TRx-237-007, Visit 7 in TRx-237-008, or Visit 10 in TRx-237-015):

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Body weight
- Blood samples for the following Baseline tests:
    - Chemistry panel
    - Hematology panel
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- MMSE
- RUD-Lite

The subject and caregiver will be provided with information about how to correctly take study drug. Study drug will be dispensed to the subject and/or the subject's caregiver. Enough study drug will be dispensed to last for approximately 13 weeks (Visit 3).

Visit 2 (Week 2 ± 3 Days)

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight

- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)

The subject and caregiver will be questioned to assess compliance with prescribed dose of study drug (no tablet count will be undertaken).

Telephone Contact (Week 6 ± 14 Days)

After the Week 2 visit (Visit 2), a telephone contact will occur with the subject's caregiver at Week 6 (± 14 days).

Visit 3 (Week 13 ± 14 Days)

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)

Study drug will be dispensed to the subject and/or the subject's caregiver. Enough study drug will be dispensed to last until the Week 26 visit (Visit 4).

Visit 4 (Week 26 ± 14 Days)

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes

- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- MMSE
- RUD-Lite
- EQ-5D-5L (applied to the subject and to the caregiver on behalf of the subject)

Study drug will be dispensed to the subject and/or the subject's caregiver. Enough study drug will be dispensed to last until the Week 39 visit (Visit 5).

Visit 5 (Week 39 ± 14 Days)

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight

- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)

Study drug will be dispensed to the subject and/or the subject's caregiver. Enough study drug will be dispensed to last until the Week 52 visit (Visit 6).

Visit 6 (Week 52 ± 14 Days)

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- MMSE
- RUD-Lite
- EQ-5D-5L (applied to the subject and to the caregiver on behalf of the subject)

Subjects who complete treatment through the Week 52 on-treatment visit (Visit 6) will be offered an opportunity to continue in the open-label study, provided the investigator judges that the potential benefit of continued treatment outweighs the potential risk. Consent forms will have been given to both the subject and his/her caregiver prior to this visit. Those subjects who wish to continue in the subsequent extension phase (and/or their caregivers) will be consented at Visit 6 before further supplies of study drug are dispensed.

Early Termination Visit (± 14 Days of Last Dose of Study Drug)

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- MMSE
- RUD-Lite
- EQ-5D-5L (applied to the subject and to the caregiver on behalf of the subject)

Subjects who do not wish to continue with open-label treatment will cease taking study drug after the Week 52 or early termination visit. They will be seen for a post-treatment follow-up visit 4 weeks (± 14 days) after the last dose of study drug (Visit 7); otherwise, the post-treatment follow-up visit will not be required for subjects who elect to continue as they will transition directly into the additional extension phase.

Unscheduled Visit

Subjects are to bring all remaining study drug to the clinic to assess compliance (to be assessed by counting returned tablets as well as by questioning the subject and caregiver).

The following assessments will be performed as appropriate in response to safety concerns:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes

- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Body weight
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- Recording of adverse events
- Concomitant medication recording/review
- Any additional assessments (such as pulse co-oximetry) required to monitor a treatment-emergent AE to resolution or stabilization

The subject is to be scheduled to return to the clinic for the next scheduled visit or additional unscheduled visits as appropriate.

Post-Treatment Follow-up Visit (If Applicable) – Visit 7 (Week 56 ± 14 Days)

A follow-up visit will be performed approximately 28 (± 14) days after the last dose of study drug for those subjects who do not wish to continue with open-label treatment.

The following assessments will be performed:

- Blood pressure and pulse measured with subject in a seated position for at least 5 minutes
- Respiratory rate and preferably oral (sublingual) temperature; aural temperature is an acceptable, but less preferable, alternative
- Concomitant medication recording/review
- Adverse events review
- Blood samples for the following tests:
    - Chemistry panel
    - Hematology panel
    - Serum pregnancy test for women of childbearing potential only
- Body weight
- 12-lead ECG measurements performed in triplicate (three ECG tracings within an approximate 5-minute interval)
- Physical and neurological examination (includes an assessment for signs and symptoms of serotonin toxicity)
- MMSE

23.2 Appendix B: Summary of Changes to the Protocol

23.2.1 Protocol Version 1.1

The final protocol for Study TRx-237-020 (Version 1.0 dated 25 April 2014) has been revised (Version 1.1 dated 11 June 2014) to include the EudraCT number issued for this study (2014-002013-37), identify the responsible personnel for medical monitoring and pharmacovigilance, modify the format for study identification numbers to be assigned to subjects, and modify the administrative and financial agreement. The revisions and affected sections are summarized in the table below.

Additional revisions are editorial and intended to correct typographical errors.

Summary of Changes	Affected Sections in Revised Protocol (Version 1.1)
The EudraCT number (2014-002013-37) is now specified in the protocol.	Not applicable (only affects page headers)
The responsible personnel for medical monitoring and pharmacovigilance are now identified.	Section 1.2 Responsible Personnel
The format for study identification numbers to be assigned to subjects has been modified; subjects will now be assigned a unique study identification number with the first three digits reflecting this open-label extension study (020).	Section 4.5 Assignment of Treatment
There will be no reimbursement of subjects' travel and accommodation costs.	Section 20 Administrative and Financial Agreement

23.2.2 Protocol Version 2.0

The final protocol for Study TRx-237-020 (Version 1.1 dated 11 June 2014) has been revised (Version 2.0 dated 2 June 2015) to include modifications and/or clarifications to administrative and background information, exclusion and discontinuation/withdrawal criteria for subjects in Germany, study drug administration and storage conditions, study assessments and procedures, and regulatory requirements as summarized in the table below.

Additional revisions are included which are editorial and/or intended to add minor clarification.

Summary of Changes	Affected Sections in Revised Protocol (Version 2.0)
Administrative and Background Information	
The registered address (in Singapore) for the Sponsor has changed and has been updated accordingly.	Title Page
The Sponsor's Global Project Lead and contact for Pharmacovigilance have changed for this study and have been updated accordingly.	Section 1.2 Responsible Personnel
Updates have been incorporated to include more current data available from the ongoing double-blind studies in support of the rationale for safety assessments performed in this open-label extension study, as well as for consistency with the current Investigator's Brochure.	Section 2 Background
The approximate number of participating clinical study sites has been updated to 170 sites (previously 200-250 sites).	Synopsis Section 4.2 Population
Exclusion and Discontinuation / Withdrawal Criteria	
Clarification has been added to indicate that subjects who participated in Study TRx-237-015 and did not consent to extended treatment for up to 15 months as per Protocol v3.0 (extended from 12 months as per the original study protocol) may be enrolled into this extension study following completion of the 12-month double-blind treatment period and 4-week post-treatment follow-up visit for TRx-237-015.	Synopsis Section 4.2 Population Section 5.1 Inclusion Criteria
In response to requests received from the EC of the State of Berlin for this study, exclusion criteria have been added to specify that in Germany, subjects meeting the following criteria are to be excluded: subjects who reside in a continuous care or assisted living facility if mandated by an order issued by either the judicial or the administrative authorities, and subjects whose willingness to participate in the clinical trial may be unduly influenced by the expectation (regardless of whether justified) of benefits associated with participation, or of a retaliatory response from family, caregivers, or treating personnel in case of refusal to participate.	Synopsis Section 5.2 Exclusion Criteria
In response to requests received from the EC of the State of Berlin for this study, the discontinuation / withdrawal criteria have been modified to more clearly specify medically measureable criteria, and lack of efficacy has been expanded to include worsening of cognitive capacity; in Germany, this includes loss of the ability to give consent if the legal representative or caregiver is not available or does not agree to continued participation.	Section 5.3 Discontinuation/Withdrawal

Summary of Changes	Affected Sections in Revised Protocol (Version 2.0)
Study Drug Administration and Storage Conditions	
The protocol has been modified to indicate that in those countries where limited by a CA or EC, the maximum allowable dose is 200 mg/day (rather than 300 mg/day).	Synopsis Section 2 Background Section 3 Objectives Section 4.1 General Description Section 4.6 Study Treatment Section 6.2.2 Flexible Dosing
The protocol now indicates that interruption(s) of dosing for up to 30 days on a given occasion may be allowed at any time (rather than restricting this to Visit 2) if the investigator determines this is indicated. Subjects should now be withdrawn from treatment if there is a need for a single interruption of dosing longer than 30 days (the protocol previously allowed two 30-day dose interruptions), only for safety reasons.	Synopsis Section 2 Background Section 4.1 General Description Section 4.6 Study Treatment Section 6.2.2 Flexible Dosing
Dose escalation is to be allowed at the drug dispensing visit (Visit 3) rather than at the first post-baseline visit (Visit 2), or at any subsequent dispensing visit as determined by the investigator during the treatment period. The dose can be decreased at any time at or after Visit 2.	Synopsis Section 4.1 General Description Section 4.6 Study Treatment Section 6.2.2. Flexible Dosing
As the bvFTD subjects from Study TRx-237-007 are not required to return for a 4-week post-treatment visit prior to entering this open-label extension study, these subjects may choose to enroll in this extension study at Visit 9 (*i.e.*, on the same day that they receive the last dose of study drug) in Study TRx-237-007. Guidance has been added to clarify appropriate study drug dosing for bvFTD subjects entering this extension study.	Section 4.1 General Description Section 6.2.1 Initial Dose
Additional details have been added regarding the study drug packaging. The appropriate study drug storage temperature condition (not more than 30°C) is now specified. Guidance has been added to indicate that study drug should remain in the package as dispensed until it is ingested by the subject, and should not be placed in an alternate pill box including commonly-used weekly pill organizers.	Section 6.3 Packaging, Labeling, and Storage
Study Assessments and Procedures	
Additional guidance is provided for investigators' assessment of the acceptable risk/benefit balance and evaluation of continued benefit from study participation in any given subject. Guidance has also been added for confirming eligibility and appropriate assessment of AD subjects transferring to a geographically close investigational site (that also participated in the same originating double-blind study). Baseline assessments may be repeated (also within 42 days) as determined by the new investigator for AD subjects transferring to a new site.	Synopsis Section 2 Background Section 4.1 General Description Section 4.2 Population Section 4.4 Schedule of Assessments Section 23.1 Appendix A: Assessments by Visit
Corrections have been incorporated to indicate that the EQ-5D-5L will be performed at Baseline (as this assessment will not be evaluated in the previous double-blind study of participation).	Synopsis Section 4.4 Schedule of Assessments Section 23.1 Appendix A: Assessments by Visit
The procedure for administering the EQ-5D-5L has been modified. There will be two applications of the EQ-5D-5L at each visit: one version will be completed by the subject and a second copy of this version will be completed by the caregiver. Guidance has been added to clarify appropriate application of the scale to the subject and caregiver.	Synopsis Section 4.4 Schedule of Assessments Section 8.2 EQ-5D-5L Section 23.1 Appendix A: Assessments by Visit
Corrections have been incorporated to clarify that at Visit 2, compliance with study drug will be assessed by questioning the	Section 4.4 Schedule of Assessments Section 6.4 Dispensing

Summary of Changes	Affected Sections in Revised Protocol (Version 2.0)
subject and caregiver. At each study visit thereafter during the treatment period, compliance will also be assessed by counting returned tablets (in addition to questioning the subject and caregiver).	Section 6.5 Compliance Section 23.1 Appendix A: Assessments by Visit
Corrections have been incorporated to indicate that serum pregnancy testing should be performed (in women of childbearing potential) if Visit 1 does not coincide with the final designated visit of the previous double-blind study of participation.	Section 4.4 Schedule of Assessments Section 7.3.3 Other Laboratory Tests Section 23.1 Appendix A: Assessments by Visit
It is further clarified that the same schedule of assessments will be followed in subjects who enter subsequent 12-month extension phases (including re-consent and study drug dispensing at Visit 6), with no requirement for the Week 2 visit or Week 6 telephone contact in any subsequent year of participation.	Section 4.4 Schedule of Assessments Section 13 Informed Consent
Guidance regarding contraceptive measures now also indicates that women of childbearing potential should be encouraged to return to the clinic in the event of a delayed menstrual period to rule out possible pregnancy.	Section 4.7.7 Contraceptive Measures
Aural temperature measurement is now specified as an acceptable (but less preferable) alternative to oral (sublingual) temperature (to be measured in response to concerns about serotonin toxicity); this alternate means of measuring temperature is to be recorded in the eCRF.	Section 6.2.3.2 Serotonin Syndrome Section 7.4.2 Temperature (Optional) Section 9.6.3 Vital signs and Weight Section 23.1 Appendix A: Assessments by Visit
The discussion of AE recording has been modified to specify that when describing an AE in terms of a diagnosis, events and signs/symptoms leading up to a diagnosis should be retained.	Section 7.1 Adverse Events
For the reporting of SUSARs, a determination will now be made (on a case-by-case basis) regarding whether unblinding prior treatment is required for any unexpected events.	Section 7.1.5.2 Sponsor Reporting of SUSARs to Regulatory Authorities
The description of the RUD Lite scale has been corrected, as work status for the subject is not captured in the RUD Lite.	Section 8.1 Resource Utilization in Dementia Questionnaire (RUD Lite)
For AD subjects transferring to a geographically close investigational site, informed consent should be accompanied by a signed Authorization for Transfer of Subject Medical Records prior to transferring a subject's medical data to the new site.	Section 13 Informed Consent
Statistical Analyses	
Clarification has been added to indicate that subjects dispensed study medication who subsequently are lost to follow up without any contact are not included in the Safety Population, but will be included in the study disposition tabulation and listings. With the exception of study disposition, all tables and listings will be generated on the basis of the Safety Population.	Synopsis Section 9.3.1 Analysis Populations
A summary of the planned statistical analyses has been added for health economics and quality of life measures; a detailed description of the planned analyses, as well as intended sensitivity analyses, will be provided in the SAP.	Synopsis Section 9.3.3 Health Economic Analysis (and all subsections) Section 22 References
Regulatory	
The protocol now specifies that in the European Union, this study shall be conducted in accordance with the 1996 version of the Declaration of Helsinki as per Directive 2005/28/EC.	Section 10 Regulatory

23.2.3 Protocol Version 2.1

The final protocol for Study TRx-237-020 (Version 2.0 dated 2 June 2015) has been revised (Version 2.1 dated 22 June 2015) to no longer specify that a subject's inability to self-complete the EQ-5D-5L scale must be for reasons associated with his or her disease in order for it to be acceptable to allow rater assistance, as summarized in the table below.

Summary of Changes	Affected Sections in Revised Protocol (Version 2.1)
The protocol no longer specifies that a rater is only permitted to assist a subject with completing the EQ-5D-5L scale if the subject cannot complete the scale for reasons associated with his or her disease, as there may be other acceptable reasons to allow assistance from the rater on a case-by-case basis.	Section 8.2 EQ-5D-5L

23.2.4 Protocol Version 3.0

The final protocol for Study TRx-237-020 (Version 2.1 dated 22 June 2015) has been revised (Version 3.0 dated 24 March 2016) to include modifications to administrative and background information, inclusion criteria, study assessments and statistical analyses for safety evaluations, and other procedures. The revisions and affected sections are summarized in the table below.

Additional revisions are included which are editorial or intended to add clarification.

Summary of Changes	Affected Sections in Revised Protocol (Version 3.0)
Administrative / Background	
The Sponsor's Global Project Lead and Head of Safety and Medical Monitoring have changed for this study and have been updated accordingly. Responsible personnel for ECG assessments have also been added.	Section 1.2 Responsible Personnel
The background discussion of clinical data has been updated to reflect the most current Investigator's Brochure and Development Safety Update Report for LMTM.	Section 2 Background
Inclusion Criteria	
It is now specified that in the Netherlands, subjects must be able to provide their own written informed consent to participate in this study; continuation of treatment is not permitted if the subject is unable to give consent.	Synopsis Section 5.1 Inclusion Criterion No. 3 Section 5.3 Discontinuation/Withdrawal Section 13 Informed Consent
Safety Assessments / Procedures	
A 12-lead ECG (in triplicate) will now be obtained in all subjects at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination) and at the 4-week follow-up visit if applicable (previously, ECG testing was only to performed as needed in response to an AE or changes in the subject's physical condition or medical history). Guidance for the management of abnormalities has been added accordingly.	Synopsis Abbreviations Section 1.2 Responsible Personnel Section 2 Background Section 4.1 General Description Section 4.4 Schedule of Assessments Section 5.3 Discontinuation/Withdrawal Section 6.2.3.3 Other Safety Reasons Requiring Dose Adjustment Section 7 Assessment of Safety Section 7.5 Electrocardiography Section 9.6 Safety Analysis Section 9.6.4 Electrocardiogram (*Section added*) Section 13 Informed Consent Section 21 Study Administration Section 23.1 Appendix A: Assessments by Visit
Targeted physical and neurological examinations will now be performed in all subjects at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination) and at the 4-week follow-up visit if applicable (previously, these examinations were only to performed as needed in response to an AE or changes in the subject's physical condition or medical history).	Synopsis Section 2 Background Section 4.1 General Description Section 4.4 Schedule of Assessments Section 4.7.2 Drugs with Serotonergic Potential Section 6.2.3.2 Serotonin Syndrome Section 7 Assessment of Safety Section 7.1.3.2 Serotonin Syndrome (Toxicity) Section 7.4.2 Temperature and Respiratory Rate Section 7.6 Physical and Neurological Examinations

Summary of Changes	Affected Sections in Revised Protocol (Version 3.0)
As part of these targeted examinations, subjects will also be assessed for signs and symptoms indicative of potential serotonin toxicity (and temperature and respiratory rate will be measured for evaluation in this assessment); guidance on assessment and recording adverse events is provided in Section 7.1.3.2.	Section 9.6 Safety Analysis Section 9.6.3 Vital Signs and Weight Section 9.6.5 Physical and Neurological Examinations and Serotonin Syndrome (Toxicity) Section 13 Informed Consent Section 23.1 Appendix A: Assessments by Visit
The AESIs in this study are signs and symptoms consistent with hemolytic anemia and serotonin syndrome (toxicity). Potential interruption or discontinuation of study drug in response to these events is discussed in Section 6.2.3; guidance on monitoring subjects is now provided in Section 7.1.3.	Section 4.7.2 Drugs with Serotonergic Potential Section 5.3 Discontinuation/Withdrawal Section 6.2.3 Dose Adjustment for Selected Adverse Events / Test Abnormalities (*and all subsections*) Section 7.1.3 Adverse Events of Special Interest (*and all subsections*)
Adverse events of suicidal ideation and serotonin toxicity are no longer specified as required to be reported as SAEs per the study protocol; the reporting of these events will be left to the discretion of the investigator.	Section 7.1.4 Serious Adverse Events
For SUSAR reporting in this study, should treatment assignment in the previous double-blind study of participation not yet be unblinded, the treatment assignment for a given subject will be made available for assessment of the SUSAR and will be included in the reporting of the event to a regulatory authority (as the onset of a possible SUSAR relative to the prior treatment history is an important aspect of the assessments); guidance for SUSAR reporting and unblinding treatment allocation has been revised accordingly.	Section 7.1.6.2 Sponsor Reporting of SUSARs to Regulatory Authorities Section 7.1.6.2.1 Unblinding Treatment Allocation (*Section added*)
Clarification has been added regarding serum chemistry panel analytes (urea nitrogen, urea) and the reporting of results in the Covance CLS database.	Section 7.3.1 Serum Chemistry
Clarification has been added regarding the inclusion of subjects and selected parameters in the statistical analyses of adverse events and laboratory tests. For the analysis of adverse events, the summarization of certain TEAEs, subgroup analyses, and interactions between MT and selected concomitant medications have been removed as these analyses will be done for the Integrated Summary of Safety (which takes into consideration the totality of a subject's exposure).	Section 9.6.1 Adverse Events Section 9.6.2 Laboratory Tests
Other Assessments / Procedures	
The MMSE will now be performed at Baseline (if not available from within the prior 42 days) and approximately every 6 months thereafter (or upon early termination) and at the 4-week follow-up visit if applicable. The MMSE scores will be used to inform the evaluation for possible serotonin toxicity (to be included in the targeted physical and neurological examinations).	Synopsis Abbreviations Section 4.1 General Description Section 4.4 Schedule of Assessments Section 7.1.3.2 Serotonin Syndrome (Toxicity) Section 8.1 Mini-Mental State Examination (MMSE) Section 22 References Section 23.1 Appendix A: Assessments by Visit

Summary of Changes	Affected Sections in Revised Protocol (Version 3.0)
Clarification has been added to indicate that if a subject discontinues prematurely, an early termination visit should be conducted at which time all assessments identified for the final on-treatment visit (*e.g.*, Visit 6) should be performed. For all subjects who cease to take LMTM, a post-treatment follow-up visit 4 weeks after the last dose of study drug is to be scheduled, regardless of the reason for discontinuation.	Synopsis Section 4.1 General Description Section 4.4 Schedule of Assessments Section 5.3 Discontinuation/Withdrawal Section 23.1 Appendix A: Assessments by Visit
The protocol now also permits bvFTD subjects to transfer to a geographically close investigational site that also participated in the same study (this is no longer restricted to AD subjects).	Synopsis Section 4.1 General Description Section 4.4 Schedule of Assessments Section 13 Informed Consent Section 23.1 Appendix A: Assessments by Visit
Regarding the potential for LMTM to cause staining of underclothes and other fabrics, the protocol now also indicates that the possibility of such staining should be clearly discussed with subjects and their caregivers.	Section 6.1.1 Active Ingredient
Subject compliance with prescribed dose of study drug will be assessed by questioning the subject and caregiver at the Week 2 visit (Visit 2); clarification has been added to indicate that compliance data (including dates of any dose deviations and/or interruptions, and any other pertinent information) will also be recorded for information obtained at Visit 2 in the source documentation and on the appropriate field of the eCRF based on the investigator determination.	Section 6.5 Compliance