CLINICAL STUDY PROTOCOL: Randomized, Double-Blind, Placebo-Controlled, Three-Arm, 12-Month, Safety and Efficacy Study of Hydromethylthionine Mesylate (LMTM) Monotherapy in Subjects with Alzheimer's Disease Followed by a 12-Month Open-Label Treatment

Study Number: NCT03446001

Date: 16-Jun-2023

CLINICAL STUDY PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Three-Arm, 12-Month, Safety and Efficacy Study of Hydromethylthionine Mesylate (LMTM) Monotherapy in Subjects with Alzheimer's Disease Followed by a 12-Month Open-Label Treatment

STUDY CODE: TRx-237-039

STUDY PHASE: 3

VERSION 7.1 DATED 16 JUNE 2023

Previous Versions:
VERSION 7.0 DATED 28 JULY2021
VERSION 6.0 DATED 09 OCT 2020
VERSION 5.1 DATED 05 FEB 2020
VERSION 5.0 DATED 09 JUL 2019
VERSION 4.1 DATED 09 NOV 2018
VERSION 4.0 DATED 24 AUG 2018
VERSION 3.0 DATED 31 MAY 2018
VERSION 2.1 DATED 25 OCT 2017
VERSION 2.0 DATED 31 AUG 2017
VERSION 1.0 DATED 23 AUG 2017

TauRx Therapeutics Ltd.
3 Shenton Way, #21-04
Shenton House
Singapore 068805
Republic of Singapore

Operational Location:
395 King Street
Aberdeen AB24 5RP
Scotland, UK
Tel: +44 (0) 1224 440905

THIS PROTOCOL IS A CONFIDENTIAL DOCUMENT

1 TABLE OF CONTENTS

PAGE

TABLE OF CONTENTS - continued

TABLE OF CONTENTS - continued

TABLE OF CONTENTS - continued

TABLE OF CONTENTS - continued

PAGE

2 GCP COMPLIANCE STATEMENT

This study will be conducted in compliance with the protocol, the principles contained in the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2) (or ICH E6(R1) in those jurisdictions where ICH E6(R2) is not yet implemented by the regulatory authorities), and the applicable regulatory requirement(s).

3 PROTOCOL APPROVAL

Sponsor Signatory [redacted]	
	Signature Date
TauRx Medical Oversight [redacted]	
	Signature Date
Statistician [redacted]	
	Signature Date

4 RESPONSIBLE PERSONNEL

<table>
<tr><td>TauRx Global Project Lead(s)
[redacted]

TauRx Therapeutics Ltd.
395 King Street
Aberdeen AB24 5RP
Scotland, United Kingdom</td><td>Global Project Manager
[redacted]

Coordinating Investigator
[redacted]</td></tr>
<tr><td>North America Medical Monitor
Medical Management and Scientific Services
Clinical Solutions
Syneos Health
Contact details for specific personnel are provided in the Site Contact List in the Investigator Site File</td><td>Europe Medical Monitor
Medical Management and Scientific Services
Clinical Solutions
Syneos Health
Contact details for specific personnel are provided in the Site Contact List in the Investigator Site File</td></tr>
<tr><td>24-hour Medical Contact:
Emergency Scientific and Medical Services Global (ESMS Global)
A current list of contact details is provided in the Site Contact List in the Investigator Site File</td><td>Pharmacovigilance
Syneos Health
Safety/Pharmacovigilance Department
Farnborough Business Park – 1 Pinehurst Road,
Farnborough,
Hampshire, GU14 7BF
United Kingdom
Fax: +1 877 464 7787
Email: safetyreporting@syneoshealth.com</td></tr>
<tr><td>Investigational Medicinal Product Manufacturer (including packaging, labelling and distribution)
Piramal Healthcare UK Ltd.
Piramal Pharma Solutions
Whalton Road
Morpeth, Northumberland NE61 3YA
United Kingdom
Tel: +44 1670 562 635</td><td>Rater Training and Approval, Scale Management, Electronic Capture of Clinical Efficacy Data, Central Review of Assessments
MedAvante-ProPhase Inc.
100 American Metro Blvd, Suite 106
Hamilton, New Jersey 08619
United States
Tel.: +1 609 528 9400</td></tr>
<tr><td>Data Management
Synteract, Inc.
5909 Sea Otter Place
Carlsbad, California 92010
United States
Tel: +1 760 268 8200</td><td>Randomization and Trial Supply Management System
Bioclinica, Inc.
800 Adams Avenue
Audubon, Pennsylvania 19403
United States
Tel: +1 484 928 6886</td></tr>
</table>

Central Laboratory Labcorp Central Laboratory Services **Americas** Labcorp Central Laboratory Services LP 8211 SciCor Drive Indianapolis, Indiana 46214 United States Tel: +1 317 271 1200 Fax: +1 317 273 4030 **Europe** Labcorp Central Laboratory Services S.à r.l. 7 Rue Moïse-Marcinhès Meyrin, Geneva 1217 Switzerland Tel: +41 58 822 7000 Fax: +41 58 822 6999	**Magnetic Resonance Imaging (MRI) Imaging** Suitably Qualified Vendor **Positron Emission Tomography (PET)** Invicro 60 Temple Street, Suite 8A New Haven, Connecticut 06510 United States Tel: +1 203 401 4393 Fax: +1 203 401 4304
Methylthioninium (MT) Concentrations [redacted] Charles River Laboratories Edinburgh Ltd. (cross-validation purposes only) Elphinstone Research Centre Tranent, East Lothian, EH33 2NE United Kingdom Tel: +44 (0) 1875 614545	**Statistical Analysis of Pharmacokinetic Data** Certara USA, Inc. 100 Overlook Center, Suite 101 Princeton, NJ 08540 Amsterdam office, Tauro office building, Teleporboulevard 110, 104EJ Amsterdam, The Netherlands Tel: +31 (0)88 101 2450
Statistics Cytel Inc Geneva Branch Route de Prebois 20 1215 Geneva Switzerland Tel: +41 791021971	

5 INVESTIGATOR SIGNATURE SHEET

By signing below, I agree to the conditions relating to this study as set out in this protocol (TRx-237-039 Version 7.1 dated XX June 2023).

I agree to conduct this study according to the principles contained in the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2) (or ICH E6(R1) in those jurisdictions where ICH E6(R2) is not yet implemented by the regulatory authorities), the National Institute on Aging (NIA), the Alzheimer's Association (AA), and the applicable regulatory requirement(s).

I fully understand that any changes instituted by me without previous discussion with TauRx Therapeutics Limited or their designated representative constitute a deviation from 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:

6 SYNOPSIS

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)	
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg	
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate	
Number and Title of Study: TRx-237-039: Randomized, Double-Blind, Placebo-Controlled, Three-Arm, 12-Month, Safety and Efficacy Study of Hydromethylthionine Mesylate (LMTM) Monotherapy in Subjects with Alzheimer's Disease Followed by a 12-Month Open-Label Treatment	
Study Site(s): Sites in North America (United States and Canada) and Europe	
Study Duration: The total duration of participation for an individual subject will be up to 120 weeks, including a Screening period of up to 16 weeks (112 days), a double-blind treatment period of 52 weeks, and a further open-label treatment period of 52 weeks. It is anticipated that the study will have an overall duration of at least 40 months, depending on recruitment rate. In addition, subjects who complete the study and receive treatment with LMTM up to and including the last open-label visit may be subsequently offered an opportunity to receive treatment with LMTM in a separate Expanded Access Program (EAP).	Phase of Development: Phase 3

Objectives

The primary objectives of the study pertain to the randomized, double-blind treatment period, listed below. The secondary objectives are presented separately for the double-blind treatment period and the open-label, delayed-start phase.

Primary (double-blind treatment period):

1. To compare the LMTM dose of 16 mg/day with the placebo group on the following co-primary endpoints:
   a. Alzheimer's Disease Assessment Scale, 11-item version (ADAS-cog$_{11}$)
   b. Alzheimer's Disease Cooperative Study - Activities of Daily Living, 23-item version (ADCS-ADL$_{23}$)
2. To assess the safety and tolerability of LMTM 16 mg/day given for up to 52 weeks

Secondary (double-blind treatment period):

3. To compare the LMTM dose of 16 mg/day with the placebo group in annualized rate of whole brain atrophy over 52 weeks as measured by brain magnetic resonance imaging (MRI) and quantified using the Boundary Shift Integral (BSI)
4. To compare the LMTM dose of 16 mg/day with the placebo group in temporal lobe ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) change in Standardized Uptake Value Ratio (SUVR) (normalized to pons) over 52 weeks, restricted to subjects with Clinical Dementia Rating (CDR) 0.5 at Screening, if a predefined threshold is reached for a sufficient number of subjects providing data
5. To compare the LMTM dose of 8 mg/day with the placebo group in temporal lobe ^{18}F-FDG-PET change in SUVR (normalized to pons) over 52 weeks, restricted to subjects with CDR 0.5 at Screening, if a predefined threshold is reached for a sufficient number of subjects providing data
6. To compare the LMTM dose of 8 mg/day with the placebo group on the co-primary endpoints (ADAS-cog$_{11}$ and ADCS-ADL$_{23}$)
7. To compare the LMTM doses of 8 and 16 mg/day with the placebo group in annualized rate of temporal and parietal lobe atrophy over 52 weeks as measured by MRI and quantified using the BSI
8. To assess the safety and tolerability of LMTM 8 mg/day given for up to 52 weeks

Secondary (open-label, delayed-start phase):

9. To determine if there is a difference in disease progression on the co-primary clinical endpoints and the MRI imaging endpoint for subjects who started treatment in the double-blind treatment phase and those who started treatment in the open-label, delayed-start phase (referred to as "early" and "late" LMTM starters, respectively)
   a. Only ADAS-cog$_{11}$ will serve as a secondary endpoint; ADCS-ADL$_{23}$ and other imaging endpoints are exploratory with the aim to be directionally supportive

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

10. To evaluate safety and tolerability of LMTM given for up to 104 weeks

Sensitivity analyses, including the evaluation of the secondary imaging endpoints to confirm the absence of treatment unblinding, are described in the protocol and Statistical Analysis Plan (SAP).

Population Pharmacokinetic (PK) analyses will be performed to estimate PK exposure in each subject for use in the evaluation of exposure-response relationships; these will be defined in a separate Population PK SAP or a dedicated section of the main SAP.

Additional exploratory analyses are described in the protocol and SAP. These include analyses of:

1. ADAS-cog$_{13}$
2. A new composite endpoint/composite endpoints based on selected item of the Alzheimer's Disease Assessment Scale, 13-item version (ADAS-cog$_{13}$) and the ADCS-ADL$_{23}$, analyzed at 9 months and 12 months to evaluate its usefulness for future studies (for all subjects and also separately for subjects with CDR 0.5 and CDR 1-2 at Screening).
3. MMSE
4. CDR sum of boxes
5. Influence of Apolipoprotein E (*ApoE*) genotype

Study Design

This is a two-phase outpatient study of LMTM administered as monotherapy in 500 subjects with early to mild-moderate Alzheimer's disease (AD): a randomized, double-blind, placebo-controlled, 52-week treatment period followed by a 52-week open-label phase that represents a modified delayed start of treatment. Subjects who are not receiving concomitant AChEI and/or memantine, for whom legally acceptable informed consent has been obtained and who are found eligible on the basis of screening evaluations, will be randomly assigned at Baseline to receive either LMTM 16 mg/day, LMTM 8 mg/day, or placebo; the drug supplies for the placebo group will include tablets containing a urinary discolorant, methylthioninium chloride (MTC), 4 mg. The primary treatment group comparisons during the double-blind treatment phase are of LMTM 16 mg/day and placebo. Following completion of the 52-week treatment period, all subjects (regardless of randomized treatment assignment or response) will continue open-label treatment with LMTM 16 mg/day for a further 52 weeks; prior treatment assignment will not be unblinded.

The Screening period is to be up to 9 weeks for subjects who are not receiving an AChEI and/or memantine at the time of signing the consent (Initial Screening Visit, Visit 1). For subjects who are receiving an AChEI and/or memantine, the Screening period may be extended for up to a further 6 weeks, 15 weeks in total (+7 days at Sponsor discretion), to allow for the performance of the necessary screening tests prior to the discontinuation of an AChEI and/or memantine and to permit a washout of at least 60 days from the last dose prior to the baseline assessments (inclusive of the baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5).

A sufficient number of subjects will be recruited from sites in North America and Europe such that approximately 500 subjects are enrolled. Beginning with Protocol Version 5.0, approximately 450 subjects are to be enrolled and randomized at the Baseline/Randomization Visit (Visit 2) to the LMTM 16mg/day (200 subjects), LMTM 8mg/day (50 subjects), or placebo (200 subjects) groups. Randomization will be stratified by severity (Mini-Mental State Examination [MMSE] 16-19, 20-25, or 26-27 at study level for those randomized to Protocol Version 5.0 and above), by prior use of AChEIs and/or memantine, and by region (grouped into North America or Europe). Subjects will be assigned to the MMSE severity groups based on screening MMSE score with a target ratio of approximately 2:3:1 (MMSE 16-19, 20-25, 26-27, respectively) for those randomized to Protocol Version 5.0 and above; to achieve this target, enrollment will be monitored and controlled at the site level for high recruiting sites (i.e., sites projected to recruit more than 10% of the subjects) and capped as needed at the study level.

Eight post-Baseline visits are scheduled: five during the double-blind treatment period (Visit 3: safety, and Visits 4, 5, 6, and 7: imaging, efficacy, and safety) and three during the open-label, delayed-start phase (Visits 8 [telephone contact only], 9, and 10). A summary of modifications to the post-Baseline visits that may be implemented in response to the Coronavirus Disease 2019 Public Health Emergency (hereafter referred to as COVID-19) is described in the body of the protocol. Unscheduled visits may occur as needed for assessment, or

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

upon early termination. In addition, subjects are to be followed as needed for the resolution or stabilization of an adverse event (AE), including following the last dose, consistent with the investigator's medical judgement.

Subjects who drop out after randomization will not be replaced (however, the study partner may be replaced if the current one withdraws/drops out); subjects will be encouraged to continue with study visits until the scheduled completion of the double-blind treatment period (Visit 7). Only subjects who continue in the study and receive LMTM treatment up to and including the last visit (Visit 10) without the addition of concomitant AChEIs and/or memantine may be eligible for a separate EAP.

Sample Size

Sample size estimations to achieve 90% power (two-sided alpha = 0.05) to detect a difference between LMTM 16 mg/day and placebo, the primary treatment group comparison in the double-blind treatment period, have been performed for the two co-primary clinical endpoints. These assume a withdrawal rate of 20% to 25% over 52 weeks. The study sample size of approximately 450 subjects enrolled under Protocol Version 5.0 and above (200 subjects in each treatment group, with a further 50 subjects for secondary analyses of an LMTM 8-mg/day group) is based on the ADCS-ADL_{23}, since a larger sample size is required for this rating scale to achieve the target power.

Based on an estimated decline in ADCS-ADL_{23} over 52 weeks in the control arm of 7.7 units with an estimated standard deviation (SD) of 8.5 units, the study will have >90% power to detect a reduction in decline of 3.4 units or more. The 3.4 units are motivated by an estimated treatment effect of 5.0 ± 1.6 (mean ± standard error) units in the pooled studies TRx-237-005/TRx-237-015.

Based on an estimated decline in ADAS-cog_{11} over 52 weeks based on pooled information from studies TRx-237-005/TRx-237-015 in the control arm of 6.5 units with an estimated SD of 5.9 units, 200 subjects per treatment arm provide >90% power to detect a reduction in decline of 2.6 units or more. The 2.6 units represent a conservative value as the estimated treatment effect based on pooled studies TRx-237-005/TRx-237-015 is 5.2 ± 1.3 (mean ± standard error) units.

With 200 subjects randomized to the primary comparison in the double-blind treatment period under Protocol Version 5.0 and above, 160 to 170 subjects per arm will enter the open-label, delayed-start treatment phase assuming the 20-25% drop-out rates mentioned above. Assuming a further 10% drop out in the delayed-start phase, the key secondary analysis to demonstrate disease modification by comparing early to late starters using a non-inferiority margin of -2 ADAS-cog_{11} units has approximately 80% power.

Subject Population

Inclusion Criteria:

1. AD, encompassing probable AD and mild cognitive impairment due to AD (MCI-AD) based on 2011 National Institute on Aging (NIA) / Alzheimer's Association (AA) criteria:
   - All cause dementia and probable AD (probable AD)
     In brief, subjects with probable AD dementia must have insidious onset, worsening impairment in at least two cognitive areas (learning and recall, language, executive function, visuospatial skills), sufficient to significantly interfere with work or usual activities, that is not explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder. The accuracy of the diagnosis will be confirmed independently by the diagnosing physician at site
     OR
   - MCI-AD
     In subjects with MCI-AD, there should be evidence of concern about a change in cognition, in comparison with the person's previous level verified by a knowledgeable informant or clinician. Other mild cognitive deficits may also be present, but there must be preservation of independence in functional abilities. Subjects should not meet the criteria for dementia. The cognitive changes must be mild and there must be no evidence of a significant impairment in social or occupational functioning. Impairments must not be explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder.
2. Documented PET scan that is positive for amyloid; if most recent PET scan was performed >3 years prior to Screening and was negative, it may be repeated (a negative amyloid PET scan within the 3 years prior to Screening is exclusionary)

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

3. MMSE score of 16-27 (inclusive) at Screening, subject to stratification requirements
4. Global CDR score of 0.5 to 2 at Screening (if 0.5, including a score of > 0 in one of the functional domains: Community Affairs, Home and Hobbies, or Personal Care)
5. Age < 90 years at Screening
6. Females must meet one of the following:
   - Surgically sterile (hysterectomy, bilateral salpingectomy / oophorectomy) for at least 6 months minimum
   - Have undergone bilateral tubal occlusion / ligation at least 6 months prior
   - Post-menopausal for at least 1 year
   - Using adequate contraception (a barrier method [such as condom, diaphragm or cervical/vault cap] with spermicidal foam, gel, film, cream, or suppository; intrauterine device [IUD] or system, or oral or long-acting injected or implanted hormonal contraceptives for at least 90 days 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 be competent to use adequate contraception and to agree to continue to maintain adequate contraception throughout participation in the study (including up to 4 weeks after the last dose of study drug)
7. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) (LAR(s)), consistent with local and national law, is able to read, understand and provide written informed consent in the designated language of the study site
8. Has one (or more) identified adult study partner (*i.e.*, a caregiver or informant) who meets the following criteria:
   - Either lives with the subject, or 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 (*e.g.*, sees the subject on average for ≥1 hour/day ≥3 days/week)
   - 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 compliance with study drug
9. The subject must not have been taking either an AChEI, *i.e.*, donepezil, galantamine, or rivastigmine, and/or memantine, for at least 60 days at the time of the baseline assessments
   - Subjects never previously treated with an AChEI and/or memantine may be enrolled if initiation of treatment with these medications is not planned for the time period during which the subject will be participating in this study
10. Able to comply with the study procedures in the view of the investigator

Exclusion Criteria:

1. Significant central nervous system (CNS) disorder other than probable AD or MCI-AD, *e.g.*, Lewy body dementia, Parkinson's disease, multiple sclerosis, progressive supranuclear palsy, hydrocephalus, Huntington's disease, any condition directly or indirectly caused by Transmissible Spongiform Encephalopathy (TSE), Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), or new variant Creutzfeldt-Jakob Disease (nvCJD)
2. Significant intracranial focal or vascular pathology seen on brain MRI scan that would, based on the independent reviewer imaging evaluation, lead to a diagnosis other than probable AD or MCI-AD, including but not limited to:
   - Large confluent white matter hyperintense lesions (*i.e.*, Fazekas score of 3)
   - Other focal brain lesions judged clinically relevant by the investigator
   - Evidence of a prior or current macrohemorrhage
3. Clinical evidence or history of any of the following (within specified period prior to Baseline):
   - Cerebrovascular accident (2 years)
   - Transient ischemic attack (6 months)
   - Significant head injury, for example, associated loss of consciousness, skull fracture or persisting cognitive impairment (2 years)

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

- Other unexplained or recurrent loss of consciousness (2 years)

4. Diagnosed with epilepsy (a single prior seizure >6 months prior to Screening, is considered acceptable)
5. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria met (for any of the following within specified period):
   - Major depressive disorder (current)
   - Schizophrenia (lifetime)
   - Other psychotic disorders, bipolar disorder (within the past 5 years)
   - Substance (including alcohol) related disorders (within the past 2 years)
6. Metal implants in the head (except dental), pacemaker, cochlear implants, or any other non-removable items that are contraindications to MRI. MRI compatible prosthetics, clips, stents, or any other device proven to be compatible are allowed
7. Resides in hospital or moderate to high dependency continuous care facility (residence in low grade assisted living facility where there is sufficient autonomy to permit valid evaluation of activities of daily living is allowed so long as it is not mandated by an order issued either by the judicial or the administrative authorities)
8. Any physical disability that would prevent completion of study procedures or assessments (*e.g.*, blindness or significant uncorrected visual impairment, deafness or significant hearing loss not corrected by hearing aids, non-AD-related speech impairment)
9. 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)
10. Pregnant or breastfeeding
11. Glucose-6-phosphate dehydrogenase (G6PD) deficiency based on World Health Organization classification (<60% of normal, *i.e.*, <6.1 U/g hemoglobin [Hgb])
12. History of significant hematological abnormality or current acute or chronic clinically significant abnormality, including:
    - History of hemoglobinopathy, myelodysplastic syndrome, hemolytic anemia, or splenectomy
    - Screening Hgb value (confirmed upon repeat) below age/sex appropriate lower limit of the central laboratory normal range

    Subjects in whom folate is <4.0 ng/mL may be entered into the study provided folate supplementation (approximately 1 mg/day) is initiated and maintained for the duration of the study.
    Subjects in whom vitamin B_{12} is <150 pg/mL can be allowed if the investigator confirms that it does not affect the cognitive state of the subject and that the subject is supplemented as appropriate prior to the initiation of study drug
13. Abnormal serum chemistry laboratory value at Screening deemed to be clinically significant by the investigator. In addition, subjects with either of the following abnormalities must be excluded:
    - Creatinine clearance <30 mL/min, estimated by the central laboratory according to the Cockcroft and Gault equation
    - Thyroid stimulating hormone (TSH) above laboratory normal range (subject may be treated [if clinically indicated based on further laboratory testing] and re-screened after 90 days)
14. Clinically significant cardiovascular disease or abnormal assessments (based on the investigator's interpretation of the locally obtained electrocardiogram [ECG]) such as:
    - Hospitalization for acute coronary syndrome (acute myocardial infarction or unstable angina) or symptoms consistent with angina pectoris, within the 12 months preceding Baseline
    - Signs or symptoms of clinical heart failure within the 12 months preceding Baseline
    - Atrial fibrillation on screening ECG or history of atrial fibrillation that is not currently controlled (heart rate ≥ 85 bpm and/or inappropriate anticoagulation)
    - QTcF (QT corrected for heart rate using Fridericia's formula) at Screening >460 msec in males or > 470 msec in females, or low or flat T waves making measurement of QT interval unreliable
    - Recent history of poorly controlled hypertension, systolic blood pressure >180 mmHg, or diastolic blood pressure >100 mmHg, after 5 minutes in a seated position at Screening
    - Hypotension: systolic blood pressure <100 mmHg after 5 minutes in a seated position at Screening

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

- Heart rate <48 bpm or >96 bpm by measurement of vital signs (after 5 minutes in a seated position) or by local ECG at Screening

15. Pre-existing or current signs or symptoms of respiratory failure, *e.g.*, caused by chronic obstructive pulmonary disease, bronchial asthma, lung fibrosis, or other disease
    - Subjects with currently diagnosed moderate to severe sleep apnea should be excluded; the definition of moderate to severe includes oxygen supplementation, *e.g.*, nasal prongs or Continuous Positive Airway Pressure (CPAP)
16. Concurrent acute or chronic clinically significant (in the opinion of the investigator) immunologic, hepatobiliary (such as presence of encephalopathy or ascites), or endocrine disease (not adequately treated), and/or other unstable or major disease other than probable AD or MCI-AD; the following are specifically excluded:
    - Active hepatitis or primary biliary cirrhosis
    - Active Human T-Cell Lymphocytic Virus Type III (HTLV-III), Lymphadenopathy Associated Virus (LAV), any mutants or derivatives of HLTV-III or LAV, any condition associated with active Acquired Immunodeficiency Syndrome or similar condition however named
17. Diagnosis of cancer (excluding basal cell carcinoma, squamous cell carcinoma, or prostate carcinoma in situ [Stage 1]) meeting either of the following criteria:
    - Newly diagnosed within past 2 years
    - Previous (>2 years) diagnosis of cancer that has required any form of intervention or treatment within the past 2 years, *e.g.*, chemotherapy, radiotherapy, hormonal therapy, or surgery
18. Prior intolerance or hypersensitivity to MT-containing drug or methemoglobinemia induced by MT-containing drug, similar organic dyes, or any of the excipients
19. Treatment currently or within 90 days before Baseline with any of the following:
    - Souvenaid®
    - Antipsychotics
        - Clozapine (and there is no intent to initiate therapy during the course of the study)
        - Other antipsychotics are allowable provided they have not been initiated within 90 days before Baseline and preferably at a stable dose and regimen
    - Carbamazepine, primidone, valproate
    - Drugs for which there is a warning or precaution in the labeling about methemoglobinemia at approved doses (*e.g.*, dapsone, local anesthetics such as benzocaine used chronically, primaquine and related antimalarials)
20. Current or prior participation in a clinical trial as follows:
    - Any clinical trial of LMTM
    - Clinical trial of a product for cognition prior to Baseline in which the last dose was received within 90 days prior to Baseline unless confirmed to have been randomized to placebo
    - A clinical trial of any other investigational drug, biologic, device, or medical food in which the last dose was received within 28 days prior to Baseline

Dose/Route/Regimen

Throughout the study, all subjects will receive four tablets orally per day (two in the morning and two in the evening), to be taken at the same time (and same meal condition) to the extent possible. Study drug should be swallowed whole and MUST NOT be broken, crushed, chewed, or dissolved in fluids prior to ingestion.

For the 52-week, double-blind treatment period, subjects will be randomized 4:1:4 (beginning with Protocol Version 5.0) to one of the following treatment groups:

- LMTM 16-mg/day group: Two 4-mg tablets in the morning and two 4-mg tablets in the evening
- LMTM 8-mg/day group: One 4-mg tablet and one placebo tablet in the morning, and one 4-mg tablet and one placebo tablet in the evening
- Placebo group: Two “dummy” tablets in the morning and two “dummy” tablets in the evening, one of which may be replaced by a 4-mg MTC tablet to maintain the treatment blind (the remainder being placebo tablets)

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate
The first dose of study drug (Visit 2) and the morning dose at Visit 3 (after 4 weeks of study drug), Visit 7 (after 52 weeks of study drug), and Visit 10 (after 104 weeks of study drug) will be administered in the clinic. These visits should be scheduled to occur in the morning and subjects will be required to remain at the site for at least 4 hours post-dose on each occasion. Alternative arrangements for dosing and dispensing study drug supplies due to COVID-19 may be permitted and are further described in the body of the protocol. Interruption of dosing for up to a maximum of 14 consecutive days may be allowed if the investigator determines this is indicated (*e.g.*, due to an AE or any other reported change in the subject's physical condition in the judgment of the investigator) on a maximum of two occasions. Dose reduction is not permitted. The reason for dose interruption should be recorded in the source documentation. After the completion of the 52-week double-blind treatment period, beginning with supplies dispensed at Visit 7 (Baseline/Day 1 for the open-label phase), all subjects will receive LMTM 16 mg/day (two 4-mg tablets in the morning and two 4-mg tablets in the evening) from a newly dispensed open-label study kit for an additional 52 weeks during the open-label, delayed-start phase. The in-clinic dose of study drug at Visit 7 is to be taken after pre-dose assessments have been completed (refer to Table 10-3 for the pre-dose and post-dose assessments to be performed at Visit 7).
Methodology All subjects should have a likely diagnosis of probable AD or MCI-AD prior to being offered the consent forms, on the basis of investigator interview and examination. Subjects currently using an AChEI and/or memantine must be willing to discontinue such medication before continuing with screening (for timing of withdrawal reference Table 10-1). Following provision of written informed consent by the subject (and/or legal representative[s]) and study partner(s), consistent with national and/or local law, eligibility for enrollment will be assessed initially during the Screening period which may require multiple visits (collectively designated Visit 1). These will occur no earlier than 63 days before Visit 2 for subjects not using an AChEI and/or memantine. For subjects using an AChEI and/or memantine at the time of signing the consent document or who have recently discontinued use, Screening visits can occur no earlier than 105 days before Visit 2. The diagnosis of probable AD or MCI-AD should be confirmed per the 2011 NIA/AA criteria, documented in the subject's medical records and independently confirmed by site diagnosing physician. MMSE and CDR will then be completed at Screening for eligibility assessment. Note that MMSE should be conducted first, followed by the CDR assessment only if the subject meets the MMSE inclusion criteria. If the subject does not qualify with either of these scales, no further assessments should be performed and the subject should be considered a screen failure. If, however, the subject meets the MMSE and CDR inclusion criteria, a blood sample for clinical laboratory testing should be obtained and medical screening assessments performed. In subjects for whom it is appropriate to proceed with further screening, a PET scan that is positive for amyloid and an MRI scan that excludes other CNS pathology are required at Screening to confirm subject eligibility. The amyloid PET scan can have been documented previously as positive or, alternatively, be based on the local read (or central for those sites not able to read locally) of a PET scan using an approved amyloid ligand and according to criteria recommended as standard by the manufacturer of the ligand. All images (including prior images with subject consent) will be sent to an imaging core laboratory, either as a repository (amyloid PET) or for evaluation by a trained technologist for acceptable quality (MRI). MRIs will be reviewed by an independent neuroradiologist (reader) who is trained in the evaluations and is not involved in the clinical conduct of the study to confirm eligibility of the subject. The reader's MRI assessment will be communicated to the site within 5 business days of image transfer to the imaging core laboratory (or of resolution of any quality issues). Subjects willing to discontinue AChEI and/or memantine in order to take part in the study must be documented to be eligible according to clinical inclusion / exclusion criteria, screening MRI and amyloid positive PET scan, before these drugs are discontinued. Only subjects with a CDR 0.5 will undergo ^{18}F-FDG-PET. ^{18}F-DG-PET images are to be obtained prior to Visit 2 (and at least 60 days after the last dose of AChEI and/or memantine) for purposes of establishing the baseline assessment. Completion of this scan must be confirmed prior to randomization; other than confirmation of acceptable quality, the results per se are not considered for eligibility at the Screening visit. The baseline

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

^{18}F-FDG-PET image will be sent to a core imaging laboratory and will be reviewed by an independent, appropriately trained nuclear medicine reader. Imaging receipts will be sent in all cases; only in those instances where the scan is deemed unacceptable will the site and imaging laboratory be further notified.

At the Baseline/Randomization visit (Visit 2), eligibility will be confirmed, subjects will be randomized, and baseline safety and efficacy assessments will be completed. Subjects will be treated with study drug for 52 weeks on an outpatient basis. During the double-blind, treatment period, on-treatment, post-Baseline study visits will occur at time points approximately 4, 13, 26, 39, and 52 weeks after Baseline. All subjects will receive a supply of study drug according to their randomization, to take home for use until Visit 4 (13 weeks after Baseline). Study drug will be resupplied at Visits 4, 5, and 6 (13, 26, and 39 weeks after Baseline). Visit 7 (the final visit in the double-blind treatment period) will serve as the open-label Baseline. During the open-label, delayed-start phase, study visits will occur at approximately 4 weeks (by telephone), 26 weeks, and 52 weeks after the open-label Baseline (Visits 8, 9, and 10), with a supply of open-label study drug from a newly dispensed study kit provided at Visits 7 and 9. Alternative arrangements for study procedures and assessments in response to COVID-19 are described in the body of the protocol.

The study will be monitored for safety by a Data and Safety Monitoring Board (DSMB) throughout its duration.

Assessments

Efficacy:

Imaging assessments will be made by central readers as follows:

- Brain MRI will be evaluated for temporal, parietal, whole brain, lateral ventricular, hippocampal, putamen, nucleus accumbens, and nucleus basalis volumes at Screening and after 13, 26, 39, and 52 weeks, or upon early termination. Change in MRI volumetric parameters will be quantified at the imaging core laboratory. The image hyperintensities will also be quantified. MRIs will also be obtained and evaluated after the additional 26 and 52 weeks of open-label treatment.
- Brain ^{18}F-FDG-PET will be evaluated in subjects with CDR 0.5 for normalized temporal, parietal, and frontal lobe SUVR at Baseline and after 52 weeks, or upon early termination. Other regions of interest will also be examined including, but not restricted to, inferior temporal gyrus, angular gyrus, anterior and posterior cingulate gyrus, and cerebellum. Change in SUVR parameters will be quantified by the imaging core laboratory.

Two primary clinical efficacy scales will be used, ADAS-cog$_{13}$ and ADCS-ADL$_{23}$. Clinical assessments will be made by suitably trained Efficacy Raters who are not involved in safety assessments, using the instruments on an electronic tablet (and captured via an audio recording of the assessment for independent evaluation). The following will be assessed at Baseline; after 13, 26, 39, and 52 weeks during the double-blind treatment period; and after the additional 26 and 52 weeks of open-label treatment, or upon early termination:

- ADAS-cog$_{13}$
  - As the primary endpoint is ADAS-cog$_{11,}$ in order to be able to link the results of this study to the recently completed Phase 3 studies TRx-237-005 and TRx-237-015, an ADAS-cog$_{11}$ will be derived from the ADAS-cog$_{13}$.
- ADCS-ADL$_{23}$

The MMSE and CDR will be repeated at the final double-blind treatment period visit (Visit 7) and the final open-label visit (Visit 10) or upon early termination.

The clinical efficacy scale assessments should be performed at approximately the same time of day throughout the study for a given subject, to the greatest extent possible.

Safety and Tolerability:

Safety assessments will be performed during Screening to assess subject eligibility for enrollment. All safety assessments will be performed by an independent qualified assessor not involved in efficacy assessments; where specified below, the assessments must be made by a medical assessor (physician, doctor of medicine [MD], or doctor of osteopathic medicine [DO]). For enrolled subjects, safety assessments will be made at Baseline and at each clinic visit (*i.e.*, after 4, 13, 26, 39, and 52 weeks during the double-blind treatment period as well as after 26 and 52 weeks in the open-label, delayed-start phase); during a telephone contact after 4 weeks in the open-label, delayed-start phase; when needed to follow up on an AE; and upon early termination. All AEs, vital signs,

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

ECG, clinical laboratory findings, physical and neurological examinations, and ophthalmological examinations (as applicable) will be assessed according to the following:

- AEs will be recorded from the time informed consent is signed and recording will continue throughout the study and, if pertinent, until resolution of the event; AEs with an onset after the first dose of study drug or that worsen in intensity or treatment relationship after the first dose will be considered treatment-emergent (and must be reviewed by a medical assessor).
- Blood pressure and pulse will be obtained at Screening, on Day 1 (pre-dose and approximately 2 hours post-dose), and at each clinic visit thereafter or upon early termination. Blood pressure and pulse will be measured after the subject has been in a seated position for at least 5 minutes.
- Height will be measured at Screening only. Body weight will be measured at Screening and at each clinic visit thereafter or upon early termination.
- A 12-lead ECG will be obtained at Screening, with the site assessing eligibility based on the local clinical interpretation by a medical assessor.
- TSH, vitamin B_{12}, folate, haptoglobin, and G6PD will be measured at Screening; a thyroid panel may be obtained in response to an elevated TSH. Standard clinical laboratory testing, including hematology and blood chemistry, will be performed at Screening and each subsequent clinic visit (or upon early termination). Testing may also be performed as needed in response to an AE. All laboratory testing results must be reviewed by a medical assessor.
- A blood sample for a serum pregnancy test will be collected from all women of childbearing potential at Screening and at each subsequent clinic visit (or upon early termination).
- Complete physical and neurological assessments will be performed at Screening. Targeted examinations will be performed pre-dose and approximately 3 hours after administration of the first dose of study drug (Visit 2). Thereafter, targeted examinations are to be performed at each subsequent clinic visit (or upon early termination). At a minimum, targeted examinations should include heart and lung auscultation and brief neurological assessment guided by any reported signs/symptoms/AEs (*e.g.*, evaluating subjects for potential serotonin toxicity). These examinations are to be performed by a medical assessor.
- Ophthalmological examination (slit lamp) of subjects with history of lens implants will be performed by a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor prior to the first dose of study drug (during the Screening procedures or as part of the baseline assessments), at Visit 7, and at Visit 10 / early termination (after completion of efficacy assessments), to assess whether the lens has been discolored during the trial. A slit lamp examination should also be performed if a subject has cataract surgery/lens implantation at any point during his or her study participation (as soon as possible after the surgery), as well as in response to visual complaints if suggestive of lens discoloration.
- At Screening, medications administered within the last 90 days will be recorded; the exception is for anti-dementia medications, where lifetime use (as far as possible) is to be recorded. Changes in concomitant medications and any new medications will be recorded at all subsequent visits, including the telephone contact, and reviewed by a medical assessor.

Other Assessments:

- At Visit 2, Visit 3, Visit 7, and Visit 10, blood will be collected on the same day on three occasions for determination of plasma MT and whole blood concentrations (parent MT/LMT, *N*-desmethyl MT, and total MT, to the extent possible); these visits should be scheduled to occur in the morning. Samples will be collected prior to dosing (in the clinic) and again approximately 1 to 2 hours post-dose; a third sample will be collected approximately 4 hours after the dose. Times of dose and blood sampling (and at Visits 3, 7, and 10, times of the prior dose taken on the preceding day) will be recorded. At any early termination visit, if the subject has not yet discontinued study drug and is willing to take a final in-clinic dose, three blood samples will be collected as described above. If, however, the subject has already discontinued study drug or is unwilling to take a final in-clinic dose, a single blood sample only for determination of MT concentrations will be collected, irrespective of the date or time of the last dose of study drug. The date and time of the last dose will be collected and recorded. For subjects who continue in the study off-treatment (the off-treatment-on-study [TOTOS] group), blood samples will not continue to be collected for the determination of MT concentrations.
- A single blood sample for *ApoE* will be obtained from subjects who provide legally acceptable informed consent; the blood sample may be collected any time after eligibility for randomization and continued participation in the study has been confirmed but prior to Visit 7 (end of the double-blind treatment period).

Name of Sponsor / Company: TauRx Therapeutics Ltd (TauRx)
Name of Finished Product: LMTM (TRx0237) Film-coated Tablets, 4 mg
Name of Active Ingredient (Drug Substance): Hydromethylthionine Mesylate

Statistical Analyses

Double-blind Treatment Period:

The primary target of estimation is the difference in ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ over 52 weeks in subjects receiving LMTM in a dose of 16 mg/day as compared to placebo.

The primary efficacy analyses for FDA will be performed on the Efficacy Modified Intent-to-Treat (E-MITT) which will include all randomized subjects who took at least one dose of study drug and have a baseline and a valid post-baseline efficacy assessment, and for EMA on the Intent-to-Treat (ITT) population with conservative assumptions about disease progression made for subjects who have missing post-baseline assessments. Subjects will be analyzed in the treatment group and according to the stratification variables to which they were randomized.

Changes from baseline to Week 52 on the co-primary efficacy endpoints and other modalities with repeated measures such as MRI will be analyzed using a linear mixed model for repeated measures with unstructured covariance matrix. The linear mixed model will contain fixed effects for time, treatment, and a treatment-by-time interaction; additionally, the baseline value of the corresponding endpoint will be included as a covariate and the randomization stratification variables of prior usage of AChEIs and/or memantine, severity based on MMSE (16-19, 20-25, or 26-27) as determined at Screening, and region will be included as fixed effects in the model. ^{18}F-FDG-PET and other modalities with only one planned post-baseline assessment will be analyzed using an ANCOVA; the covariates for this model will be adjusted accordingly by removing terms with time.

More details about the exact contrast statements used for these tests as well as further sensitivity analyses, additional analyses of the primary variables (such as responder analyses and subgroup analyses), analyses of the secondary and exploratory endpoints, and modifications to be implemented regarding sensitivity analyses due to COVID-19 are described in the body of the protocol and SAP.

Open-Label, Delayed-Start Phase:

"Late" starters, *i.e.*, subjects originally randomized to placebo, will be compared to "early" starters, *i.e.*, those originally randomized to LMTM 16 mg/day or 8 mg/day (pooled, and individually for both groups as a sensitivity analysis). The last assessment prior to start of open-label treatment (Visit 7) will serve as the baseline assessment for these comparisons. The analyses will be based on a similar linear mixed model for repeated measures with the aim to investigate whether there is a difference in change in primary and MRI imaging endpoints dependent on LMTM treatment history. The comparison will be implemented through a non-inferiority test. The non-inferiority margin for the primary endpoint of ADAS-cog$_{11}$ will be 2 units, motivated by the fact that these 2 units are small compared to the estimated treatment effect of > 5 units (~40% of this effect size). Margins for other endpoints which are exploratory to support a disease modifying argument will be defined in the SAP. The results will also be presented with the Visit 2 Baseline as baseline and treatment visits Week 26 and Week 52 in the open-label, delayed-start phase as Week 78 and Week 104.

7 ABBREVIATIONS

Abbreviations	Definitions
AA	Alzheimer's Association
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's Disease
ADAS-cog$_{11}$	Alzheimer's Disease Assessment Scale – Cognitive Subscale (11-item)
ADAS-cog$_{13}$	Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-item)
ADCS-ADL$_{23}$	Alzheimer's Disease Cooperative Study – Activities of Daily Living (23-item)
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADR	Adverse Drug Reaction
AE	adverse event
AESI	adverse event of special interest
ApoE	Apolipoprotein E gene
ATC	Anatomical Therapeutic Classification
AUC	area under the plasma concentration *versus* time curve
BCRP	breast cancer resistance protein
bid	twice daily
BSI	Boundary Shift Integral
BSA	body surface area
bvFTD	behavioral variant frontotemporal dementia
CDR	Clinical Dementia Rating
CJD	Creutzfeldt-Jakob Disease
CL/F	apparent plasma clearance
C_{max}	peak plasma concentration
$C_{max, ss}$	peak steady-state plasma concentration
CMP	Clinical Monitoring Plan
CNS	central nervous system
COVID-19	Coronavirus Disease 2019 Public Health Emergency
CT	computerized tomography
CYP	Cytochrome P450 isoenzyme
DO	Doctor of Osteopathic Medicine
DSMB	Data and Safety Monitoring Board
EAP	Expanded Access Program
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
E-MITT	Efficacy Modified Intent-to-Treat
eTMF	electronic Trial Master File
EU	European Union
FDA	Food and Drug Administration (United States)
^{18}F-FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
g, kg, mg, pg	gram, kilogram, milligram, picogram
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GI	gastrointestinal

Abbreviations	Definitions
GMP	Good Manufacturing Practice
Hgb	hemoglobin
HTLV-III	human T-cell lymphocyte virus Type III
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	intrauterine device
L, mL, dL	liter, milliliter, deciliter
LAR	Legally Acceptable Representative
LAV	Lymphadenopathy Associated Virus
LDH	lactate dehydrogenase
LMT	hydromethylthionine, leuco-methylthioninium
LMTB	leuco-methylthioninium bis(hydrobromide)
LMTM	hydromethylthionine mesylate, leuco-methylthioninium bis(hydromethanesulfonate)
LSM	Least Squares Mean
LVV	lateral ventricular volume
MAO	monoamine oxidase
MATE	Multidrug And Toxin Extrusion (protein)
MCI-AD	mild cognitive impairment due to AD
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
min, msec	minutes, millisecond
MI-MITT	MRI Imaging Intent-to-Treat
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MT	Methylthioninium
MTC	methylthioninium chloride
NIA	National Institute on Aging
NMDA	N-methyl-D-aspartate
NOAEL	no-observed-adverse effect-level
nvCJD	new variant Creutzfeldt-Jakob Disease
OAT	Organic Anion Transporter
OCT	Organic Cation Transporter
PET	Positron Emission Tomography
P-gp	P-glycoprotein
PHF	paired helical filament
PI	principal investigator
PI-MITT	Imaging Modified Intent-to-Treat
PK	Pharmacokinetic
PP	Per Protocol

Abbreviations	Definitions
QA	Quality Assurance
RBC	red blood cell
ROI	region of interest
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SI	Sub-Investigator
SOC	System Organ Class
SOP	Standard Operating Procedure
SPM	statistical parametric mapping
SUSAR	suspected unexpected serious adverse event
SUVR	Standardized Uptake Value Ratio
$T_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
tid	three times daily
TOTOS	The-Off-Treatment-On-Study (subjects)
TSE	Transmissible Spongiform Encephalopathy
TSH	thyroid stimulating hormone
UGT	UDP-glucuronosyltransferase
USAN	United States Abbreviated Name
USP	United States Pharmacopeia
vCJD	variant Creutzfeldt-Jakob Disease
WBC	white blood cell
WHO	World Health Organization

8 BACKGROUND AND RATIONALE FOR THE STUDY

Hydromethylthionine (International Nonproprietary Name [INN] and United States Abbreviated Name [USAN]), the reduced form of methylthioninium (MT) that is also known as leuco-methylthioninium (LMT), is proposed for treatment of tauopathies and other protein misfolding disorders. Tauopathies are a class of neurodegenerative diseases associated with pathological aggregation of tau protein in the human brain. The tauopathies include diseases that primarily affect cognition such as Alzheimer's disease (AD). 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 (PHF) forming neurofibrillary tangles that 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 and are also seen by imaging using recently developed tau ligands (Lockhart *et al*., 2016; Xia *et al*., 2017; Pontecorvo *et al*., 2017.

The repeat-domain tau fragment originally identified biochemically as a structural constituent of the tangle PHF core (Wischik *et al*., 1988a,b) has recently been confirmed using cryo-electron microscopy (Fitzpatrick *et al*., 2017). This fragment assembles spontaneously *in vitro* to form PHF-like filaments (Al-Hilaly *et al*., 2017). The active moiety required both to block filament assembly and to disassemble formed filaments is the reduced LMT form of MT (Al-Hilaly *et al.*, 2018).

As of 2020, drugs currently available to treat AD, such as acetylcholinesterase inhibitors (AChEIs) or memantine, are symptomatic treatments that address certain central neuronal dysfunctions associated with AD, but are not known to directly affect the neurofibrillary tangles in the brain that represent a core pathological component of AD. Controlled studies with the AChEIs donepezil, rivastigmine, and galantamine have demonstrated small improvements in cognitive tests and global measures of change in selected subjects with mild to moderate AD over 3 to 12 months (Birks and Harvey, 2003; Olin and Schneider, 2002). However, improvements in function and behavior have been demonstrated less reliably with AChEIs. Furthermore, although these medications provide benefits for some subjects, their effectiveness often is limited in duration and they do not affect the rate of progression of the disease (Courtney *et al.*, 2004).

Memantine is a noncompetitive, low-affinity, N-methyl-D-aspartate (NMDA) receptor antagonist that might prevent calcium-mediated glutamate excitatory toxicity in AD. Studies with memantine over 6 months in subjects with moderate to severe AD have shown small benefits on cognition, global measures, daily living activities, and behavior (Reisberg *et al*., 2003), but evidence for a benefit is lacking in mild AD (Schneider *et al*., 2011).

Aduhelm™ (aducanumab), an amyloid beta-directed antibody, was recently granted accelerated approval by FDA in June 2021 for early AD based on a biomarker (reduction of amyloid plaque). One particularly significant limitation in the widespread use of such drugs is the requirement for monthly intravenous infusions of the monoclonal antibody preparations that target aggregated forms of amyloid, which has a substantial impact on the costs of production, distribution, and administration of such treatments. Based on the clinical trials to date, there are uncertainties regarding the effectiveness of aducanumab on clinical outcomes.

In addition, there is a significant risk of triggering amyloid-related imaging abnormalities, requiring regular monitoring by magnetic resonance imaging (MRI) scans (summarized in the Aduhelm FDA Drug Approval Package, June 2021).

Therefore, an unmet need exists to develop new medications for AD that more directly modify the underlying disease pathology and offer longer-term and greater efficacy. LMTM, the investigational product, is believed to have the potential to confer benefits over existing treatments for AD due to its ability to affect the process of tau aggregation responsible for the underlying neurofibrillary pathology of AD. Available nonclinical and clinical evidence supports the clinical evaluation of LMTM in AD.

8.1 Background

8.1.1 Investigational Product

The investigational product is LMTM (USAN hydromethylthionine mesylate, also referred to as leuco-methylthioninium bis(hydromethanesulfonate), hydromethylthionine bis(hydromesylate), leucomethylene blue dimesylate, and its code name, TRx0237). As a dihydromethanesulfonate salt (also known as mesylate), LMTM stabilizes the reduced crystalline form of the MT moiety in the solid state.

LMTM is provided as 4-mg, immediate-release tablets, to be taken twice daily; the pharmacokinetics (PK) of LMTM 4 mg as a single dose and given twice daily at steady state (8 mg/day) are described in Section 8.1.3.1. Following dissociation of the counter ions, the uncharged (reduced) LMT form, *i.e*., the active moiety, is absorbed passively. The charged (MT^+) form does not have the conformation necessary to block filament assembly and to disassemble formed filaments (Al-Hilaly *et al*., 2018). When dosed as the charged (MT^+) form (as in methylthioninium chloride [MTC], also known as methylene blue), it is postulated that MT^+ requires an additional reduction step (to LMT) to be distributed to the brain. Within cells, MT exists in equilibrium between the reduced (LMT) and oxidized (MT^+) forms, the predominant form present depending on the cellular milieu, *i.e*., pH and reductive capacity within that cell, with the LMT form predominating intracellularly (May *et al*. 2004).

Matching placebo tablets are provided. The drug supplies for the placebo group will include tablets containing a urinary discolorant, MTC, 4 mg, in order to provide urinary discoloration and maintain the treatment blind.

8.1.2 Nonclinical Data

In cell models, LMT (including as LMTM) has been shown to prevent aggregation and facilitate disaggregation of pre-existing oligomers and fibers. In transgenic mouse models, facilitation of clearance of tau aggregates and associated improvements in cognitive and motor learning abilities have been demonstrated. Tau pathology in these transgenic mouse models has been shown to be ameliorated in certain brain regions (*e.g.,* entorhinal cortex, hippocampus, and neocortex) following treatment with LMTM.

The primary toxicity of MT is hematological, manifesting as methemoglobinemia and a regenerative hemolytic anemia. Depending on the species, Heinz body formation also occurs. A no-observed-adverse effect-level (NOAEL) of 3 to 5 mg MT/kg/day was established in rats, regardless of salt or duration, depending on the low dose in a given study; the parent

MT/LMT plasma levels (exposure) at these doses are comparable to human exposure at an LMTM dose of 8 mg/day. In monkeys, the NOAEL for hematological toxicity was 0.9 mg MT/kg/day in the 6-month MTC phase (toxicokinetic data at this dose are not available); the NOAEL in the subsequent 9-month LMTB phase in which higher doses were given was <20 mg MT/kg/day (the lowest dose studied). Hematological toxicity was seen in minipigs even at the lowest dose studied; therefore, the NOAEL is considered to be <3 mg MT/kg/day. The hematological effects in rats occur at exposures that are 2.1-fold higher than in humans at an LMTM dose of 16 mg/day and in minipigs at exposures that are 1.2-fold higher. In rats and minipigs (but not monkeys) at the hematologically toxic doses, myeloid generation is also affected, and extramedullary hematopoiesis is seen. Pigment (hemosiderin) deposition becomes evident in liver and renal cortical tubules (some lipofuscin is also present in minipigs) with no adverse effect on either liver or kidney function evident. At relatively high doses, effects on white blood cells (WBCs) are seen, but not consistently across species (seen only in rats, not monkeys or minipigs). Decreases in circulating neutrophils occurred with an exposure-based safety margin of 8.9.

The other potential significant toxicities observed include effects on the heart, described as myocardial necrosis, generally occurring at rapidly lethal doses that exceed the maximum tolerated doses for chronic administration. In the minipig, no cardiac toxicity was observed at the highest dose administered chronically, providing safety margins of >7.5-fold relative to an LMTM dose of 16 mg/day in humans. Gastric irritation is seen in rodents and urinary bladder irritation is seen in mice and minipigs (with single cell necrosis in the latter species).

MT is genotoxic *in vitro* and damages DNA *in vitro*, but is not genotoxic *in vivo.* There is no evidence of an interaction with or damage to DNA *in vivo*, a difference which may be due to differences in the predominant redox state of MT *in vitro* and *in vivo*. In addition, MT^+, as a photosensitizer, is activated *in vitro* by visible light to form reactive hydroxyl and superoxide radicals and has been found to be mutagenic *in vitro* only in the presence of light; there is no evidence that MT administered orally undergoes photo-oxidation. According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[1], "When a positive result occurs in an *in vitro* mammalian cell assay, clearly negative results in two well-controlled *in vivo* assays, in appropriate tissues and with demonstrated adequate exposure, are considered sufficient evidence for lack of genotoxic potential *in vivo*." Thus, MT (and by extension its active metabolite *N*-desmethyl MT) is considered to have no clinically relevant genotoxic potential.

As reviewed by the U.S. National Toxicology Program, there is "some evidence of carcinogenic activity"[2] of MTC in male rats based on increased incidences of pancreatic islet cell adenoma and adenoma or carcinoma (combined) and in male mice based on increased incidences of carcinoma and of adenoma or carcinoma (combined) in the small intestine. When data are evaluated using the U.S. Food and Drug Administration (FDA) criteria for a positive response[3], there were no statistically significant neoplastic findings in either species. However, FDA concluded that the combined incidence of pancreatic islet cell adenomas and carcinomas in male rats was higher than in historical controls, particularly at the mid-dose of

[1] ICH S2(R1): Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (2012)

[2] Text in quotation marks refers to the interpretation of results provided by the U.S. National Toxicology Program, the sponsoring organization. These analyses were not consistent with FDA statistical guidelines.

[3] FDA Guidance for Industry: Statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals (draft, May 2001).

19 mg MT/kg/day, and thus caused by MT. At this dose, the exposure-based safety margin relative to a human LMTM dose of 16 mg/day is 3.0-fold.

MT has no effect on mating performance or pregnancy rate in rats when administered orally. The exposure-based safety margin is >8.3-fold and >10.1-fold in males and females, respectively, for an LMTM dose of 16 mg/day.

Two embryo-fetal development studies have been performed by NTP wherein MT was dosed orally during organogenesis. There was no evidence of teratogenicity in rats (NOAEL safety margin of 92-fold relative to a human LMTM dose of 16 mg/day, adjusted for differences in body surface area [BSA]); evaluation of fetotoxicity was confounded by maternal toxicity at all doses. In rabbits, the NOAEL for teratogenicity was the lowest dose studied, a 46-fold safety margin; fetotoxicity (abortions) occurred at the lowest dose (a dose that was maternally toxic). The observed malformations in rabbits, umbilical hernia, are of unclear relevance to humans. Thus, the nonclinical reproductive toxicity studies do not raise a strong suspicion of human teratogenicity/fetotoxicity at clinical doses of LMTM to be studied. Results of studies in other species and by other routes of administration are presented in the Investigator's Brochure. There have been no reports of human teratogenicity in early pregnancy. Thus, MT is considered to have "unlikely human terotogenicity/fetotoxicity in early pregnancy"[4].

In a standard study performed in male Long-Evans pigmented rats, MT does not cause phototoxicity.

Additional details regarding findings from nonclinical studies with various salt forms of MT (LMTM, leuco-methylthioninium bis(hydrobromide) [LMTB], and MTC) are described in the Investigator's Brochure.

8.1.3 Clinical Data

8.1.3.1 Pharmacokinetics

A single- and multiple-dose pharmacokinetic study has been completed in older (≥50 years), healthy, male and female volunteers (TRx-237-036). Following a single 4-mg dose, the mean peak (C_{max}) plasma parent MT/LMT concentration is 0.1 ng/mL, occurring approximately 1 to 1.5 hours post dose. From review of individual concentration *versus* time profiles, split peaks and one or more secondary peaks are evident within the first 12 hours following dosing in the majority of subjects, consistent with a possible biliary recirculation.

Following a single 125-mg dose of LMTM, the presence of food delays absorption by about 1 hour. C_{max} of parent MT/LMT increases, but not to a clinically meaningful extent; there is no difference in area under the plasma concentration *versus* time curve (AUC).

There is evidence of a possible saturation of absorption with increasing doses. With single-dose administration beginning with a dose of 75 mg, plasma concentrations increase proportionally until a dose of 500 mg. At higher doses up to 1000 mg, there is a delay in C_{max} and plateau in AUC.

MT is not highly protein bound: 69.1% to 74.9% in human blood.

[4] Clinical Trials Facilitation Group: Recommendations related to contraception and pregnancy testing in clinical trials (Version 1.1, September 2020)

Hepatic metabolism to *N*-desmethyl MT, an active metabolite, occurs, mediated primarily by cytochrome P450 isoenzyme (CYP) 1A2 and, to a minor extent, by CYP3A4. Plasma levels of this metabolite are approximately 10% to 30% of parent MT/LMT based on C_{max} and AUC following single or multiple doses (however, plasma concentrations could not be reliably measured).

Conjugation to the inactive *N*-glucuronide is the primary route of metabolism of LMTM. The primary UDP-glucuronosyltransferase (UGT) isoform responsible is UGT1A4; UGT1A7 and UGT1A9 may contribute, as well as UGT1A8 and UGT1A10 to a lesser extent. "Total" MT, *i.e*., predominantly LMT-glucuronide(s), is present in concentrations that are >1000-fold higher than those of parent MT/LMT in plasma, whether based on C_{max} or AUC following a single 4-mg dose or 8 mg/day. This is consistent with extensive first pass metabolism (particularly glucuronidation) and rapid distribution of MT from the central compartment, as MT is absorbed and passed through the intestine and liver to the systemic circulation and deep compartments.

Steady-state plasma concentrations of parent MT/LMT are achieved within 10 days of dosing (the first timepoint at which trough plasma concentrations were measured in TRx-237-036). At an LMTM dose of 8 mg/day (given daily as two divided doses), plasma parent MT/LMT C_{max} is 0.3 ng/mL. Based on C_{max} and AUC, there is no unexpected accumulation with multiple dosing. At steady state, the mean terminal elimination half-life ($T_{½}$) of parent MT/LMT is 35.6 hours; mean $T_{½}$ of total MT is shorter (19.1 hours).

At the higher doses (150 and 250 mg/day dosed to steady state), there is a linear but greater than proportional increase in parent MT/LMT exposure and a less than proportional increase in total MT. As a result, at steady state, total MT-to-parent MT/LMT ratios are 243- to 388-fold for C_{max} and 249- to 291-fold for $AUC_{0-\tau}$ over the dosing interval, suggesting either a saturation in formation of the glucuronide conjugate or proportionately more extensive distribution into deep compartments at high doses.

LMT is not a substrate of either P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporters. MT^+ (but not LMT) is a substrate of the hepatic uptake transporter, organic cation transporter 1 (OCT1); the renal uptake transporter, organic cation transporter 2 (OCT2); and the renal/hepatic efflux transporters, multidrug and toxin extrusion proteins 1 and 2K (MATE1 and MATE2K). Neither LMT nor MT^+ is a substrate of the other transporters tested (organic anion transporters 1 and 3 [OAT1 and OAT3], or organic anion transporting polypeptides 1B1and 1B3 [OATP1B1 and OATP1B3]).

There are no clinically meaningful differences in apparent clearance (CL/F) between men and women (adjusted for differences in body weight) or between Caucasians and non-Caucasians.

In cross study comparisons, the CL/F of parent MT/LMT is lower in older subjects, possibly attributable to renal and/or hepatic impairment of varying degrees. The mean $T_{½}$ of parent MT/LMT after a single oral dose in healthy older subjects is 20.7 hours as compared to approximately 15.8 hours in younger healthy volunteers[5].

[5] Average based on Studies TRx-237-019, TRx-237-021, and TRx-237-024.

Renal clearance of parent MT/LMT in healthy volunteers represents 13% of CL/F. Most of a radiolabeled dose (72%) is recovered in the urine, with 24% as unchanged drug and the remainder as metabolites, primarily LMT-glucuronide (28% of the dose). Apparent clearance of parent MT/LMT and total MT is decreased in subjects with renal impairment; correspondingly, AUC increases and $T_{½}$ is prolonged. AUC for parent MT/LMT increases by 1.5-fold in subjects with mild impairment to 4.8-fold in subjects with severe impairment; in subjects with severe impairment, C_{max} is also affected (1.7-fold increase). $T_{½}$ of parent MT/LMT after a single dose increases with worsening degree of impairment (mean 24.4 hours, 29.3 hours, and 46.2 hours in mildly, moderately, and severely impaired subjects, respectively), relative to a mean $T_{½}$ of 15.7 hours in generally younger healthy controls [and in a cross-study comparison, 21.3 hours in older healthy volunteers]); the longest $T_{½}$ was 81.9 hours in a subject with severe impairment.

Apparent clearance of parent MT/LMT (but not total MT) is decreased in subjects with mild to moderate hepatic impairment; some of the subjects with mild to moderate hepatic impairment also had markedly elevated bilirubin (including due to Gilbert's syndrome) and/or history of cholecystectomy. When compared to control subjects with normal hepatic function, C_{max} was 2.1- to 3.2-fold higher with mild and moderate impairment, respectively; AUC was 1.4- to 2.1-fold higher, respectively. Mean $T_{½}$ was prolonged 54% to 87% relative to a mean $T_{½}$ of 15.2 hours in generally younger healthy controls (and in a cross-study comparison, 21.3 hours in older healthy volunteers as noted above); the longest $T_{½}$ was 50.1 hours in a subject with mild impairment.

Approximately 23% of an orally administered dose is recovered from the feces (primarily as parent MT/LMT). The observation of secondary peaks in plasma concentrations (and the demonstrated excretion into bile of bile duct-cannulated rats) is consistent with biliary recirculation, indicating that the fecal excretion cannot be attributed solely to unabsorbed drug.

Results of a drug-drug interaction study in healthy volunteers given LMTM (225 mg twice daily [bid]) for 3 days or 10 days indicate that MT is a weak inhibitor of CYP3A4, CYP2C8, and CYP2C19. LMTM is also a weak inducer of CYP2B6 and P-gp. These data indicate that MT may also increase exposure to other co-administered drugs that are substrates of CYP3A4, CYP2C8, or CYP2C19, and decrease exposure to substrates of CYP2B6 or P-gp. However, the extent to which this occurs at the lower LMTM doses of 8 or 16 mg/day is not known. LMTM is not an inducer or inhibitor of CYP1A2, CYP2C9, CYP2D6, or CYP2E1.

When evaluated *in vitro*, neither the reduced form (LMT) nor the oxidized form (MT^+) inhibits UGT enzyme activity or the OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2k, or the bile salt export pump (BSEP) transporters at clinically relevant test concentrations. LMT (but not MT^+) inhibits BCRP at clinically relevant test concentrations.

8.1.3.2 Cardiac Pharmacodynamics

LMTM given in single, supra-therapeutic doses of 250 and 875 mg (62.5- and 218.8-fold higher than an LMTM 4-mg dose administered at one time) does not prolong the QT interval and is not associated with any other abnormalities of cardiac repolarization.

8.1.3.3 Efficacy

In a double-blind, placebo-controlled Phase 2 study (TRx-014-001) of male and female subjects with mild or moderate AD (AChEIs and memantine excluded), MTC was administered orally at doses of 30 mg three times daily (tid), 60 mg tid, and 100 mg tid (total doses of 69 mg/day, 138 mg/day, and 228 mg/day MT base equivalents, respectively). MT 138 mg MT/day appeared to slow the clinical rate of decline on the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE) measured over 1 year. These effects and the benefit on the ADAS-cog, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, and MMSE scales were already evident in subjects with moderate disease at Baseline within the first 6 months in an analysis of the entire population with severity as an interaction term. The 6-month analysis and methodology were pre-specified as part of the primary analysis. The result in subjects with moderate disease severity at 6 months remained significant after correction for multiple comparisons. Longer term efficacy was confirmed in mixed mild/moderate subjects by *post hoc* analyses at 50 weeks and 102 weeks, and efficacy was also confirmed in analyses of a variety of secondary endpoints (Wischik *et al*., 2015). The lower dose (69 mg MT/day) was below the minimally effective dose. The capsule formulation used limited the absorption of MT at the 228 mg MT/day dose due to a combination of dose-dependent delay in dissolution of the 100-mg MTC capsules used in the study and a formulation-independent limitation in the ability to absorb MT at the highest dose in the presence of food when administered as MTC. When both of these factors were taken into account, the clinically effective dose available for release within 60 minutes in subjects receiving a nominal dose of 228 mg MT/day was equivalent to approximately 69 mg MT/day (Baddeley *et al*., 2015), and the total available dose was equivalent to 109 mg MT/day (Wischik *et al*., 2015).

Evidence of clinical efficacy was supported by neuroimaging in 138 mild and moderate AD subjects imaged at Baseline and at 24 weeks. Despite lack of decline over this time detected by neuropsychological measures such as ADAS-cog in subjects with mild disease at Baseline, statistically significant decline in neuronal function as measured by regional cerebral blood flow was detected using hexamethylpropylamine oxime-single photon emission computed tomography in all predefined lobes in the region-of-interest analysis and was particularly marked in the inferior medial temporal and temporo-parietal regions of the neocortex on the statistical parametric mapping (SPM) analysis, areas characteristically affected by the tau aggregation pathology of AD and the regions primarily affected in the Braak staging system (Braak and Braak, 1991). MTC at a dose of 138 mg MT/day was found to eliminate this decline entirely (Wischik *et al*., 2015). A similar effect was seen in a smaller group of 20 subjects imaged by ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) to measure neuronal function by glucose uptake. The effect on functional neuroimaging markers at 24 weeks in subjects with mild AD was found to be predictive of a clinical response at 50 weeks (Wischik *et al*., 2015). The reduced efficacy of the 100-mg capsule dose (228 mg MT/day) relative to the 60-mg capsule dose (138 mg MT/day) was also confirmed by neuroimaging.

Two Phase 3 studies of LMTM in AD subjects have recently been completed (Gauthier *et al*., 2016; Wilcock *et al*. 2018); final study reports are in preparation. These were a 15-month study in subjects with mild to moderate AD comparing doses of 150 mg/day and 250 mg/day with a control arm of 8 mg/day (TRx-237-015), and an 18-month study in subjects with mild AD comparing a dose of 200 mg/day and the 8-mg/day control (TRx-237-005). AChEIs and/or memantine were used concomitantly by approximately 80% to 85% of the subjects

depending on study. Briefly, there was no statistically significant difference between LMTM in the higher doses of 150 to 250 mg/day in either of the two co-primary clinical efficacy endpoints or lateral ventricular volume (LVV) when compared with the dose of LMTM 8 mg/day, intended as a control. Based on the results of the Phase 2 study, it was assumed that a dose of 8 mg/day of LMTM would be without activity and could thus be used to control for urinary discoloration because of concerns about blinding. Further analyses of results from both studies suggest that LMTM 8 mg/day given as monotherapy may be effective in delaying progression of mild to moderate AD on co-primary clinical efficacy endpoints, the 11-item version of the ADAS-cog (ADAS-cog$_{11}$) or the Alzheimer's Disease Cooperative Study - Activities of Daily Living scale, 23-item version (ADCS-ADL$_{23}$), and also on imaging measures of progression of brain atrophy (MRI and ^{18}F-FDG-PET), and that there is no added benefit to using approximately ≥20-fold higher doses than 8 mg/day.

Recent population PK studies suggest that there are concentration-response relationships for cognitive and neuroimaging outcomes at the 8-mg/day dose. This is seen whether LMTM is taken alone or as add-on to symptomatic treatments (Schelter *et al*., 2019). In a within-cohort meta-analysis of both studies, LMTM at a dose of 8 mg/day as monotherapy was found to produce significant deceleration in the annualized rate of whole brain atrophy after 9 months of treatment. The magnitude of the concentration-dependent treatment effects was reduced by approximately half when LMTM was given to subjects who were concurrently using AChEIs and/or memantine. The reduction in treatment effects of LMTM by treatment with an AChEI or memantine has been reproduced in a tau transgenic mouse model, and appears to reflect a generalized homeostatic downregulation that is induced in multiple brain systems to compensate for the activating effects of symptomatic treatments (Riedel *et al*., 2020).

8.1.3.4 Safety

As of 17 December 2020, 2678 subjects have received at least a single dose of MT (as LMTM, MTC, or an earlier reduced salt studied previously). With respect to LMTM, a total of 2283 subjects (337 healthy volunteers, 40 hepatically or renally impaired subjects, 1688 subjects with AD and 218 subjects with bvFTD) have received at least one dose (ranging from 8 to 1000 mg/day) in completed TauRx-sponsored studies. A total of 321 subjects with AD participated in the 2-year Phase 2 study, TRx-014-001, of whom 307 were exposed to at least one dose of MTC.

The most common adverse events (AEs) associated with MT are anemia and gastrointestinal (GI), genitourinary, and central nervous system (CNS) effects; these are also the most common reasons for discontinuing treatment. These were seen in both the Phase 2 study performed with MTC (given in MT doses up to 228 mg/day) as well as in the Phase 3 studies with LMTM given in MT doses up to 250 mg/day. When all treatment-emergent adverse events (TEAEs) reflective of anemia are grouped, the overall incidence is 13% in subjects randomized to LMTM 8 mg/day. The GI and genitourinary TEAEs are less common at LMTM 8 mg/day than at higher doses. Overall, GI events occurred in 21% of subjects randomized to LMTM 8 mg/day; diarrhea and nausea were amongst the most common individual treatment-related TEAEs, occurring in 7% and 2% of subjects, respectively. The most common urinary TEAEs were frequency, urgency, and incontinence, each treatment related in 1 to 2%. Other less likely TEAEs were agitation, dizziness, fatigue, headache (each with an incidence of 2%), and confusional state (with an incidence of 1%).

Additional details regarding clinical findings from studies are described in the Investigator's Brochure.

8.2 Rationale

The two recently completed Phase 3 studies conducted in subjects with mild to moderate AD (TRx-237-015) and mild AD (TRx-237-005) were designed on the basis of results from the earlier Phase 2 study of MTC as monotherapy in mild to moderate AD. In that study, the minimum dose required for benefit on clinical and imaging endpoints was found to be 138 mg/day. Both of the Phase 3 studies were therefore designed on the assumption that a dose of 8 mg/day of LMTM could be used to control for urinary discoloration because of concerns about blinding. As noted earlier, results from both Phase 3 studies in subjects with mild to moderate AD suggest that LMTM 8 mg/day given as monotherapy may be effective in delaying progression of AD and that there is no added benefit to using doses of 150 to 250 mg/day.

The results of the first of the studies to become available (TRx-237-015) showed that there was no statistically significant difference between LMTM in doses of 150 mg/day or 250 mg/day in either of the two co-primary clinical efficacy endpoints or LVV when compared with the dose of LMTM 8 mg/day intended as a control. However, of the pre-specified terms in the analysis model used in the primary analysis, use of approved AD co-medications (AChEIs and/or memantine) at Baseline was a highly significant term. Further pre-specified analyses in which monotherapy and add-on subjects in the higher dose treatment arms were compared separately with the control group as randomized suggested that LMTM may be effective when given as monotherapy, but not when taken as add-on to approved treatments for AD. LMTM 8 mg/day as monotherapy was also found to differ significantly from 8 mg/day as add-on to existing AD treatments. In light of these results from TRx-237-015, the Statistical Analysis Plan (SAP) of TRx-237-005 was modified prior to database lock and unblinding to specify as primary two similar parallel analyses, each at a statistical threshold of 0.025, to examine 200 mg/day as monotherapy compared with the 8 mg/day control group as randomly assigned, and also 8 mg/day as monotherapy compared with 8 mg/day as add-on to approved AD treatments. Both of these sets of comparisons were statistically significant at the 0.025 threshold for both of the co-primary clinical efficacy endpoints, as well as LVV. No difference in baseline characteristics has been identified in either of the two Phase 3 studies that accounts for the discrepant responses between subjects taking and not taking approved AD treatments, nor is a pharmacokinetic basis for an interaction evident. As indicated above, a within-cohort meta-analysis of both studies showed that LMTM at a dose of 8 mg/day as monotherapy was associated with significant deceleration in the annualized rate of whole brain atrophy after 9 months of treatment.

In the continued development of LMTM, the efficacy of LMTM is to be confirmed in a placebo-controlled study at a dose of 16 mg/day. A population PK model was developed based on Study TRx-237-036 and applied to plasma concentrations from the Phase 3 studies. Using per-patient peak steady-state plasma concentration ($C_{max,ss}$) estimates, concentration-response analyses for ADAS-cog_{11} decline over 65 weeks were performed and a $C_{max,ss}$ threshold of 0.373 ng/mL was identified. The clearance of parent MT/LMT is most significantly associated with renal function, suggesting that the most important predictor of whether or not a subject achieves a parent MT/LMT $C_{max,ss}$ above the threshold is creatinine clearance. At a dose of 8 mg/day, approximately 60% of subjects with normal renal function

would be expected to have plasma concentrations above the threshold, whereas at a dose of 16 mg/day, all subjects would.

The co-primary endpoints are ADAS-cog$_{11}$ and ADCS-ADL$_{23}$, consistent with trials in subjects with mild to moderate AD. Based on the prior studies, a 12-month duration is deemed sufficient to demonstrate superiority to placebo. To address concerns regarding inadvertent unblinding due to urinary discoloration, subjects randomized to placebo may receive a 4-mg MTC tablet as one of the four tablets to be taken daily. As subjects with early AD (also referred to as prodromal AD/mild cognitive impairment due to AD [MCI-AD]) are also included in the study, ^{18}F-FDG-PET and clinical composite scales are included as sensitive endpoints for this subset of subjects.

An open-label, "delayed-start" phase is also included to demonstrate a disease-modifying drug effect. During the delayed-start phase, placebo subjects are switched to receive the active treatment and thus become delayed-start subjects or "late" starters. Active-treatment subjects continue to receive active treatment (all at a dose of 16 mg/day) during the delayed-start phase and are labeled as "early" starters. The rationale of a delayed-start design is that under the null hypothesis, when the active drug has a purely symptomatic effect and has no effect on neuropathologic process, a delay in administration should have no lasting effect on subjects. An effect that slows the progression of disease by modifying the underlying biological pathology, rather than only attenuating symptoms, would be evident if late starters fail to "catch up" to early starters. Demonstrating a disease-modifying effect would imply a sustained benefit of starting such drugs early. Throughout (that is, both the placebo-controlled and delayed-start phases), all subjects and study personnel are blinded to each subject's randomization to the early-start or late-start treatment group.

9 OBJECTIVES

The primary objectives of the study pertain to the randomized, double-blind treatment period. The secondary objectives are presented separately for the double-blind treatment period and the open-label, delayed-start phase. Further exploratory analyses and exploratory analyses compared to external data are described in Section 17.5.

9.1 Primary Objectives

1. To compare the LMTM dose of 16 mg/day with the placebo group on the following co-primary endpoints:
    a. ADAS-cog$_{11}$
    b. ADCS-ADL$_{23}$
2. To assess the safety and tolerability of LMTM 16 mg/day given for up to 52 weeks

9.2 Secondary Objectives

9.2.1 Double-Blind Treatment Period

3. To compare the LMTM dose of 16 mg/day with the placebo group in annualized rate of whole brain atrophy over 52 weeks as measured by brain magnetic resonance imaging (MRI) and quantified using the Boundary Shift Integral (BSI)

4. To compare the LMTM dose of 16 mg/day with the placebo group in temporal lobe ^{18}F-FDG-PET change in Standardized Uptake Value Ratio (SUVR) (normalized to pons) over 52 weeks, restricted to subjects with Clinical Dementia Rating (CDR) 0.5 at Screening, if a predefined threshold is reached for a sufficient number of subjects providing data
5. To compare the LMTM dose of 8 mg/day with the placebo group in temporal lobe ^{18}F-FDG-PET change in SUVR (normalized to pons) over 52 weeks, restricted to subjects with CDR 0.5 at Screening, if a predefined threshold is reached for a sufficient number of subjects providing data
6. To compare the LMTM dose of 8 mg/day with the placebo group on the co-primary endpoints (ADAS-cog$_{11}$ and ADCS-ADL$_{23}$)
7. To compare the LMTM doses of 8 and 16 mg/day with the placebo group in annualized rate of temporal and parietal lobe atrophy over 52 weeks as measured by MRI and quantified using the BSI
8. To assess the safety and tolerability of LMTM 8 mg/day given for up to 52 weeks

9.2.2 Open-Label, Delayed-Start Phase

9. To determine if there is a difference in disease progression on the co-primary clinical endpoints and the MRI imaging endpoint for subjects who started treatment in the double-blind treatment phase and those who started treatment in the open-label, delayed-start phase (referred to as "early" and "late" LMTM starters, respectively)
    a. Only ADAS-cog$_{11}$ will serve as a secondary endpoint; ADCS-ADL$_{23}$ and other imaging endpoints are exploratory with the aim to be directionally supportive
10. To assess the safety and tolerability of LMTM given for up to 104 weeks

Population PK analyses will be performed to estimate PK exposure in each subject for use in the evaluation of exposure-response relationships. These will be defined in a separate Population PK SAP or a dedicated section of the SAP.

Additional analyses including exploratory and sensitivity analyses are described in Section 17 and further detailed in the SAP.

10 STUDY DESIGN

10.1 General Description

This is a two-phase outpatient study of LMTM administered as monotherapy in subjects with early to mild-moderate AD: a randomized, double-blind, placebo-controlled, 52-week treatment period followed by a 52-week open-label, delayed-start phase. In the latter, all subjects are to continue with open-label treatment, such that subjects originally randomized to placebo are "late" starters of LMTM and subjects originally randomized to LMTM 8 mg/day or 16 mg/day are "early" starters. The total duration of participation for an individual subject will be up to 120 weeks, including a Screening period of up to 16 weeks. Subjects are to have pathophysiological changes as confirmed by positive amyloid PET and severity determined by a Mini-Mental State Examination (MMSE) score of 16-27 / Global Clinical Dementia Rating (CDR) score of 0.5 to 2 at Screening. Subjects must not have used an AChEI and/or memantine within the 60 days prior to the baseline assessments (inclusive

of the baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5). The primary treatment group comparisons are of LMTM 16 mg/day and placebo; secondary comparisons will be done for subjects receiving LMTM 8 mg/day *versus* placebo. Following completion of the 52-week treatment period, subjects will continue open-label treatment with LMTM 16 mg/day for a further 52 weeks; prior treatment assignment will not be unblinded. (However, upon completion of the initial 52-week, double-blind, placebo-controlled treatment period, the database will be locked and unblinded for analysis; individual subject prior treatment assignment will not be divulged to subjects or individuals involved in the operational conduct of the ongoing open-label, treatment phase). A description of the study is provided below; see Section 10.2 for a summary of the alternate arrangements that may be implemented due to the Coronavirus Disease 2019 Public Health Emergency (hereafter referred to as COVID-19).

Following provision of written informed consent by the subject (and/or LAR, consistent with national and/or local law) and study partner(s), eligibility will be assessed initially during the Screening period which may require multiple visits (collectively designated as Visit 1).

A sufficient number of subjects will be recruited from sites in North America (United States and Canada) and Europe such that approximately 500 subjects are enrolled. Beginning with Protocol Version 5.0, approximately 450 are to be enrolled and randomized in a 4:1:4 ratio (at the study level) to the LMTM 16-mg/day (200 subjects), LMTM 8-mg/day (50 subjects), and placebo (200 subjects) groups. The randomization will be stratified by severity (three levels: MMSE 16-19, 20-25, or 26-27, with a target ratio of approximately 2:3:1 for those randomized to Protocol Version 5.0 and above), prior use of AChEIs and/or memantine (two levels: prior use of either any AChEIs and/or memantine or none), and region (two levels: North America or Europe).

Eligibility will be confirmed during the Screening period, with the duration of screening depending on whether or not the subject enters the study using an approved AD medication, described as follows (and illustrated in Table 10-1):

- The Screening period will be up to 9 weeks for subjects who are not receiving an AChEI and/or memantine at the time of signing the Informed Consent (Initial Screening Visit, Visit 1).
- The Screening period will be extended for up to a further 6 weeks, 15 weeks in total (+7 days at Sponsor discretion), for subjects who are receiving an AChEI and/or memantine at the time of signing the Informed Consent to allow for the performance of necessary screening tests to confirm eligibility prior to the discontinuation of AChEI and/or memantine and to permit a washout of at least 60 days from the last dose prior to the baseline assessments (inclusive of the baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5).
- The Screening visit window may be further extended at the discretion of the Sponsor when justification is provided.

For eligible subjects, one Baseline/Randomization (Visit 2: imaging, efficacy, and safety), and five post-Baseline double-blind visits (Visit 3: safety, and Visits 4, 5, 6, and 7: efficacy, imaging, and safety), and three open-label treatment visits (Visits 8 [telephone contact only], 9, and 10) are scheduled. Unscheduled visits may occur as needed for assessment, or upon early termination. In addition, subjects are to be followed as needed to monitor for the resolution or acceptable stabilization of AEs (including after the last dose), consistent with the investigator's medical judgement. For women of childbearing potential this includes a

return visit to the clinic for pregnancy testing within 3 months of last exposure to study drug in the event of delayed menstruation.

Visit 2 (Baseline/Randomization) must be scheduled to occur in the morning when the first dose of study drug will be administered in the clinic. Visit 3 (after 4 weeks of study drug), Visit 7 (after 52 weeks of study drug), and Visit 10 (after 104 weeks of study drug) should also be scheduled to occur in the morning; subjects are to be instructed not to take the morning dose of study drug as it will be administered in the clinic. Subjects will be required to remain at the clinic for at least 4 hours post-dose on each occasion to allow for safety assessments and PK blood sample collection.

Cognitive and functional assessments using two standard scales, ADAS-cog$_{13}$ and ACDS-ADL$_{23}$, will be performed at Baseline, approximately every 3 months during the double-blind treatment period (Visits 4, 5, 6, and 7), and after the additional 26 and 52 weeks of open-label treatment (Visits 9 and 10), or upon early termination. These will be captured electronically on tablets and subject to independent review. The MMSE and CDR will be repeated after 52 weeks of double-blind treatment (Visit 7) and at the final open-label visit (Visit 10) or upon early termination. To the greatest extent practicable, a consistent rater(s) for a given subject is to be maintained throughout the study.

The MRI obtained during Screening will also be the basis for the baseline volumetric MRI; volumetric MRI will be repeated approximately every 13 weeks (Visits 4, 5, 6, and 7). The imaging endpoints will be quantified by independent core laboratories. MRI will also be done after the additional 26 and 52 weeks of open-label treatment (Visits 9 and 10).^{18}F-FDG-PET imaging will be performed at Baseline and Visit 7 (after 52 weeks), or upon early termination, only in subjects with CDR 0.5.

Safety assessments (AE and concomitant medication review, vital sign review, targeted physical and neurological examinations, and review of clinical laboratory results) will be performed by an independent qualified assessor not involved in efficacy assessments; where specified, the assessments must be made by a medical assessor (physician, doctor of medicine [MD], or doctor of osteopathic medicine [DO]). These will be performed at each clinic visit during the double-blind treatment period (Visits 2 to 7) and after 26 and 52 weeks of open-label treatment (Visits 9 and 10), and when needed to follow up on an AE. Selected safety assessments will also be performed during a telephone contact after 4 weeks in the open-label, delayed-start phase (Visit 8). An ophthalmological examination (only to be conducted in subjects with lens implants) will be performed prior to the first dose of study drug (during the screening procedures or as part of the baseline assessments) and at the final visits in each of the study phases (Visits 7 and 10), or upon early termination, to assess for potential discoloration of the lens. See Table 10-2, Table 10-3 and Section 15.4 for more details on these assessments and the qualifications required to perform them.

Other assessments include collection of blood for plasma and whole blood MT concentration determination and (optionally) collection of a blood sample for Apolipoprotein E (*ApoE*) genotyping.

10.2 Changes Implemented Due to COVID-19

Based on ongoing risk assessment regarding the impact of COVID-19 on this study as described in Section 21.2, selected changes to the performance of study conduct and

monitoring are to be implemented as deemed necessary to protect subjects due to COVID-19 as described in Sections 10.2.1 and 10.2.2, respectively. For subjects already enrolled under earlier versions of the protocol (prior to Protocol Version 6.0), subjects will be re-consented at their next in-clinic visit; in the interim, verbal consent will be obtained as needed for changes to study procedures. Changes to the statistical analyses, including sensitivity analyses to address any impact of COVID-19 on study outcomes, are described in Section 10.2.3.

10.2.1 Changes to Study Conduct

If a subject is undergoing screening assessments, but cannot have protocol-required assessments performed due to COVID-19, the subject should be put on screening pause until such time as COVID-19 impacts have ceased and abstention from treatment with an AChEI and/or memantine should be retained. Screening MMSE/CDR/DV, brain scans, and G6PD blood sample collection do not require repetition if already confirmed. The approach for individual assessments is described further below. Re-screening is addressed in Section 11.3.

Both the Screening visit (including informed consent and all screening assessments) and the Baseline/Randomization visit must continue to occur in the clinic at the study site. The first dose of study drug (Visit 2) will be administered in the clinic. This visit should be scheduled to occur in the morning and subjects will be required to remain at the site for at least 4 hours post-dose.

The intervening post-Baseline visits, *i.e.*, Visits 3, 4, 5, 6 and 7 (after 4, 13, 26, 29, and 52 weeks of double-blind study drug), for clinical safety assessments (adverse event and concomitant medication recording/review), safety and PK blood sample collection (inclusive of the optional genotyping blood sample collected any time after Baseline but prior to Visit 7), as well as efficacy assessments, may be completed in-clinic at the site, in the subject's home by visiting study personnel, or at other safe, suitable alternative location, if deemed necessary to protect a subject due to COVID-19. Similarly, Visits 9 and 10 (after 26 and 52 weeks of open-label treatment) may also be completed in the clinic at the site, in the subject's home by visiting study personnel, or at other safe, suitable alternative location. Efficacy scales may also be performed remotely, if approved by the Sponsor in advance on a case-by-case basis, as further described below. The principal investigators (PIs) retain unilateral decision-making and discretion regarding ongoing subject participation dependent on local circumstance and authority recommendations. Travel to the investigational site is the subject's decision. The following procedures are also to be implemented as necessary:

- Consideration may be given on an individual site basis to expand the allowable time windows for study visits if a site closure is anticipated to be short-term.
- Alternative arrangements for dispensing study drug supplies (*e.g.*, home delivery that would not raise new safety risks) may be permitted if deemed necessary to protect subjects due to COVID-19. If a trial site is not able to deliver study drug to subjects, the study drug may, as an exception, be shipped directly to the subjects by a distributor independent from and acting on behalf of the Sponsor, in line with national law or temporary emergency measures. Requirements for obtaining subject consent consistent with local and national requirements, maintaining the specified study drug storage conditions and handling, accountability, and compliance monitoring will be addressed and documented. In the event that a given subject cannot attend a visit at the study site, the study personnel will make reasonable attempts to assess study drug

compliance with the subject or study partner(s) and document the assessment in the source until it can be verified.

- The ADAS-cog$_{13}$ may be performed in the clinic at the site or, if deemed necessary to protect subjects due to COVID-19, in the subject's home or at other safe, suitable alternatives, in person or remotely via videoconference. For remote administrations to avoid loss of data, MedAvante ProPhase will provide clinical sites with electronic tablets provisioned with Zoom (or equivalent) videoconferencing software only[6]. The electronic tablets will be shipped by the clinical sites directly to subjects, and guidance will be provided to subjects and study partners regarding the use of the electronic tablets for remote scale administration as well as instructions for returning the electronic tablets to the sites. When assessments are performed remotely, the rater will confirm the identity of the subject and study partner before proceeding. The approved site raters will administer the scales through the videoconferencing software and will document the assessment as they would if performing the assessment in person; source data and audio recordings will still be captured via the Virgil system.
    - In the remote administration of the ADAS-cog$_{13}$ (if applicable at that visit), the standard (*i.e.*, validated) mode of administration has been adapted to enable data to be captured by videoconference, with the exception of Commands (only partially supported, and thus a total score cannot be calculated for this subset), Ideational Praxis, and Number Cancellation. Due to these missing data (not all subtests can be administered remotely), total scores will not be calculated directly for the remote administration of the ADAS-cog$_{13}$ but a derived upscaled score will be used for analysis as defined in the SAP.
- The MMSE, CDR, and ADCS-ADL$_{23}$ may be performed either in the clinic at the site or, if deemed necessary to protect subjects due to COVID-19, in the subject's home or at other safe, suitable alternatives in person or remotely by speakerphone. If assessments are performed remotely, the rater will confirm the identity of the subject and study partner before proceeding. The approved site raters will document the assessment as they would if performing the assessment in person; source data and audio recordings will still be captured via the Virgil system.
    - In the remote administration of the MMSE (if applicable at that visit), the approved site rater will administer as much of the MMSE as possible. For those elements that cannot be administered remotely, the rater will confirm that these were omitted before submitting the data to MedAvante-ProPhase per usual practice. Due to missing data, total MMSE scores for remote assessments will not be directly calculated but upscaled as per the SAP.
    - In the remote administration of an ADCS-ADL$_{23}$ or CDR (if applicable at that visit), all items will be scored.
- All MRI scans are to be performed at approved MRI centers using approved scanners; no alternative scanners will be accepted and there is to be no change in scanner for a given subject over the course of the study.
    - Guidance will be provided for scheduled MRI visits at approved imaging centers that may be closed due to COVID-19, including acceptable windows outside the scheduled visit window during which MRI scans can still be performed at approved imaging centers and would be accepted for analysis.

[6] While remote administration of the ADAS-cog$_{13}$, MMSE, CDR, and ADCS-ADL$_{23}$ has not been validated, MedAvante ProPhase will prepare written instructions for the rater that detail how to alter administration of each of the scales in order to minimize any impact on the data collected, and to minimize loss of data.

- In subjects with CDR 0.5 at Screening, ^{18}F-FDG-PET imaging will be performed at Baseline (unless the Sponsor approves subject randomization without a brain ^{18}F-FDG-PET scan, if the scan cannot be performed due to COVID-19). All ^{18}F-FDG-PET scans are to be performed at approved PET centers using approved scanners; no alternative scanners will be accepted and there is to be no change in scanner for a given subject over the course of the study.
    - If a Baseline ^{18}F-FDG-PET scan cannot be done due to lack of imaging facility, a follow-up ^{18}F-FDG-PET scan will not be required
- Blood samples for safety laboratory assessments and PK as well as optional genotyping may be collected from subjects in the clinic at the site, in the subject's home, or at other safe, suitable alternative location, using the central laboratory (Labcorp) kits for sample collection; samples are to be shipped to Labcorp for analysis using a designated courier service, and the shipment parameters as per the laboratory manual must be adhered to during transfer (*e.g.*, between the subject's home, primary care provider, or clinical site).
    - If blood samples for safety laboratory assessments cannot be shipped to Labcorp, sample analysis for hematology testing will be performed at a local laboratory. As the first post-Baseline (Visit 3) hematology sample analysis is key in monitoring the adverse event of special interest (AESI) of hemolytic anemia, clinical sites will not be permitted to randomize a subject if the Visit 3 blood collection plan is not in place. Blood chemistry and genotyping samples can also be analyzed at a local laboratory or may be stored at -20 °C at the clinical site until shipment to the central laboratory.
    - If blood samples for PK laboratory assessments cannot be shipped to Labcorp, plasma PK samples should be stored at -20 °C at the clinical site; whole blood PK data may be compromised as the samples are stable for a limited period. The University of Aberdeen GLP Test Facility must analyze the PK whole blood sample within 22 days after the sample is taken to confirm it is acceptable for analysis. Results are to be entered into the eCRF by the site.
    - For serum pregnancy testing performed in women of childbearing potential, such women should be encouraged to return to the clinic or request serum pregnancy testing (to be performed at the subject's home or at other suitable, safe alternatives) in the event of a delayed menstrual period to rule out possible pregnancy, during study conduct and for up to 3 months after the last dose of study drug. Site follow up on such subjects should be recorded in the source documentation.
    - For PK blood sample collection at Visit 2, Visit 3, Visit 7, and Visit 10, the third sample to be collected approximately 4 hours after the dose is not required if the visit occurs in the subject's home (although timing of previous dose should be ascertained as accurately as possible).
- Multiple study partners participating only as caregivers will be permitted for a given subject, either simultaneously or as replacements for previous study partners, with no specified maximum. For study partners participating as informants providing data from assessments of the subject, a maximum total of two study partners (*i.e.*, one replacement) would normally be permitted for a given subject; however, up to a total of four study partners (*i.e.*, three replacements) are permitted if circumstances change due to COVID-19 and provided they have sufficient contact with the subject to act as a reliable informant. Information obtained from study partners participating as informants will be appropriately identified to distinguish each informant in the event that a given subject has more than one study partner providing data for analysis.

10.2.2 Changes to Study Monitoring

As part of ongoing risk assessment regarding the impact of COVID-19, the Sponsor has assessed the risk associated with the collection of post-baseline data for this study. All study subjects should continue to attend clinic visits as defined in the protocol as long as it is safe and feasible to do so. However, in the event that subjects and/or study partners are unable to attend post-Baseline visits at the clinic in person, guidance for continued data collection to be completed in the subject's home or at other safe, suitable alternatives is described in Section 10.2.1. Any impact of COVID-19 on subject participation in the study will be recorded in the eCRFs.

Due to the unpredictable nature of COVID-19, remote monitoring may be conducted *in lieu* of onsite monitoring, including the targeting of critical data and source (for example to include consent, eligibility, subject safety and drug accountability) for periods where a source data verification backlog exists due to inaccessibility of the site to the clinical monitor. Any change to monitoring of the study as a direct result of COVID-19, such as remote monitoring policies and procedures, will be captured through an addendum/amendment to the Clinical Monitoring Plan (CMP). Every effort will be made to complete the same monitoring tasks remotely as would be conducted onsite while accommodating site-specific policies and limitations. Every effort will also be made to ensure the continued protection of subject safety, subject rights, and data integrity. Any deviations from the CMP will be clearly documented.

There is the possibility of increased amounts of missing data and protocol deviations due to limitations on protocol implementation imposed by COVID-19. Clinical sites are expected to maintain documentation of missing data and protocol deviations in source documents with data entered accordingly in the eCRFs.

As the study continues, there will be a need to address other new and challenging scenarios in real time as they arise at different clinical sites during COVID-19. The Sponsor will continue to assess any limitations imposed on protocol implementation that may pose safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures such that subject safety, trial integrity, and compliance with regulations are assured.

10.2.3 Changes to Statistical Analyses

Changes to the Statistical Analyses will be outlined in the SAP and will follow the most recent regulatory guidelines. This section describes briefly the general approach followed and addresses particular challenges related to this study. A detailed list of analyses will be provided in the SAP including the conditions that need to be met in order to trigger these analyses. At a minimum, the number of missing or likely impacted assessments and data points will be provided.

Sites projected to recruit more than 10% of the subjects will be closely monitored to ensure that the MMSE balance is met as closely as possible. It is acknowledged that COVID-19 will have an impact on certain MMSE groups as they are more likely to be asked to take social distancing precautions; corresponding sensitivity analyses will be implemented to assess the impact as briefly described below and summarized further in the SAP.

As COVID-19 can impact specific assessments and lead to missing data due to missed visits, various sensitivity analyses will be provided assessing the impact of COVID-19 on the results. Dependent on the actual number of assessments impacted by COVID-19, a more or less exhaustive set of analyses will be provided taking account of regulatory guidelines and as specified in the SAP.

Among these additional analyses, some will focus on the impact on primary endpoints. If more than 5% of all the assessments (over all subjects and visits) of a given primary endpoint are impacted by COVID-19 (based on the eCRF Covid-19 Impact Assessment), the assessments impacted by COVID-19 will be excluded and upscaled when the respective primary endpoint is analyzed.

Other sensitivity analyses include:

- Subgroup analysis by the way of endpoint ascertainment (in-clinic, remote). A subject is assigned to the subgroup with the most visits done with respect to in-clinic or remotely (excluding Baseline and Week 52, which must be performed in-clinic).
- ADAS-cog_{11}: Include only the subset of items (for all visits), which can be administered remotely by telephone or video call.
- ADCS-ADL_{23}: Exclude items which are affected by COVID-19 restrictions.
- A composite scale designed as a COVID-19 impact free joint score ("COVID-19 Composite Scale") will be analyzed. It will include items, selected from ADAS-Cog_{11} and ADCS-ADL_{23}, that are not expected to be impacted by COVID-19.

Details and further analysis will be specified in the SAP.

If a significant number of assessments is impacted by COVID-19, a sample size increase may be applied. The conditions for this to happen will be outlined and specified before any analyses/assessments are conducted.

As indicated above, a more exhaustive list will be provided accounting for regulatory guidelines in the SAP.

10.3 Study Population

To be eligible for randomization, subjects are to have AD based on a diagnosis of probable AD or MCI-AD according to the criteria of the 2011 National Institute on Aging [NIA] / Alzheimer's Association [AA] with documented pathological changes as confirmed by positive amyloid PET (McKhann *et al*., 2011; Albert *et al*., 2011). The allowable severity will be a MMSE score of 16 to 27 (inclusive) and Global CDR score of 0.5 to 2 (if 0.5, including a score of >0 in one of the functional domains). Inclusion and exclusion criteria are given in Section 11.

The study will be conducted in approximately 150 study sites in North America and Europe.

Approximately 2000 subjects may be screened to have approximately 500 subjects who will be enrolled, of whom approximately 450 are to be enrolled and randomized under Protocol Version 5.0 and above. Randomization will be such that subjects will be assigned to the MMSE severity groups at study level based on screening MMSE score with a target ratio of approximately 2:3:1 (MMSE 16-19, MMSE 20-25, MMSE of 26-27, respectively) for those

randomized to Protocol Version 5.0 and above. To achieve this target, enrollment will be monitored and controlled at the site level for high recruiting sites (*i.e.*, sites projected to recruit more than 10% of the subjects) as per Section 10.2.3 and capped as needed at the study level *via* the Randomization and Trial Supply Management (RTSM) system. Subjects who drop out after randomization will not be replaced; subjects will be encouraged to continue with study visits until the scheduled completion of the double-blind treatment period (Visit 7). Only subjects who continue in the study and receive LMTM until and including the last open-label visit (Visit 10) may be eligible for a separate EAP.

10.4 Duration

The total duration of participation for an individual subject will be up to 120 weeks, including a Screening period of up to 16 weeks (112 days, with further extension permitted at the discretion of the Sponsor when justification is provided), a double-blind treatment period of 52 weeks, and a further open-label, delayed-start phase of 52 weeks. It is anticipated that the study will have an overall duration of at least 40 months, depending on recruitment rate. The current study will be concluded after the last visit for the last subject under this protocol.

10.5 Schedule of Assessments

10.5.1 Screening Assessments

All subjects should have a likely diagnosis of probable AD or MCI-AD prior to being offered the consent forms on the basis of investigator interview and examination. Subjects for whom legally acceptable informed consent has been obtained will be screened at trial sites for determination of eligibility to enter the study on the basis of further diagnostic evaluations, cognitive assessments, and safety assessments (clinical laboratory testing, vital signs, complete physical and neurological examinations, and a local 12-lead electrocardiogram [ECG]). An overview of the screening assessments is provided in Table 10-1 below; assessments must be performed in the sequence presented. Where required and indicated, eligibility should be confirmed prior to progressing to the next screening assessment. ^{18}F-FDG-PET, to be evaluated only in subjects with CDR 0.5 at Screening, is not an eligibility assessment; however, a valid baseline scan is required prior to randomization, hence it is included on this table. See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

Table 10-1: Schedule of Screening Assessments (Over Multiple Visits, Collectively Designated Visit 1)

Required Sequence of Assessments	Time Frame	
	On AChMem at Start of Screening	**Not on AChMem at Start of Screening**
1. Likely diagnosis of probable AD or MCI-AD (M)	9 to 16 weeks before Baseline, Days -112 to -63 (+7 days at Sponsor discretion)[d]	≤9 weeks before Baseline, Days -63 to -1[d]
2. Informed consent by Subject (and/or LAR) and Study Partner(s) (M[a])		
3. Demographics		
4. Medical history and concomitant medication review (M)		
5. NIA/AA probable AD or MCI-AD clinical diagnosis confirmed (M)		
6. MMSE		
7. CDR		
8. Diagnostic Verification Form (M)		
9. Medical assessments (M): Vital sign measurement[b] Physical/neurological examinations[c] 12-lead electrocardiogram Laboratory testing: Serum chemistry Hematology Haptoglobin Folate / vitamin B_{12} Thyroid stimulating hormone Glucose-6-phosphate dehydrogenase Serum pregnancy test (women of childbearing potential only)		
10. Wait for Confirmation of Eligibility email received from MedAvante-ProPhase and laboratory testing confirmation of compliance by Labcorp Central Laboratory Services before moving to step 11		
11. Amyloid PET scan • Documentation of prior positive scan OR • If no negative scan within prior 3 years, perform using approved amyloid ligand		
12. Wait for Amyloid PET scan confirmation of compliance by local / central imaging center (if scan required)		
13. MRI scan		
14. Wait for MRI confirmation of compliance by Bioclinica		
15. Withdraw AChEI/memantine	≥ 60 days before baseline assessments	Not applicable
16. Medical history and concomitant medication review, serum chemistry, hematology, serum pregnancy test (M)	Repeat within 42 days of Baseline	Repeat if not performed within 42 days of Baseline
17. ^{18}F-FDG-PET only in subjects with CDR 0.5 (Not an eligibility assessment, but independent confirmation of a valid baseline ^{18}F-FDG-PET)	Within 42 days before randomization, but at least 60 days after the last dose of AChEI and/or memantine	Within 42 days before randomization
18. Wait for ^{18}F-FDG-PET confirmation of scan quality by Invicro for subjects with CDR 0.5	Before randomization	

Abbreviations: AChEI = anticholinesterase inhibitor; ACh/Mem = AChEI and/or memantine; AD = Alzheimer's disease; CDR = Clinical Dementia Rating; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose positron emission tomography; LAR = Legally Acceptable Representative; MCI-AD = mild cognitive impairment due to Alzheimer's disease; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography
Note: (M) requires medical assessor (physician / MD / DO); study partner = caregiver or informant

[a] At all study sites, the PI or SI who obtains informed consent must be a physician (such as a neurologist, psychiatrist) or other medically qualified assessor (physician/MD/DO); in the case of subjects with reduced decision-making capacity, LARs, consistent with national and/or local law, may provide written informed consent
[b] Vital signs include seated blood pressure and pulse, height, and body weight
[c] Based on medical history, subjects with a history of lens implantation should be scheduled for an ophthalmological examination by a licensed ophthalmologist, optometrist, or other suitably qualified medical assessor (physician/MD/DO) to occur prior to the first dose of study drug (once eligibility has been confirmed), during the screening procedures or as part of the baseline assessments
[d] The Screening visit window may be further extended at the discretion of the Sponsor when justification is provided.

10.5.1.1 Diagnostic and Cognitive Eligibility Assessments

After consent is obtained, the principal investigator (PI) (or sub-investigator [SI]) is required to review medical records and confirm the accuracy of the diagnosis during the examination of each subject. The NIA/AA diagnostic interview must be conducted with the subject, and the designated study partner (*i.e.*, a caregiver or informant) providing data from assessments of the subject, by the PI (or SI). In brief:

- Subjects with probable AD dementia must have insidious onset, worsening impairment in at least two cognitive areas (learning and recall, language, executive function, visuospatial skills), sufficient to significantly interfere with work or usual activities, that is not explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder.
- In subjects with MCI-AD, there should be evidence of concern about a change in cognition in comparison with the person's previous level verified by a knowledgeable informant or clinician. There should also be evidence of lower performance in episodic memory than would be expected for the subject's age and educational background (typically 1 to 1.5 standard deviations below the mean). Other mild cognitive deficits may also be present, but there must be preservation of independence in functional abilities. Subjects should not meet the criteria for dementia. The cognitive changes must be mild and there must be no evidence of a significant impairment in social or occupational functioning. Impairments must not be explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder.

The diagnostic interview should be completed and documented in the subject's medical records prior to administering the MMSE and CDR. The MMSE will be the first evaluation at Screening (Visit 1), followed by the CDR, to obtain Severity Ratings. These will be assessed on a Virgil tablet. Note that the CDR assessment should only be performed if the subject meets the MMSE inclusion criterion. If the subject does not qualify with either of these scales, no further assessments should be made and the subject should be considered a screen failure. If eligible, a Diagnostic Verification Form will be completed by the PI/SI and submitted to independent reviewers at MedAvante-ProPhase Inc., who will confirm the accuracy of the diagnosis and Severity Ratings and will provide confirmation (by e-mail) that the subject is eligible to proceed to the remaining screening assessments. The PI must acknowledge receipt of this independent confirmation prior to subject randomization. In the event that MedAvante-ProPhase central reviewers identify issues that cannot be resolved, the subject will be deemed not eligible. The subject may be re-screened (after a wait of 90 days from last MMSE), inclusive of repeat of MMSE and CDR which will again be subject to the independent review to confirm eligibility.

Eligibility assessments include documentation of a previous PET scan that was positive for amyloid. If such documentation is absent, or if the subject has a negative amyloid PET scan that is dated >3 years prior to Screening, an amyloid PET scan must be conducted as part of screening. A negative amyloid PET scan within 3 years prior to Screening is exclusionary and no amyloid PET scan should be performed. If a new amyloid PET scan is performed as part of screening, local determination (or central for those sites not able to read locally) of positivity using criteria routinely applied at the local imaging facility and using an amyloid PET ligand that is approved in the country of participation will be accepted. With subject (and/or LAR) consent, these and previous amyloid PET scans will be sent to a core imaging laboratory for storage and later exploratory analysis.

The screening assessments should be performed so that MRI is the last of the key eligibility assessments to be scheduled. The screening MRI scan(s) results (of sufficient quality) must be available for the purpose of inclusion/exclusion review and confirmation of compliance with inclusion and exclusion criteria by an independent neuroradiologist. If the initial screening MRI is not of sufficient quality, then a repeat screening scan may be performed. If the repeat scan cannot be accomplished within the pertinent window (see Table 10-1), then the subject must be re-consented and re-screened. For subjects who are re-screened for other reasons and an acceptable MRI scan was already completed during the original Screening window, the scan does not require repetition. See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

In subjects receiving an AChEI and/or memantine at Screening, documentation of amyloid positive PET imaging (either by prior history or in the sequence of screening tests) and confirmation of compliance with inclusion and exclusion criteria by the independent neuroradiologist (inclusive of screening MRI), must be available prior to the discontinuation of such medication.

At any step, should any of the assessments indicate the subject's ineligibility, the screening process should be stopped immediately (no further assessments performed) and the subject considered a screen failure. The reason(s) for screen failure is (are) to be documented.

10.5.1.2 Other Medical Screening Assessments

Medical screening assessments will include a review of medical history and concomitant medications. Physical and neurological examinations will be conducted by a qualified medical assessor (physician/MD/DO) at Screening. The complete physical examination is to consist of an evaluation of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, lymph nodes, abdomen, and extremities. The complete neurological examination is to consist of an evaluation of appearance and behavior (including observation for tremor and abnormal movements) and an evaluation of the following: speech, cranial nerves (2-12), motor (muscle strength), muscle tone, sensory abnormalities, coordination, gait, and tendon reflexes. At Screening, the primary aim of this assessment is to exclude neurological disorders other than the condition of interest. Any abnormalities noted on either the physical or neurological examination should be described.

An ophthalmological examination will be performed by a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor (physician/MD/DO) prior to the first dose of study drug (during the screening procedures or as part of the baseline assessments) in subjects with a history of lens implantation.

At Screening, vital signs will be measured (seated blood pressure and pulse, body weight, and height), blood obtained for clinical laboratory testing, and a 12-lead ECG performed. Clinical laboratory testing at Screening will include hematology, serum chemistry panels, glucose-6-phosphate-dehydrogenase (G6PD) activity, haptoglobin, vitamin B_{12}, and folate. A serum pregnancy test will be performed in women of childbearing potential only. Thyroid stimulating hormone (TSH) will be measured during screening, with a thyroid hormone panel obtained only in the event of an elevated TSH, if clinically warranted, to determine further treatment before re-screening. Clinical laboratory testing (serum chemistry, hematology, and serum pregnancy test) and medical history and concomitant medication review should be repeated within 42 days of Baseline if the initial screening assessments were performed earlier. Review of the clinical laboratory and ECG results should be performed by a medical assessor (physician/MD/DO).

Should a subject be found to have met one or more of the exclusion criteria, he/she will be considered a screen failure; the reason(s) will be documented. For eligible subjects, findings will be documented in the subject's medical record and in the electronic Case Report Form (eCRF).

10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period

The baseline and post-randomization assessments during the double-blind treatment period are presented below in Table 10-2. The procedures are further described, briefly, in the subsections that follow (with reference to more detailed discussions). See Section 10.2 for a summary of alternate arrangements that may be implemented related to COVID-19.

Table 10-2: Schedule of Post-Screening Assessments (Double-Blind Treatment Period)

Visit Name	Baseline[a]		Double-Blind Treatment Period				
Visit Number	2		3	4	5	6	7 (or ET) Also Baseline/ Day 1 for Open-Label Phase
Weeks Relative to Baseline	-		4 weeks	13 weeks	26 weeks	39 weeks	52 weeks
Allowable Time Window in Days	Pre-Dose	Post-Dose	(±3)	(±14)	(±14)	(±14)	(±14)
^{18}F-FDG-PET (see Table 10-1) [b]							X
Randomization	X						
MRI [c]				X	X	X	X
ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ [d, o]	X			X	X	X	X
AE/Concomitant Medication Recording/Review [e] (M)	X	X	X	X	X	X	X
Targeted Physical/Neurological Examinations [f] (M)	X	X	X	X	X	X	X
Ophthalmological Examination [g] (M/O)	X						X
Clinical Laboratory Testing [h] (M)	X		X	X	X	X	X
Pregnancy Testing [i]	X		X	X	X	X	X
Blood Pressure, Pulse, Body Weight [j]	X	X	X	X	X	X	X
Study Drug Dispensing	X			X	X	X	X[p]
Study Drug Compliance Assessment [k]			X	X	X	X	X
Blood Sample for MT Concentration [l]	X	X	X				X
Blood Sample for Genotyping (optional) [m]	X						
MMSE [n, o]							X
CDR [n, o]							X

Abbreviations: ADAS-cog$_{13}$ = Alzheimer's Disease Assessment Scale – cognitive subscale (13-item); ADCS-ADL$_{23}$ = Alzheimer's Disease Cooperative Study – Activities of Daily Living (23-item); AE = adverse event; CDR = Clinical Dementia Rating; EOT/ET = end of treatment/early termination; ^{18}F-FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; MT = methylthioninium.
Note: Screening assessments, which include a PET scan for amyloid and a 12-lead ECG, are described in Table 10-1
Note: (M) = assessment of the result requires medical assessor (physician / doctor of medicine [MD] / doctor of osteopathic medicine [DO]); M/O = licensed optometrist/ophthalmologist or other suitably qualified medical assessor (physician/MD/DO)

[a] The Baseline visit (Visit 2) may span over 2-3 days if necessary; Day 1 will commence with the administration of the first in-clinic dose of study drug.

[b] ^{18}F-FDG-PET should be performed only in subjects confirmed to meet all inclusion and exclusion criteria and a screening CDR 0.5. The Baseline ^{18}F-FDG-PET should be performed within a 42-day window prior to Baseline (Visit 2), at least 60 days after the last dose of AChEI and/or memantine, and as described in Table 10-1. A valid scan must be confirmed by the independent neuroradiologist prior to randomization at Visit 2.
If the subject's last ^{18}F-FDG-PET scan was performed ≥30 days prior to the early termination date, the ^{18}F-FDG-PET scan must be repeated as part of the ET visit assessments within the time window of the EOT/ET visit (*i.e.*, ± 14 days of the EOT/ET visit).
Note: Use of sedatives is not permitted within 24-hours prior to ^{18}F-FDG-PET scans and the subject's fasting (for at least 4 to 6 hours) blood glucose should be <180 mg/dL (<9.9 mmol) for the injection to take place.

[c] Volumetric MRI scans will be obtained at Screening (which also will be the baseline scan) and approximately every 13 weeks after randomization; the screening MRI will also be used for purposes of confirmation of compliance with inclusion and exclusion criteria by an independent neuroradiologist. Subjects may or may not be receiving concomitant treatment with AChEI and/or memantine at the time of the screening MRI; the screening MRI will be used as the baseline. For subjects who terminate early, if the subject's last MRI scan was performed <90 days prior to the ET date, no additional scan is required.

[d] At each applicable time point, clinical efficacy assessments should be administered before vital signs measurement and blood sample collection. All ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ assessments will be subject to central review by MedAvante-ProPhase clinicians in the native language.

[e] AEs and concomitant medication use will be evaluated by a medical assessor (M) and recorded on an ongoing basis starting after signing of informed consent, including at each scheduled visit; unscheduled visits should occur as needed to follow up an AE (including after the last dose of study drug), consistent with the physician/MD/DO judgment.

[f] Targeted examinations will be performed by a medical assessor (M) pre-dose and approximately 3 hours after administration of the first dose of study drug (Visit 2). Thereafter, targeted examinations are to be performed at each subsequent clinic visit (or upon ET). At a minimum, targeted examinations should include heart and lung auscultation and brief neurological assessment guided by any reported signs/symptoms/AEs (*e.g.*, evaluating subjects for potential serotonin toxicity).

[g] Ophthalmological examination (slit lamp) is to be performed only in those subjects with history of lens implant to evaluate discoloration of lens. The initial examination will be performed prior to the first dose of study drug (during the screening procedures or as part of the baseline assessments); performance of this examination is not restricted to the 2 to 3 days before the first dose of study drug. The final evaluation (EOT/ET) should be done after completion of the efficacy assessments.

[h] At each identified time point, blood samples will be obtained for chemistry and hematology panels; results are to be reviewed by a medical assessor (M). Testing is also to be performed as needed to follow-up on an AE.

[i] Serum pregnancy testing is to be performed at each identified time point in women of childbearing potential only.

[j] Within 1 hour prior to dosing on Day 1, blood pressure and pulse will be measured with subjects in a seated position (for at least 5 minutes). The post-dose measurement on Day 1 is to be made approximately 2 hours post-dose (after the 1-2 hour PK sample is taken). Body weight will be measured at each visit (pre-dose at Visit 2).

[k] Compliance with study drug will be assessed by counting returned tablets (see Section 12.6).

[l] At Visits 2, 3, and 7, blood will be collected on *the same day on three occasions*, pre-dose and again approximately 1 to 2 hours post-dose (these should be morning appointments); and a third sample with time of dose and sample at approximately 4 hours after the dose. Note: The time of the dose from the previous day must be collected and recorded at Visits 3 and 7, in addition to the time of the dose given in the clinic. For any ET visit, if the subject has not yet discontinued study drug and is willing to take a final in-clinic dose, three blood samples will be collected as described above. If, however, the subject has already discontinued study drug or is unwilling to take a final in-clinic dose, a single blood sample only for determination of MT concentrations will be collected, irrespective of the date or time of the last dose of study drug. The date and time of last dose must be collected and recorded. If a subject has discontinued study drug but wants to continue to attend study visits off-treatment (the off treatment on study [TOTOS] group), then MT concentration blood samples will not continue to be collected.

[m] A single blood sample for *ApoE* can be collected any time after eligibility for randomization and continued participation in the study has been confirmed (but prior to Visit 7, the end of the double-blind treatment period) for subjects who provide legally acceptable consent.

[n] These are to be rated by the same rater, where possible, as at Screening, after all other efficacy assessments have been completed. MMSE and CDR assessments will be subject to central review by MedAvante-ProPhase clinicians in the native language.

[o] The clinical efficacy scale assessments should be performed at approximately the same time of day throughout the study for a given subject, to the greatest extent possible.

[p] In-clinic dose at Visit 7 to be taken after pre-dose assessments, from newly dispensed Visit 7 open-label study drug kit (see Table 10-3 for the pre-dose and post-dose assessments to be performed at Visit 7).

10.5.2.1 Imaging Efficacy Assessments in Double-Blind Treatment Period

Only in subjects with CDR 0.5 at Screening, ^{18}F-FDG-PET will be performed within the 42 days before Baseline (but not earlier) and after 52 weeks of double-blind treatment or upon early termination. The purpose is to assess reduction in decline of glucose uptake in regions of interest. If the subject's last ^{18}F-FDG-PET scan was performed ≥30 days prior to the early termination date, the ^{18}F-FDG-PET scan must be repeated as part of the early termination visit assessments within the time window of the early termination visit (*i.e.*, ± 14 days of the last dose of study drug). ^{18}F-FDG-PET data will be evaluated by an independent, nuclear medicine staff physician experienced in neuro ^{18}F-FDG-PET, not involved in the clinical conduct of the study, and trained on the study endpoints. Note: The use of sedatives is not permitted within 24 hours prior to ^{18}F-FDG-PET scans and the subject should have a fasting (at least 4 to 6 hours) blood glucose level <180 mg/dL (<9.9 mmol/L) in order for the injection to take place.

Brain MRI (obtained at Screening and approximately every 13 weeks during the double-blind treatment period after randomization or upon early termination) will be evaluated for change in various parameters to determine whether there is reduction of temporal, parietal, whole brain, lateral ventricular, hippocampal, putamen, nucleus accumbens, and nucleus basalis

atrophy rates over the period of the study. Changes in the brain volumes above will be quantified at the imaging core laboratory.

For subjects who terminate early, if the subject's last MRI scan was performed <90 days prior to the early termination date, no additional MRI scan is required.

The obtainment and assessment of imaging data are further described in Section 15.3.

10.5.2.2 Clinical Efficacy Assessments in Double-Blind Treatment Period

The ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ will be performed at Baseline and every 13 weeks after randomization (or upon early termination) during the double-blind treatment period by an approved Efficacy Rater using electronic tablets. Assessments will be recorded and reviewed independently as further described in Section 15.2.

As exploratory clinical efficacy assessments, the MMSE and CDR sum of boxes will be performed after 52 weeks of double-blind treatment (or upon early termination). For a given subject, these are to be performed by the same rater, where possible, who made the screening assessments and recorded on electronic tablets, as further described in Section 15.2. These are to be the last assessments performed, *i.e*., after all other efficacy assessments have been completed.

All clinical efficacy assessments will be subject to independent review (all subjects, all applicable time points).

10.5.2.3 Safety Assessments in Double-Blind Treatment Period

Safety assessments (described in Section 15.4) will be performed throughout study participation, including at Baseline (prior to dosing and during the 4-hour post-dose evaluation at Visit 2) and during the balance of the double-blind treatment period (Visits 3, 4, 5, 6, and 7, or upon early termination). Safety assessments will be performed by an independent qualified assessor not involved in efficacy assessments; where specified, the assessments must be made by a medical assessor (physician/MD/DO). Study visits during the double-blind treatment period will occur at time points approximately 4, 13, 26, 39, and 52 weeks after Baseline.

At each in-clinic visit, AEs and changes in concomitant medications will be recorded. These must be reviewed by a medical assessor (physician/MD/DO).

Other post-screening assessments include measuring vital signs, performing targeted physical and neurological examinations, clinical laboratory testing (*e.g.,* hematology, serum chemistry panels), and serum pregnancy testing (women of childbearing potential only). The targeted physical and neurological examinations and review of the clinical laboratory results should be performed by a medical assessor (physician/MD/DO).

Subjects with a history of lens implant will undergo an ophthalmologic examination by a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor (physician/MD/DO) prior to the first dose of study drug (during the screening procedures or as part of the baseline assessments) and at Visit 7 of the double-blind treatment period or

upon early termination (after completion of the efficacy assessments), to evaluate whether the lens has become discolored. Sites that do not have access to a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor (physician/MD/DO) are not permitted to screen subjects with a history of lens implant.

10.5.2.4 Other Assessments in Double-Blind Treatment Period

At Visits 2, 3, and 7, blood will be collected for determination of MT concentrations. Samples will be collected pre-dose, approximately 1 to 2 hours post-dose, and approximately 4 hours post-dose. To achieve this sample collection schedule, these should be morning appointments (and for Visits 3 and 7, subjects instructed not to take their morning dose at home). See Section 15.5.1 for further details.

For any early termination visit during the double-blind treatment period, also refer to Section 15.5.1 for blood sampling requirements for determination of MT concentrations.

ApoE genotype will be determined for subjects who provide legally acceptable consent. A single blood sample may be collected any time after eligibility for randomization and continued participation in the study has been confirmed at Baseline (Visit 2), but prior to Visit 7 (end of the double-blind treatment period). Sample collection is further described in Section 15.5.2.

10.5.3 Assessments in the Open-Label, Delayed-Start Phase

The assessments during the open-label, delayed-start phase are presented below in Table 10-3. The procedures are further described, briefly, in the subsections that follow (with reference to more detailed discussions in Section 15). See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

Table 10-3: Schedule of Assessments (Open-Label, Delayed-Start Phase)

Visit Name	Baseline/Day 1 for Open-Label Phase		Continued Open-Label Treatment		
Visit Number	7		8 (TC)	9	10 (OL-EOT or OL-ET)
Weeks Relative to Visit 2 Baseline	52 weeks		56 weeks	78 weeks	104 weeks
Allowable Time Window in Days	(±14 days)		(±3 days)	(±14 days)	(±14 days)
	Pre-Dose	Post-Dose			
^{18}F-FDG-PET (see Table 10-1 and Table 10-2)	X				
MRI [a]	X			X	X
ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ [b, l]	X			X	X
AE/Concomitant Medication Recording/Review [c] (M)	X	X	X	X	X
Targeted Physical/Neurological Examinations [d] (M)	X			X	X
Ophthalmological Examination[e] (M/O)	X				X
Clinical Laboratory testing [f] (M)	X			X	X
Pregnancy Testing [g]	X			X	X
Blood Pressure, Pulse, Body Weight [h]	X			X	X
Study Drug Dispensing	X[m]			X	
Study Drug Compliance Assessment [i]	X		X	X	X
Blood Sample for MT Concentration [j]	X	X			X
MMSE [k, l]	X				X
CDR [k, l]	X				X

Abbreviations: ADAS-cog$_{13}$ = Alzheimer's Disease Assessment Scale – cognitive subscale (13-item); ADCS-ADL$_{23}$ = Alzheimer's Disease Cooperative Study – Activities of Daily Living (23-item); AE = adverse event; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; OL-EOT = open-label end of treatment; OL-ET = open-label early termination; TC = telephone contact.

Note: Visit 7 results from Table 10-2 provide baseline values for the open-label, delayed-start phase.

Note: (M) = requires medical assessor (physician/doctor of medicine [MD]/doctor of osteopathy [DO]); M/O = licensed optometrist/ophthalmologist or other suitably qualified medical assessor (physician/MD/DO) is also acceptable

[a] For subjects who terminate early, if the subject's last MRI scan was performed <90 days prior to the ET date, no additional scan is required.

[b] At each applicable time point, clinical efficacy assessments should be administered before vital signs measurement and blood sample collection. All ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ assessments will be subject to central review by MedAvante-ProPhase clinicians in the native language.

[c] AEs and concomitant medication use will be evaluated by a medical assessor and recorded on an ongoing basis starting after signing of informed consent, including at each scheduled visit; unscheduled visits should occur as needed to follow up an AE (including after the last dose of study drug), consistent with the physician/MD/DO judgment.

[d] Targeted examinations are to be performed by a medical assessor at each clinic visit (or upon ET). At a minimum, targeted examinations should include heart and lung auscultation and brief neurological assessment guided by any reported signs/symptoms/AEs (*e.g.*, evaluating subjects for potential serotonin toxicity).

[e] Ophthalmological examination (slit lamp) is to be performed only in those subjects with history of lens implant to evaluate discoloration of lens. The final evaluation (OL-EOT or OL-ET) should be done after completion of the efficacy assessments.

[f] At each identified time point, blood samples will be obtained for chemistry and hematology panels; results are to be medically reviewed by a medical assessor. Testing is also to be performed as needed to follow-up on an AE.

[g] Serum pregnancy testing is to be performed at each identified time point in women of childbearing potential only.

[h] Blood pressure and pulse will be measured with subjects in a seated position (for at least 5 minutes).

[i] Compliance with study drug will be assessed by counting returned tablets (see Section 12.6); compliance will also be queried in the TC.

[j] At Visits 7 and 10, blood will be collected on *the same day on three occasions*, pre-dose and again approximately 1 to 2 hours post-dose (these should be morning appointments); and a third sample with time of dose and sample at approximately 4 hours after the dose. Note: The time of the dose from the previous day must be collected and recorded at Visits 7 and 10, in addition to the time of the dose given in the clinic. For any ET visit, if the subject has not yet discontinued study drug and is willing to take a final in-clinic dose, three blood samples will be collected as described above. If, however, the subject has already discontinued study drug or is unwilling to take a final in-clinic dose, a single blood sample only for determination of MT concentrations will be collected, irrespective of the date or time of the last dose of study drug. The date and time of last dose must be collected and recorded. If a subject has discontinued study drug but wants to continue to attend study visits off-treatment (TOTOS group), then MT concentration blood samples will not continue to be collected.

[k] These are to be rated by the same rater, where possible, as at Screening, after all other efficacy assessments have been completed. MMSE and CDR assessments will be subject to central review by MedAvante-ProPhase clinicians in the native language.
[l] The clinical efficacy scale assessments should be performed at approximately the same time of day throughout the study for a given subject, to the greatest extent possible.
[m] In-clinic dose at Visit 7 to be taken after pre-dose assessments, from newly dispensed Visit 7 open-label study drug kit.

10.5.3.1 Imaging Efficacy Assessments in the Open-Label, Delayed-Start Phase

Brain MRI will be obtained after the additional 26 and 52 weeks of open-label treatment (Visit 9/Week 78 and Visit 10/Week 104) and will be evaluated and quantified as briefly described in Section 10.5.2.1 for the double-blind treatment period. The obtainment and assessment of imaging data are further described in Section 15.3.

For subjects who terminate early, if the subject's last MRI scan was performed <90 days prior to the early termination date, no additional MRI scan is required.

10.5.3.2 Clinical Efficacy Assessments in the Open-Label, Delayed-Start Phase

The ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ will be performed after the additional 26 and 52 weeks of open-label treatment (Visit 9/Week 78 and Visit 10/Week 104) by an approved Efficacy Rater using electronic tablets. Assessments will be recorded and reviewed independently as further described in Section 15.2.

As exploratory clinical efficacy assessments, the MMSE and CDR sum of boxes will be performed after the additional 52 weeks of open-label treatment (Visit 10/Week 104 or upon early termination). These are to be performed by the same rater, where possible, who made the screening assessments and recorded on electronic tablets, as further described in Section 15.2. These are to be the last assessments performed, *i.e.*, after all other efficacy assessments have been completed.

All clinical efficacy assessments will be subject to independent review (all subjects, all applicable time points).

10.5.3.3 Safety Assessments in the Open-Label, Delayed-Start Phase

Safety assessments (described in Section 15.3) will be performed after 26 and 52 weeks (Visit 9/Week 78 and Visit 10/Week 104) of open-label treatment and will include AE review, concomitant medication recording and review, targeted physical and neurological examinations, clinical laboratory testing (*e.g.*, hematology and serum chemistry panels), serum pregnancy testing (women of childbearing potential only), and vital sign measurements. In addition, AEs and changes in concomitant medications will be recorded during a telephone contact after 4 weeks of open-label treatment (Visit 8/Week 56). The targeted physical and neurological examinations along with review of any AEs, changes in concomitant medications, and clinical laboratory results should be performed by a medical assessor (physician/MD/DO).

Subjects with a history of lens implant will undergo an ophthalmologic examination by a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor (physician/MD/DO) at the final visit of the open-label treatment period (Visit 10/Week 104), or upon early termination (after completion of the efficacy assessments), to evaluate whether the lens has become discolored.

10.5.3.4 Other Assessments in Open-Label, Delayed-Start Phase

At Visit 10/Week 104, blood will be collected for determination of MT concentrations. Samples will be collected pre-dose, approximately 1 to 2 hours post-dose, and approximately 4 hours post-dose. To achieve this sample collection schedule, this should be a morning appointment and subjects instructed not to take their morning dose at home. See Section 15.5.1 for further details.

For any early termination visit during the open-label phase, also refer to Section 15.5.1 for blood sampling requirements for determination of MT concentrations.

10.6 Data and Safety Monitoring Board

Safety will be overseen by a Data and Safety Monitoring Board (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 unblinded to the subject level 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. 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.

10.7 Definition of End of Study

The end of study will occur when the last subject has completed the final study visit in the open-label, delayed-start phase (whether or not the visit occurs as scheduled). As noted in Section 17.9, an analysis will be performed after the last subject completes the last visit in the double-blind treatment period.

Subjects who complete the study and receive treatment with LMTM up to and including the last open-label visit may be offered an opportunity to subsequently receive treatment with LMTM in a separate EAP.

11 SUBJECT ENROLLMENT AND WITHDRAWAL

11.1 Inclusion Criteria

To be eligible for enrollment in this study, a subject must meet all of the following inclusion criteria:

1. AD, encompassing probable AD and MCI-AD based on 2011 NIA/AA criteria:
   - All cause dementia and probable AD (probable AD)
     In brief, subjects with probable AD dementia must have insidious onset,

worsening impairment in at least two cognitive areas (learning and recall, language, executive function, visuospatial skills), sufficient to significantly interfere with work or usual activities, that is not explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder. The accuracy of the diagnosis will be confirmed independently by the diagnosing physician at site.

OR

- MCI-AD
  In subjects with MCI-AD, there should be evidence of concern about a change in cognition, in comparison with the person's previous level verified by a knowledgeable informant or clinician. Other mild cognitive deficits may also be present, but there must be preservation of independence in functional abilities. Subjects should not meet the criteria for dementia. The cognitive changes must be mild and there must be no evidence of a significant impairment in social or occupational functioning. Impairments must not be explained by delirium, drugs, major psychiatric disorder, medical illness, cerebrovascular disease, other forms of dementia, or neurological disorder.

2. Documented PET scan that is positive for amyloid; if most recent PET scan was performed >3 years prior to Screening and was negative, it may be repeated (a negative amyloid PET scan within the 3 years prior to Screening is exclusionary)
3. MMSE score of 16-27 (inclusive) at Screening, subject to stratification requirements
4. Global CDR score of 0.5 to 2 at Screening (if 0.5, including a score of >0 in one of the functional domains: Community Affairs, Home and Hobbies, or Personal Care)
5. Age <90 years at Screening
6. Females must meet one of the following:
   - Surgically sterile (hysterectomy, bilateral salpingectomy / oophorectomy) for at least 6 months minimum
   - Have undergone bilateral tubal occlusion / ligation at least 6 months prior
   - Post-menopausal for at least 1 year
   - Using adequate contraception (a barrier method [such as condom, diaphragm or cervical/vault cap] with spermicidal foam, gel, film, cream, or suppository; intrauterine device [IUD] or system, or oral or long-acting injected or implanted hormonal contraceptives for at least 90 days 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 be competent to use adequate contraception and to agree to continue to maintain adequate contraception throughout participation in the study (including up to 4 weeks after the last dose of study drug)
7. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) (LAR(s)), consistent with local and national law, is able to read, understand, and provide written informed consent in the designated language of the study site
8. Has one (or more) identified adult study partner (*i.e.*, a caregiver or informant) who meets the following criteria:
   - Either lives with the subject, or 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 (*e.g.,* sees the subject on average for ≥1 hour/day ≥3 days/week)
- Is willing to provide written informed consent for his/her own participation
- Is able to read, understand, and speak the designated language(s) at the study site
- Agrees to accompany the subject to each study visit
- Is able to verify compliance with study drug

9. The subject must not have been taking either an AChEI, *i.e*., donepezil, galantamine, or rivastigmine, and/or memantine, for at least 60 days at the time of the baseline assessments
    - Subjects never previously treated with an AChEI and/or memantine may be enrolled if initiation of treatment with these medications is not planned for the time period during which the subject will be participating in this study
10. Able to comply with the study procedures in the view of the investigator

11.2 Exclusion Criteria

The exclusion criteria are:

1. Significant central nervous system (CNS) disorder other than probable AD or MCI-AD, *e.g*., Lewy body dementia, Parkinson's disease, multiple sclerosis, progressive supranuclear palsy, hydrocephalus, Huntington's disease, any condition directly or indirectly caused by Transmissible Spongiform Encephalopathy (TSE), Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), or new variant Creutzfeldt-Jakob Disease (nvCJD)
2. Significant intracranial focal or vascular pathology seen on brain MRI scan that would, based on the independent reviewer imaging evaluation, lead to a diagnosis other than probable AD or MCI-AD, including but not limited to:
    - Large confluent white matter hyperintense lesions (*i.e.*, Fazekas score of 3)
    - Other focal brain lesions judged clinically relevant by the investigator
    - Evidence of a prior or current macrohemorrhage
3. Clinical evidence or history of any of the following (within specified period prior to Baseline):
    - Cerebrovascular accident (2 years)
    - Transient ischemic attack (6 months)
    - Significant head injury, for example, associated loss of consciousness, skull fracture or persisting cognitive impairment (2 years)
    - Other unexplained or recurrent loss of consciousness ≥15 minutes (2 years)
4. Diagnosed with epilepsy (a single prior seizure >6 months prior to Screening is considered acceptable)
5. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria met (for any of the following within specified period):
    - Major depressive disorder (current)
    - Schizophrenia (lifetime)
    - Other psychotic disorders, bipolar disorder (within the past 5 years)
    - Substance (including alcohol) related disorders (within the past 2 years)

6. Metal implants in the head (except dental), pacemaker, cochlear implants, or any other non-removable items that are contraindications to MRI. MRI compatible prosthetics, clips, stents, or any other device proven to be compatible are allowed
7. Resides in hospital or moderate to high dependency continuous care facility (residence in low grade assisted living facility where there is sufficient autonomy to permit valid evaluation of activities of daily living is allowed so long as it is not mandated by an order issued either by the judicial or the administrative authorities)
8. Any physical disability that would prevent completion of study procedures or assessments (*e.g*., blindness or significant uncorrected visual impairment, deafness or significant hearing loss not corrected by hearing aids, non-AD-related speech impairment)
9. 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)
10. Pregnant or breastfeeding
11. G6PD deficiency based on World Health Organization (WHO) classification (<60% of normal, *i.e.,* <6.1 U/g hemoglobin [Hgb])
12. History of significant hematological abnormality or current acute or chronic clinically significant abnormality, including:
    - History of hemoglobinopathy, myelodysplastic syndrome, hemolytic anemia, or splenectomy
    - Screening Hgb value (confirmed upon repeat) below age/sex appropriate lower limit of the central laboratory normal range

    Subjects in whom folate is <4.0 ng/mL may be entered into the study provided folate supplementation (approximately 1 mg/day) is initiated and maintained for the duration of the study; subjects in whom vitamin B_{12} is <150 pg/mL can be allowed if the investigator confirms that it does not affect the cognitive state of the subject and that the subject is supplemented as appropriate prior to the initiation of study drug
13. Abnormal serum chemistry laboratory value at Screening deemed to be clinically significant by the investigator. In addition, subjects with either of the following abnormalities must be excluded:
    - Creatinine clearance <30 mL/min, estimated by the central laboratory according to the Cockcroft and Gault equation
    - TSH above laboratory normal range (subject may be treated [if clinically indicated based on further laboratory testing] and re-screened after 90 days)
14. Clinically significant cardiovascular disease or abnormal assessments (based on the investigator's interpretation of the locally obtained ECG) such as:
    - Hospitalization for acute coronary syndrome (acute myocardial infarction or unstable angina) or symptoms consistent with angina pectoris, within the 12 months preceding Baseline
    - Signs or symptoms of clinical heart failure within the 12 months preceding Baseline
    - Atrial fibrillation on screening ECG or history of atrial fibrillation that is not currently controlled (heart rate ≥85 bpm and/or inappropriate anticoagulation)
    - QTcF (QT corrected for heart rate using Fridericia's formula) at Screening >460 msec in males or >470 msec in females, or low or flat T waves making measurement of QT interval unreliable

- Recent history of poorly controlled hypertension, systolic blood pressure >180 mmHg, or diastolic blood pressure >100 mmHg, after 5 minutes in a seated position at Screening
- Hypotension: systolic blood pressure <100 mmHg after 5 minutes in a seated position at Screening
- Heart rate <48 bpm or >96 bpm by measurement of vital signs (after 5 minutes in a seated position) or by local ECG at Screening

15. Pre-existing or current signs or symptoms of respiratory failure, *e.g.*, caused by chronic obstructive pulmonary disease, bronchial asthma, lung fibrosis, or other disease
    - Subjects with currently diagnosed moderate to severe sleep apnea should be excluded; the definition of moderate to severe includes oxygen supplementation, *e.g.*, nasal prongs or Continuous Positive Airway Pressure (CPAP)
16. Concurrent acute or chronic clinically significant (in the opinion of the investigator) immunologic, hepatobiliary (such as presence of encephalopathy or ascites), or endocrine disease (not adequately treated), and/or other unstable or major disease other than probable AD or MCI-AD; the following are specifically excluded:
    - Active hepatitis or primary biliary cirrhosis
    - Active Human T-Cell Lymphocytic Virus Type III (HTLV-III), Lymphadenopathy Associated Virus (LAV), any mutants or derivatives of HLTV-III or LAV, any condition associated with active Acquired Immunodeficiency Syndrome or similar condition however named
17. Diagnosis of cancer (excluding basal cell carcinoma, squamous cell carcinoma, or prostate carcinoma in situ [Stage 1]) meeting either of the following criteria:
    - Newly diagnosed within past 2 years
    - Previous (>2 years) diagnosis of cancer that has required any form of intervention or treatment within the past 2 years, *e.g.*, chemotherapy, radiotherapy, hormonal therapy, or surgery
18. Prior intolerance or hypersensitivity to MT-containing drug or methemoglobinemia induced by MT-containing drug, similar organic dyes, or any of the excipients
19. Treatment currently or within 90 days before Baseline with any of the following:
    - Souvenaid®
    - Antipsychotics
        - Clozapine (and there is no intent to initiate therapy during the course of the study)
        - Other antipsychotics are allowable provided they have not been initiated within 90 days before Baseline and preferably at a stable dose and regimen
    - Carbamazepine, primidone, valproate
    - Drugs for which there is a warning or precaution in the labeling about methemoglobinemia at approved doses (*e.g.*, dapsone, local anesthetics such as benzocaine used chronically, primaquine, and related antimalarials)
20. Current or prior participation in a clinical trial as follows:
    - Any clinical trial of LMTM
    - Clinical trial of a product for cognition prior to Baseline in which the last dose was received within 90 days prior to Baseline unless confirmed to have been randomized to placebo

- A clinical trial of any other investigational drug, biologic, device, or medical food in which the last dose was received within 28 days prior to Baseline

11.3 Re-screening

Re-screening of a subject is allowed in selected instances, as listed below (to a maximum of two re-screening occasions). Upon re-consent and re-screening, the subject must continue to meet all of the inclusion and exclusion criteria described in Section 11.1 and Section 11.2, respectively. Prior to re-consent, the PI (or SI) should confirm that the subject continues to meet the diagnosis of AD, encompassing probable AD and MCI-AD, of the acceptable severity (MMSE 16-27 and CDR score of 0.5 to 2 [if 0.5, including a score of >0 in one of the functional domains]), and has not used an AChEI and/or memantine for at least 60 days prior to the baseline assessments (inclusive of the baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5). Screening may also be paused at a given site due to COVID-19 as described in Section 10.2.1; such subjects do not require re-consent but otherwise, the principles listed below with respect to repeat testing apply.

1. At the initial Screening, MMSE score will be obtained first to determine eligibility. CDR scores will also be obtained for eligibility. A Diagnostic Verification Form will be completed to confirm diagnosis of probable AD or MCI-AD. These assessments will be subject to independent review. If scoring discrepancies are found that cannot be resolved, the subject will be deemed not eligible. The subject may be re-screened (after a wait of 90 days from last MMSE), inclusive of repeat of MMSE and CDR which will again be subject to the independent review to confirm eligibility. For the avoidance of doubt, re-screening is not allowed if a valid MMSE or CDR score falls outside the acceptable criteria.
2. If the initial screening MRI scan is not of sufficient quality as determined by the core imaging laboratory, a repeat scan may be performed. If the repeat scan cannot be accomplished within the time window specified in Table 10-1, the subject must be re-consented and re-screened. For subjects who are re-screened for other reasons and an acceptable MRI scan was already completed during the original Screening window, the scan does not require repetition.
3. Evidence of atrial fibrillation on initial screening ECG or history of atrial fibrillation that is not currently controlled (heart rate ≥85 bpm and/or inappropriate anticoagulation) is not allowed. If better control of the heart rate and/or of anticoagulation can be achieved after adequate treatment, the subject may be entered into the study if still within the 42-day window; otherwise the subject must be re-consented and re-screened. A cardiology consult should be sought for further ECG evaluation if deemed necessary by the investigator.
4. Subjects with vitamin B_{12} levels <150 pg/mL at initial screening which cannot be corrected during the Screening period may be reconsented and re-screened after the deficit has been corrected (see Section 13.8 for further details).
5. Subjects with a TSH above laboratory normal range at the initial screening may be treated (if clinically indicated) and re-consented and re-screened after 90 days.

Any other criterion not listed above would require justification and approval by TauRx.

No other minimum time is required for re-screening unless specifically stated above or elsewhere in the protocol.

11.4 Discontinuations / Withdrawals

11.4.1 Handling of Subjects Who Discontinue Study Drug

For a discussion of reasons for permanent discontinuation of study medication on the basis of safety, see Section 16.11. These include, but are not limited to, clinically evident hemolytic anemia (Section 16.11.1) and decrease in renal function when it raises renal concerns (Section 16.11.3).

Subjects may discontinue study drug at any time for any reason. Furthermore, the investigator also has the right to discontinue study medication if he or she judges that treatment is no longer appropriate, if the subject's clinical condition is worsening, or for an AE.

If study drug is discontinued, the reason and the last date of study drug should be recorded on the eCRF.

For subjects who cease taking study drug but who wish to continue in the study, the planned schedule of assessments should be followed, except for the collection of blood samples for MT concentrations. These subjects will be classified as "the off-treatment-on-study" (TOTOS) group. Subjects who continue in the study off-treatment will not be eligible for a separate EAP. The handling of data for these subjects is discussed in Section 17.4.11.4.

As discussed in Section 13.1, study drug must be discontinued in subjects who initiate treatment with an AChEI and/or memantine. The handling of data for these subjects is discussed in Section 17.4.11.3.

11.4.2 Handling of Study Discontinuation / Withdrawal

Subjects may withdraw (drop out) from the study at any time for any reason. A study partner (who is functioning as an informant) may also withdraw his or her consent from study participation at any time for any reason. If a study partner withdraws his or her consent, the subject must then also be withdrawn if alternative arrangements are not available (*e.g.*, an alternate study partner). (See Section 11.4.3 for replacement of study partners.)

If the subject withdraws from study participation, the reason should be recorded on the eCRF as one of the following:

- Adverse event
- Death
- Lack of efficacy (including progressive disease or worsening of cognitive capacity)
- Lost to follow-up
- Withdrawal by subject or legally acceptable representative (or study partner), including specific reason(s), wherever possible
- Protocol deviation
- Non-compliance with study drug
- Pregnancy
- Study terminated by Sponsor
- Physician decision, including specific reason(s), wherever possible
- COVID-19
- Other (specify)

If the reason for discontinuation of study is an AE, the principal event 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 a serious adverse event (SAE), this must be documented and an SAE form completed.

For subjects who withdraw from the study for reasons other than death or subject/LAR or study partner consent withdrawn, a visit should be scheduled as soon as possible after the last dose of study drug and the End-of-Treatment safety evaluations for the current treatment period performed. For subjects or legally acceptable representatives who withdraw consent or when a study partner withdraws consent without available alternate study partner, the investigator should request that the reason be specified and the subject have any clinically indicated safety assessments performed.

11.4.3 Replacements

Subjects who are withdrawn from the study will not be replaced nor can they be re-enrolled or enter the EAP.

In the event a study partner participating as an informant withdraws, one replacement is normally permitted. However, as noted in Section 10.2.1, up to a total of three replacements may be allowed if necessitated by COVID-19, and the replacement study partner has sufficient contact with the subject to permit informed responses regarding their ADL functioning. Multiple study partners participating only as caregivers will be permitted for a given subject, either simultaneously or as replacements for previous study partners, with no specified maximum.

12 STUDY DRUG

12.1 Treatments Administered: Form, Dosage and Administration

Study drug is available as blue, round, film-coated, immediate-release tablets (5-mm diameter, approximately 55-mg core weight) manufactured and packed for TauRx in accordance with Good Manufacturing Practice (GMP), as detailed in the European Union (EU) Guide to GMP. These and visually matching placebo tablets are debossed on one side with the Greek “Tau” symbol.

12.1.1 Active Ingredient

The active ingredient (drug substance) is LMTM (USAN hydromethylthionine mesylate, also known as leuco-methylthioninium bis(hydromethanesulfonate) or the code name, TRx0237). It is included in the tablets as 4 mg LMT (expressed as MT base equivalent).

12.1.2 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).

12.2 Study Regimens

All subjects will receive four tablets orally per day (two in the morning and two in the evening) in a double-blind fashion for 52 weeks in one of the following three study regimens, in a 4:1:4 ratio for Protocol Version 5.0 and above:

- LMTM 16-mg/day group: Two 4-mg tablets in the morning, and two 4-mg tablets in the evening
- LMTM 8-mg/day group: One placebo tablet and one 4-mg tablet in the morning, and one placebo tablet and one 4-mg tablet in the evening
- Placebo group: Two "dummy" tablets in the morning, and two "dummy" tablets in the evening; one of which may be replaced by a 4-mg MTC tablet to maintain the treatment blind (the remainder being placebo tablets)

After the completion of the 52-week double-blind treatment period, beginning with supplies dispensed at Visit 7, all subjects will receive open-label LMTM 16 mg/day (two 4-mg tablets in the morning and two 4-mg tablets in the evening) for an additional 52 weeks in the open-label, delayed-start phase of the study.

Tablets may be taken with or without meals. Subjects will be instructed to take each dose of study medication with a full glass of water. Study drug should be swallowed whole and MUST NOT be broken, crushed, chewed, or dissolved in fluids prior to ingestion.

The first dose of study drug (Visit 2) and the morning dose at Visit 3 (after 4 weeks of study drug), Visit 7 (after 52 weeks of study drug), and Visit 10 (after 104 weeks of study drug) will be administered in the clinic. These visits should be scheduled to occur in the morning, with subjects instructed not to take their morning dose at home; subjects will be required to remain in the clinic for at least 4 hours post-dose on each occasion. The time of the dose (and at Visits 3, 7 and 10, also the time of the prior dose taken on the preceding day) will be recorded. Note: the Visit 7 dose must be taken from a newly dispensed Visit 7 open-label treatment study drug kit, after pre-dose assessments have been completed (see Table 10-3 for the pre-dose and post-dose assessments to be performed at Visit 7).

All other doses will be taken on an outpatient basis. The subject/study partner will be asked to establish the times of day that the subject will take the study medication (twice daily), with further inquiry as to whether this will be before or after a meal. They will be asked to adhere, to the best of their capability, to the same administration schedule throughout the study.

Alternative arrangements for dosing and dispensing study drug supplies due to COVID-19 may be permitted and are further described in Section 10.2. Requirements for obtaining subject consent consistent with local and national requirements, maintaining the specified study drug storage conditions, accountability, and compliance monitoring will be addressed and documented.

12.2.1 Maximum Anticipated Dosage

The maximum dosage of study drug will be LMTM 16 mg/day.

Note: Dose reduction is not permitted.

12.2.2 Dose Interruption

Interruption of dosing for up to a maximum of 14 consecutive days may be allowed if the investigator determines this is indicated (*e.g.*, due to an AE or any other reported change in the subject's physical condition in the judgment of the investigator) on a maximum of two occasions. The reason for dose interruption should be recorded in the source documentation. If this is exceeded, study drug would need to be discontinued; however, the subject will be encouraged to continue study participation off-treatment. Subjects who continue in the study off-treatment will not be eligible for a separate EAP.

12.3 Randomization

Subjects will be randomized to one of three study regimens described in Section 12.2: LMTM 16 mg/day, LMTM 8 mg/day, or placebo (4:1:4, at the study level). Randomization will be stratified according to severity (three levels: MMSE 16-19, 20-25, or 26-27) at study level for those randomized to Protocol Version 5.0 and above, prior use of standard AD treatment (two levels: AChEI/memantine or none), and region (two levels: North America or Europe).

Enrollment will be such that subjects are assigned to the MMSE severity groups based on screening MMSE score with a target of approximately 2:3:1 (MMSE 16-19, MMSE 20-25, and MMSE 26-27, respectively) for those randomized to Protocol Version 5.0 and above; to achieve this target, enrollment will be monitored and controlled at the site level for high recruiting sites and capped as needed at the study level.

Randomization, stratification, and enrollment cap requirements will be controlled by a web-based RTSM system.

12.4 Packaging, Labeling, and Storage

Study drug will be packaged, labeled, and distributed to study sites by a designated vendor.

Study drug supplied to subjects will be in individual aluminum blister wallets containing 28 tablets. An appropriate number of blister wallets will be contained within cardboard cartons with sufficient supplies until the next scheduled study visit at which dispensing is planned (see Section 12.5, Dispensing). Additional 28-tablet blister wallets will be included in cartons as needed to allow for delays in visit scheduling (or if original medication is lost or damaged).

Study drug package labels will be compliant 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 as required.

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, an 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 25°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. The packaging protects the study drug from light and moisture.

Subjects and study partners should also be provided with information about required storage conditions. Study drug should be ingested immediately after removal from the blister wallet.

12.5 Dispensing

At the Baseline/Randomization visit (Visit 2), all subjects/study partners will receive a supply of study drug according to their randomization to take home for use until Visit 4 (13 weeks after Baseline). At subsequent drug-dispensing visits, Visits 4, 5, 6, and 7 (13, 26, 39, and 52 weeks after Baseline, respectively) of the double-blind treatment period, as well as Visit 9 (78 weeks after Baseline) of the open-label delayed-start phase, all subjects/study partners will be required to return the complete study drug kit, including all unused study drug and empty packaging, dispensed at the preceding drug-dispensing visit (Visits 2, 4, 5, 6, and 7) before receiving a re-supply of either randomized study drug or open-label treatment, to take home for use until the next scheduled visit. Visit 7 is Baseline/Day 1 of the open-label treatment phase, at which study drug from a newly dispensed Visit 7 open-label study drug kit should be administered after pre-dose assessments (see Table 10-3 for the pre-dose and post-dose assessments to be performed at Visit 7).

Subjects and study partners 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 also be informed that tablets should be swallowed whole and MUST NOT be broken, crushed, chewed, or dissolved in fluids prior to ingestion. If there are swallowing difficulties which prevent taking the medication as instructed, subjects should not be entered into the study. Subjects and study partners should be warned that if the product is not swallowed immediately and is allowed to dissolve in the mouth, it may cause discoloration of teeth and oral mucosa.

In the event of a dose interruption, the subjects and study partners will be provided with updated dosing instructions.

See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

12.6 Compliance

At Visits 2, 4, 5, 6, and 7 during the double-blind treatment period and at Visit 9 during the open-label, delayed-start phase, the number of tablets dispensed to the subject/study partner will be recorded.

At the Week 4 visit (Visit 3) and at each clinic visit thereafter (Visits 4 to 7 during the double-blind treatment period, and Visits 9 and 10 during the open-label, delayed-start phase), the subject/study partner will bring the complete study drug kit, including unused study drug and empty packaging, to the study site. The number of tablets (all tablets remaining in unopened blister wallets plus any tablets that have been removed from the blister wallets) will be counted and recorded by study site staff. Following the compliance check, the complete study drug kit, including unused study drug and empty packaging, should

be retained by the study site, except at Visit 3, when the drug kit should be returned to the subject/study partner.

Subject compliance with prescribed study drug will also be assessed at each clinic visit (Visits 4 to 7 during the double-blind treatment period, and Visits 9 and 10 during the open-label, delayed-start phase) as well as during the telephone contact (Visit 8) by questioning the subject and study partner. 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 study partner.

Any dose interruptions will also be recorded in the source documentation and will be captured in the eCRF.

If during participation in the study, a subject's compliance is determined to be <80% or >120% (taking into consideration any dose interruptions), the subject and study partner should be re-educated 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.

12.7 Study Drug 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. Drug accountability will be recorded in the RTSM system.

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 returned to the Sponsor or designee after study completion according to provided instructions.

12.8 Breaking the Blind for Double-Blind Treatment Period

The randomization list for the double-blind treatment period will be maintained within the RTSM system and in secure locations by individuals who are not directly involved in the conduct of the study. This is limited to the unblinded statistician and unblinded programmer at the statistics vendor, the project management personnel at the drug product manufacturer, and project management/system build personnel at the RTSM system vendor.

The blind for an individual subject should not be broken during conduct of the study except in the case of a medical situation for which it is deemed essential to know which treatment the subject has received during the double-blind treatment period to provide appropriate care. If possible, discussion with the Sponsor should be sought before the blind is broken. In an emergency, the investigator may unblind a specific subject and determine the identity of treatment using the RTSM System. Instructions regarding treatment identification using the RTSM System will be available in separate guidance documents. In such circumstances, the Medical Monitor must be contacted and informed of any unblinding as soon as possible. The date, time, and reason for unblinding must be documented. In case of after-hours emergency

unblinding or in circumstances when the investigator is not available, a 24/7 emergency number (provided on patient cards) will be available to determine the identity of the treatment. This will be achieved *via* a "peek blind" function within the RTSM system, whereby an end user with appropriate access can view the unblinded treatment group on screen. Completion of the peek blind transaction will reinstate the blinded status of the subject.

If a subject is unblinded, study drug will be discontinued and the subject will be followed until resolution or stabilization of the event. He/she will then be discontinued from the study.

Information about any subject for whom an unblinding occurs will be provided to the DSMB by the Sponsor or designee within 15 days (within 7 days in the event of a fatal event). For requirements and unblinding procedures for suspected unexpected serious adverse event (SUSAR) reporting, refer to Section 16.8.

After the last subject completes the 52-week, double-blind, treatment period, that portion of the database will be locked and subject populations determined by blinded data review. The database will then be unblinded for purposes of performing primary and secondary efficacy analyses, and a report will be prepared (see Section 17.9); individual subject treatment assignment will not be revealed either to the subjects or personnel involved in the ongoing management and assessment of subjects in the open-label treatment phase.

13 CONCOMITANT MEDICATIONS AND SUBJECT RESTRICTIONS

All concomitant medications and medications administered within the past 90 days from Screening, as well as a lifetime history (as far as possible) of AChEI and/or memantine use will be recorded at the Screening visit (Visit 1). While in the clinic at Baseline (Visit 2; before and after the first dose of study drug is administered), any medications administered will be recorded. "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 subsequent scheduled visit (*i.e.*, Visits 3 to 7 during the double-blind treatment period, and Visits 8 to 10 during the open-label, delayed-start phase) or upon early termination, any changes to existing concomitant medication and any new concomitant medication will be reviewed and recorded. These must be reviewed by a medical assessor (physician/MD/DO).

Concomitant medications identified at Screening generally should be maintained at a constant dose for the duration of the study if clinically indicated. The investigator should evaluate any changes in the doses 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.

Disallowed treatments and the time windows are listed in Section 28.1.

13.1 AChEI and/or Memantine

Subjects are not to be treated with an AChEI and/or memantine within the 60 days prior to the baseline assessments (inclusive of the baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5). If a subject decides to discontinue AD medication in order to enter

the study, a letter will be sent to his/her primary care physician informing him/her of the subject's decision. The withdrawal / discontinuation of AD medication for study inclusion should not occur until the subject has been confirmed eligible for the study.

If a subject begins an AChEI and/or memantine during the study, LMTM will be discontinued and LMTM will not be made available *via* the EAP. Subjects will be encouraged to continue with scheduled assessments if willing to do so without LMTM. Handling of data for such subjects is described in Section 17.4.11.3.

13.2 Drugs with Serotonergic Potential

Methylene blue (MTC) has been shown to be an inhibitor of monoamine oxidase (MAO) and to be associated with serotonin toxicity in conjunction with other serotonergic drugs (discussed in the Investigator's Brochure). Most cases have followed intravenous administration. Two cases have also been reported, one each following enteral and oral administration; however, neither case provides compelling evidence of MT-induced serotonin toxicity via these routes. There is a theoretical potential for serotonin toxicity following administration of oral LMTM alone, as well as a theoretical possibility of clinically significant drug interaction following co-administration of LMTM with a serotonergic medication. There have been four potential cases in the Phase 3 studies of LMTM; it is difficult to determine from the available information whether any represents a true case of serotonin toxicity.

There is no proscription against the use of serotonergic drugs; however, investigators should evaluate subjects for potential serotonin toxicity. For additional details regarding clinical findings from studies, refer to the Investigator's Brochure. A list of drugs with serotonergic potential will be provided separately.

13.3 CYP and P-gp Substrates

Results of a completed drug-drug interaction study using LMTM 450 mg/day indicate that LMTM is generally 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 an 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 AEs 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 P-gp transporter at concentrations relevant to higher doses (see the Investigator's Brochure for examples of substrates); the extent to which this might occur at LMTM doses of up to 16 mg/day is not known. Co-administration 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 while on study. Any such results obtained from the local laboratory should be entered into the eCRF.

13.4 Drugs Used to Manage Behavioral Disturbance

Subjects may be treated with antipsychotics (other than clozapine) provided they have been used in a stable dose and regimen for at least 90 days prior to Baseline. There should be no

intent to initiate such therapy during the course of the study. Should treatment be initiated, 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, with the exception of prior to ^{18}F-FDG-PET scans to be obtained in subjects with CDR 0.5 at Screening only (the use of sedatives is not permitted within 24 hours prior to ^{18}F-FDG-PET scans). These must not be used within the 12 hours prior to cognitive testing.

13.5 Other Medications

The medical food and other medications listed in Exclusion Criterion No. 19 (see Section 11.2) are specifically prohibited during participation in this study.

Anxiolytics and/or sedatives/hypnotics may be used as sedation for claustrophobia or agitation or to manage excessive movement during MRI scans; however, use of sedatives is not permitted within 24 hours prior to ^{18}F-FDG-PET scans in subjects with CDR 0.5. Regular or occasional benzodiazepines, chloral hydrate, low dose trazodone (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.

13.6 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. There have also been no effects on blood pressure. Nonetheless, as a precaution, subjects and their study partners (caregivers/informants) 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, sausages and salamis; aged 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.

13.7 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/oophorectomy for at least 6 months minimum), either must have undergone

bilateral tubal ligation or occlusion at least 6 months prior to Baseline or must use adequate contraception. Subjects must be competent to use adequate contraception and must agree to continue to maintain adequate contraceptive measures throughout study participation and for at least 4 weeks after the last dose of study drug. Examples of adequate contraception include:

- Use of a barrier method (condom, diaphragm or cervical/vault cap) with spermicidal foam, gel, film, cream, or suppository
- IUD or system
- Oral or long-acting injected or implanted hormonal contraceptives for at least 90 days prior to Baseline
- 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, and post-ovulation methods) and withdrawal are not acceptable methods of birth control.

Serum pregnancy testing will be performed at each scheduled study visit in women of childbearing potential. Such women should be encouraged to return to the clinic in the event of a delayed menstrual period to rule out possible pregnancy, during study conduct and for up to 3 months after the last dose of study drug. Alternative arrangements related to COVID-19 for pregnancy monitoring may be permitted and are described in Section 10.2.

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 10 days after cessation of study treatment. The investigator must provide appropriate counsel to male subjects regarding this issue.

13.8 Folate and Vitamin B_{12}

The manufacturer of the test kits used by the central laboratory for measuring folate and vitamin B_{12} has established the following normal ranges (healthy U.S. males and females aged 18 years and older): 5.9-24.8 ng/mL for folate and 180-914 pg/mL for vitamin B_{12}. However, these values are not applicable for all geographical areas as food in the United States is supplemented with these vitamins. Prior to initiating study drug, subjects with folate levels <4.0 ng/mL or vitamin B_{12} levels <150 pg/mL (*i.e.*, deficient according to WHO Technical Consultation, 2008, 2012), should be supplemented for the duration of the study. Subjects with folate levels <4.0 ng/mL may be entered into the study provided they are supplemented (approximately 1 mg/day folate). Subjects with vitamin B_{12} levels <150 pg/mL should be referred to their primary care physician for evaluation and treatment or the Medical Monitor consulted. There must be a treatment plan in place for any applicable chronic condition. If a condition is diagnosed that the primary care physician believes cannot be reliably or continuously corrected, the subject should be excluded from the study. If review and correction can be achieved within the Screening window, the subject may be entered into the study; otherwise the subject must be re-consented and re-screened after the deficit has been corrected.

14 TERMINATION OF THE STUDY

The Sponsor reserves the right to terminate the study for duly justified reasons in accordance with the national laws. 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

Continued access to investigational study drug may be available as detailed in separate EAP Protocols or by other legally acceptable means.

15 STUDY ASSESSMENTS

15.1 Demographic Data/Medical History

The PI (or SI) must complete the NIA/AA diagnostic interview with the subject and study partner. The NIA/AA criteria should be used as a guide and the information recorded in the subject's medical records. The accuracy of the diagnosis will be confirmed independently by MedAvante-ProPhase (Section 10.5.1.1).

The investigator should collect the following demographic data: age of the subject at informed consent, gender, ethnicity, race, and geographic region.

General baseline characteristics that should be collected are height, weight, creatinine clearance, smoking history, and age at leaving full-time education. Further information indicating years spent in full-time education and its type before the age of 26 years is to be collected (see Section 28.3); also, main occupation during working life is to be provided as indicated.

Disease-specific baseline characteristics that should be collected are time from diagnosis of AD to informed consent (years); amyloid biomarker confirmation; MMSE; CDR; use of an AChEI and/or memantine (previous use or never used and if previous use, drug[s], how long used, when stopped, and reason for stopping); and use of other anti-dementia treatments or medical foods other than AChEIs or memantine. Medical history (including history of lens implantation) will be recorded.

Recently used medications (lifetime use of antidementia medications and within 90 days prior to Screening for other medications) will be recorded at Screening. Concomitantly used medications will be recorded throughout study participation.

15.2 Assessment of Efficacy

15.2.1 Raters

Efficacy instruments (ADAS-cog$_{13}$, ADCS-ADL$_{23}$, MMSE, and CDR) will be completed by assessors/raters who are not involved in the assessment of safety parameters that could result in unblinding. These will be administered using Virgil tablets in the local language. Efficacy assessments should be performed at approximately the same time of day throughout the study for a given subject, to the greatest extent possible. For a given subject, raters should remain constant throughout the study. Investigators and other raters will be trained and approved by

MedAvante-ProPhase; only individuals approved to complete each assessment will receive access via the Virgil System. Rater performance and consistency will be subject to surveillance throughout the study. One to two efficacy raters are required at each site (with back-ups as needed).

Information obtained from study partners providing data from assessments of the subject (*i.e.*, informants) will be appropriately identified to distinguish each informant in the event that a given subject has more than one study partner providing data for analysis (see Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19).

A summary of the efficacy rater allocation and the order of efficacy assessments by visit is provided in Table 15-1.

Table 15-1: Efficacy Rater Allocation and Order of Assessments by Visit

Section 1. Rater Allocation

Assessments are made by suitably trained efficacy raters who are NOT involved in safety assessment.

It is expected that the SAME rater completes the efficacy assessments for a given subject throughout the study.

Raters should carry out assessments according to a specific allocation:

Rater Allocation 1 (Preferred)		**Rater Allocation 2**		**Rater Allocation 3**	
Rater 1	MMSE	Rater 1	MMSE	Rater 1	MMSE
	CDR	Rater 2	CDR		CDR
Rater 2	ADAS-cog$_{13}$		ADAS-cog$_{13}$		ADAS-cog$_{13}$
	ADCS-ADL$_{23}$		ADCS-ADL$_{23}$		ADCS-ADL$_{23}$

Section 2. Order of Assessments

Assessments are to be carried out in the order specified. The order of assessment depends on the visit type.

Visit	**Order**	**Assessment**
Visit 1 Screening	1.	MMSE (Eligibility)
	2.	CDR (Eligibility)
Visit 2 Baseline	1.	ADAS-cog$_{13}$
	2.	ADCS-ADL$_{23}$
Visit 4, 5, 6	1.	ADAS-cog$_{13}$
	2.	ADCS-ADL$_{23}$
Visit 7 or Double-Blind ET (Also Baseline/Day 1 for Open-Label Phase)	1.	ADAS-cog$_{13}$
	2.	ADCS-ADL$_{23}$
	3.	CDR
	4.	MMSE
Visit 9 Open-Label, Delayed-Start	1.	ADAS-cog$_{13}$
	2.	ADCS-ADL$_{23}$
Visit 10 OL-EOT or OL-ET	1.	ADAS-cog$_{13}$
	2.	ADCS-ADL$_{23}$
	3.	CDR
	4.	MMSE

Abbreviations: ADAS-cog$_{13}$ = Alzheimer's Disease Assessment Scale – cognitive subscale (13-item); ADCS-ADL$_{23}$ = Alzheimer's Disease Cooperative Study – Activities of Daily Living (23-item); CDR = Clinical Dementia Rating; ET = early termination; MMSE = Mini-Mental State Examination; OL-EOT = open label end of treatment; OL-ET = open-label early termination

15.2.2 Instruments

The main efficacy instruments include the following: ADAS-cog$_{13}$ (cognition) and ADCS-ADL$_{23}$ (activities of daily living). From these, Composite Scores will be derived as an exploratory endpoint: at least one that is designed to be sensitive to early stages of the disease as well as one that is less/not impacted by COVID-19 (all Composite Scores will be defined in the SAP prior to sign off and database lock/unblinding). The MMSE and CDR (total and sums of boxes) are rated as secondary instruments. All are described briefly below.

For a given subject, the ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ will be completed by Efficacy Raters, in the local language. The Efficacy Raters must not also elicit, record, or enter data

relating to subject safety. The instruments will be administered *via* an electronic Virgil tablet provided by MedAvante-ProPhase, which will also capture an audio recording of the assessment. Alternative arrangements that may be implemented for conducting these instruments for post-Baseline visits directly impacted by COVID-19 are summarized in Section 10.2.

Each time an efficacy instrument is administered, the person administering it will be documented within the electronic form. Efficacy Raters will be trained and their proficiency in administering applicable efficacy instruments will be confirmed. Raters must be approved by MedAvante-ProPhase prior to administering assessments. A unique identifier and password will be provided to each rater that completes and passes the rater training for applicable assessments. Raters must enter their unique password to commence a subject assessment, and again when they upload the data to verify the identity of the rater.

The MMSE and CDR questionnaires and the ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ will be assessed in the native language by an independent Clinical Reviewer at MedAvante-ProPhase by reference to audio recordings of the assessments. The objective of these independent reviews is to ensure raters adhere to the administration and scoring conventions detailed in rater training. Where necessary, raters will be requested to review their performance and confirm the scoring. For eligibility assessments (screening MMSE and CDR), adjudication will occur for any subject where assessments fall outside of the inclusion criteria. Once efficacy assessments are completed and uploaded, raters should review and discuss with MedAvante-ProPhase and receive approval prior to making any proposed change in scoring. A Diagnostic Verification Form (on the Virgil Tablet) completed by the PI (or SI) at Screening will be reviewed by an independent Clinical Reviewer at MedAvante-ProPhase prior to subjects proceeding to imaging assessments to ensure that subjects meet those elements of the inclusion criteria that relate to clinical diagnosis of probable AD or MCI-AD.

Efficacy assessments should be performed at approximately the same time of day throughout the study for a given subject, to the greatest extent possible. The clinical efficacy assessments should be administered before vital signs measurement and blood sample collection. All attempts should be made to have the same rater collect efficacy outcome data at all visits. The key efficacy scales are described below.

15.2.2.1 ADAS-cog

The ADAS was designed to evaluate the severity of cognitive and non-cognitive or behavioral symptoms of AD (Rosen *et al*., 1984). The ADAS-cog is the cognitive subscale of the ADAS, originally proposed with 11 items. The ADAS-cog$_{11}$ consists of tasks that measure memory, orientation, language, and praxis resulting in scores that range from 0 to 70, with higher numbers indicating greater impairment. Two additional items have been added in the ADAS-cog$_{13}$ to provide additional sensitivity to change in cognition at earlier stages of the disease (Mohs *et al*., 1997); these are Delayed Word Recall and Number Cancellation.

As the original ADAS-cog$_{11}$ was used in the earlier Phase 3 studies, that score will be derived from the assessment of the ADAS-cog$_{13}$ for the primary analyses. The Composite Scale described in Section 15.2.2.3 will be based on items selected from the ADAS-cog$_{13}$.

15.2.2.2 ADCS-ADL$_{23}$

The ADCS-ADL$_{23}$ includes 23 items that were derived from a larger set of items describing performance of activities of daily living (ADL) by AD patients (Galasko *et al*., 1997). Of 45 ADL items originally evaluated during the creation of this instrument, the 23 items showed good test-retest reliability over 1 to 2 months (Galasko *et al*., 2005). Scores of these items (ADCS-ADL$_{23}$) were also shown to correlate with MMSE scores of AD patients and to decline over 12 months in at least 20% of AD patients. The Composite Scale described in Section 15.2.2.3 will also be based on selected items from the ADCS-ADL$_{23}$.

15.2.2.3 Composite Scale(s)

The new Composite Scale based on selected items of the ADAS-cog$_{13}$ and the ADCS-ADL$_{23}$ will be analyzed at 9 months and 12 months during the double-blind treatment period to evaluate its usefulness for future studies. It consists of cognitive subdomains (orientation [8], constructional praxis [5], word recall, third trial [10], assessor rating of subject speech [5], and assessor rating of subject comprehension [5]) from the standard ADAS-cog$_{11}$, and functional items (use of telephone [5], keeping appointments [3], cooking and preparation of meals [4], and cleaning dishes [3]) from the standard ADCS-ADL$_{23}$. The selected cognitive items are based on a non-interventional study (Study TRx-GTD-025) examining performance of a range of psychometric tools which decline over 12 months in discriminating subjects with mild AD from age-matched healthy controls, supplemented with functional items identified as declining over 9 months in add-on treatment arms in Study TRx-237-005, independently confirmed by similar data from TRx-237-015, and supported by ADNI data. The items listed provide a maximum possible score of 48 (higher score indicates less impairment).

Additional Composite Endpoints (if any) such as one that is less/not impacted by COVID-19 will be defined in the SAP and signed off prior to database lock and unblinding.

15.2.2.4 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). A modified version of the form, supplied by Psychological Assessment Resources, is used in this study.

The utility of the MMSE as a means of assessing treatment response in AD 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). Further, 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).

15.2.2.5 Clinical Dementia Rating (CDR)

The CDR rates overall severity of dementia (Hughes *et al*., 1982). The CDR has been shown to have good reliability (Morris *et al*., 1997) and validity (Fillenbaum *et al*., 1996) and to correlate with neuropathological status (Morris *et al*., 1988). The scale is sensitive to change over longer time periods (Berg *et al*., 1988).

The CDR is administered using a worksheet and semi-structured interview of a reliable informant (*e.g*., caregiver) followed by an interview of the subject to assess the following six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is scored on a 5-point scale, where 0 = normal, 0.5 = questionable impairment, 1 = mild impairment, 2 = moderate impairment, and 3 = severe impairment. The CDR total score (also sometimes referred to as the CDR global score) is derived from individual ("box") scores for each of the six domains, in accordance with published scoring rules.

15.3 Imaging Assessments and Procedures

15.3.1 General Considerations

PET imaging using an amyloid ligand and brain MRI play a role in this protocol for eligibility determination of the subjects; brain MRI is also used as a secondary efficacy endpoint as well as to confirm a lack of treatment unblinding. ^{18}F-FDG-PET will be performed in subjects with CDR 0.5 at Screening as a secondary efficacy endpoint at all study sites, and will be assessed by an independent nuclear physician who is trained and not otherwise involved in the clinical conduct of the study. The independent central imaging core laboratories will be responsible for image collection and storing, including, with the subject's (and/or LAR's) consent, collection of amyloid PET scan performed either in the course of the study or previously. The total radiation exposure to subjects from the amyloid PET scan procedure (if not performed previously) is estimated to be 9 mSv for a single scan; the limits for radiation exposure from the ^{18}F-FDG-PET scans are discussed in Section 15.3.3.1.

With respect to ^{18}F-FDG-PET and MRI, the core laboratories will be responsible for checking the quality of imaging data, verifying that site anonymization of the images is maintained, pre-processing of images, presenting data to the reader(s) (for MRI eligibility and volumetric evaluations and ^{18}F-FDG-PET), and analyzing the data. Each core laboratory will provide SAS datasets to the data management and statistics facilities for analysis. All systems and processes used for independent and central reads of this trial will be 21 CFR Part 11 compliant.

Before commencement of central evaluations, vendor study-specific documents such as charters and manuals will be developed that will describe in detail the imaging acquisition protocols, image collection procedures, quality check procedures, site training procedures, reader training, image evaluation procedures (central determination of subjects' eligibility, efficacy, and safety), and communication plans.

All sites will be prospectively trained about imaging requirements including scanner requirements, image acquisition, image transfer to the core laboratories, and timelines that are critical for this trial.

See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

15.3.2 Site Selection and Qualification

A site imaging technical evaluation questionnaire will be distributed to potential clinical sites to evaluate their technical and personnel capabilities that will include machine description, availability of phantoms (if applicable), onsite availability of modality-specific technologist or physicist (depending on ^{18}F-FDG-PET or MRI facility), site experience in evaluating brain ^{18}F-FDG-PET and/or MRI, experience in AD and other dementia trials, *etc.* The site's capability of producing quality data that are necessary for this trial will also be evaluated by appropriate phantom imaging and/or review of imaging data of the site's first subject. Continuous monitoring of the quality of imaging data will be performed throughout the trial. Technical details of imaging and quality check procedures will be described in a separate imaging manual.

15.3.3 Imaging Methods for Efficacy

A separate imaging manual will be developed that will outline imaging methods for both ^{18}F-FDG-PET and brain MRI to harmonize image acquisition across the sites. ^{18}F-FDG-PET should be obtained with computerized tomography (CT); brain-dedicated high-resolution PET devices, such as the Siemens High Resolution Research Tomograph system, that use a transmission source for attenuation correction will also be considered from expert sites.

15.3.3.1 ^{18}F-FDG-PET

An ^{18}F-FDG-PET scan will be performed in subjects with CDR 0.5 at Screening using PET/CT or a brain-dedicated high-resolution PET device.

Use of sedatives is <u>not</u> permitted for a period of 24 hours prior to ^{18}F-FDG-PET scans. The subject's fasting (at least 4 to 6 hours) blood glucose level, carried out by the imaging center's standard operating procedures, should be <180 mg/dL (<9.9 mmol/L) in order for the injection to take place. If a screening amyloid scan is acquired under the study, there must be a minimum of 16 hours between the amyloid scan and the ^{18}F-FDG-PET scan due to the half-life of fluorine.

The baseline ^{18}F-FDG-PET scan is to be performed within 42 days before Baseline (Visit 2) only in subjects confirmed to meet all inclusion and exclusion criteria and who have a screening CDR of 0.5. Subjects who were previously treated with an AChEI and/or memantine must have received the last dose at least 60 days prior to this scan. If the initial screening/baseline ^{18}F-FDG-PET is not of sufficient quality to serve as an adequate baseline as determined by the PET Imaging Core Lab, then the scan must be repeated within 42 days before Visit 2 as long as the repeat PET does not cause radiation exposure to the subject that exceeds the limits for the clinical trial (approximately 4.7 mSv for a single scan and 14.1 mSv in total, if a repeat scan is deemed necessary). If the repeat scan cannot be accomplished within the 42-day window before Baseline, the subject must be re-consented and re-screened. For subjects who are re-screened for other reasons and an acceptable ^{18}F-FDG-PET scan was already completed during the original Screening window, the scan does not require repetition.

The Week 52 (end of double-blind treatment) ^{18}F-FDG-PET scan should be performed within ± 14 days of the designated visit. In the event of early termination, if the subject's last ^{18}F-FDG-PET scan was performed ≥30 days prior to that date, the ^{18}F-FDG-PET scan must be done as part of the early termination visit assessments within the time window of the early termination visit (*i.e.*, ± 14 days of the last dose of study drug). The allowable time window for the early termination ^{18}F-FDG-PET scan can be extended to up to 28 days after the last dose of study drug in the double-blind treatment period only with the permission of the Sponsor/Medical Monitor.

Imaging assessments will be made by central readers as follows:

- Brain ^{18}F-FDG-PET will be evaluated for temporal, parietal, and frontal lobe SUVR (normalized with respect to pons and cerebellum) at Baseline and after 52 weeks of double-blind treatment, or upon early termination. Other SUVR ROIs will also be examined including, but not restricted to, inferior temporal gyrus, angular gyrus, anterior and posterior cingulate gyrus, and cerebellum. Change in SUVR parameters will be quantified by the imaging core laboratory.
- SPM preprocessing may be performed, which involves realignment of the dynamic ^{18}F-FDG-PET images, the summation of those images, registration to the MR images in native space, normalization to atlas space, count normalization to a reference region, and smoothing for statistical purposes. After database lock, the voxelwise change in the SUVR maps may be quantified using an SPM approach (models to be characterized in the SAP). Details of analysis conducted will be reported in a separate report.

15.3.3.2 MRI

The screening MRI (to be obtained within the 9-week Screening period [Days -63 to -1] in subjects not receiving an AChEI and/or memantine, or Days -112 to -63 in subjects who begin Screening on an AChEI and/or memantine) will also be used as the baseline for volumetric measurements. The volumetric MRI will be repeated approximately every 13 weeks in the double-blind treatment period after randomization (*i.e.*, after 13, 26, 39, and 52 weeks) as well as after the additional 26 and 52 weeks of open-label treatment. For subjects who terminate early (in either the double-blind treatment or open-label treatment periods), if the subject's last MRI scan was performed <90 days prior to the early termination date, no additional MRI scan is required.

Imaging assessments will be made by central readers as follows:

- Brain MRI will be evaluated for temporal and parietal, whole brain, lateral ventricular, hippocampal, putamen, nucleus accumbens, and nucleus basalis ROI volumes. Change in MRI volumetric parameters will be quantified by the imaging core laboratory.
- T2*-weighted gradient-recalled echo is to be included to enable the detection and quantification of the image hyperintensities.
- SPM preprocessingmay be performed, which involves registration of the MR images to atlas space, segmentation into tissue types (grey, white, cerebral spinal fluid). After database lock, the voxelwise change may be quantified in the segmented MR maps using an SPM approach (models to be characterized in the SAP). Details of analysis conducted will be reported in a separate report.

15.4 Safety Assessments and Procedures

Safety assessments will be performed during Screening to assess subject eligibility for enrollment. All safety assessments will be performed by an independent qualified assessor not involved in efficacy assessments; where specified below, the assessments must be made by a medical assessor (physician/MD/DO). For enrolled subjects, safety assessments will be made at Baseline and at each clinic visit (*i.e.*, after 4, 13, 26, 39, and 52 weeks during the double-blind treatment period as well as after 26 and 52 weeks in the open-label, delayed-start phase); during a telephone contact after 4 weeks in the open-label, delayed-start phase; when needed to follow up on an AE; and upon early termination. See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19. All AEs, vital signs, ECG, clinical laboratory findings, physical and neurological examinations, and ophthalmological examinations (as applicable) will be assessed according to the following:

- AEs will be recorded from the time informed consent is signed and recording will continue throughout the study. The recording and assessment of AEs will be performed by a medical assessor (physician/MD/DO) separate from those administering the efficacy outcome scales (ADAS-cog$_{13}$ and ADCS-ADL$_{23}$ as well as the CDR and MMSE). AEs with an onset after the first dose of study drug or that worsen in intensity or treatment relationship after the first dose will be considered treatment-emergent (and must be reviewed by a medical assessor [physician/MD/DO]). Assessment should continue as needed to follow up an AE to its resolution or acceptable stabilization (including after the last dose of study drug), consistent with the medical judgment of the investigator.
- Blood pressure and pulse will be obtained at Screening, on Day 1 (within 1 hour pre-dose and approximately 2 hours post-dose), and at each clinic visit thereafter or upon early termination. Blood pressure and pulse will be measured after the subject has been in a seated position for at least 5 minutes.
- Height will be measured at Screening only. Body weight will be measured at Screening and at each clinic visit thereafter or upon early termination.
- A 12-lead ECG will be obtained at Screening, with the site judging eligibility based on the local interpretation by a medical assessor (physician/MD/DO).
- TSH, vitamin B$_{12}$, folate, haptoglobin, and G6PD will be measured at Screening; a thyroid panel may be obtained in response to an elevated TSH. Standard clinical laboratory testing, including hematology and blood chemistry, will be performed at Screening and each subsequent clinic visit (or upon early termination). Testing may also be performed at unscheduled visits as necessary to follow-up an AE (see Section 16.11.1 for testing in response to possible hemolytic anemia). All laboratory results are to be reviewed by a medical assessor (physician/MD/DO). Any abnormal laboratory test result from Screening assessments (prior to treatment) is to be added to the subject's medical history, unless deemed clinically significant by the medical assessor (MD/DO) in which case it will be recorded as an AE.
- A blood sample for a serum pregnancy test will be collected from all women of childbearing potential at Screening and at each subsequent clinic visit (or upon early termination).
- Complete physical and neurological assessments will be performed at Screening (see Section 10.5.1.2). Targeted examinations will be performed pre-dose and approximately 3 hours after administration of the first dose of study drug (Visit 2). Thereafter, targeted examinations are to be performed at each subsequent clinic visit (upon early termination). At a minimum, targeted examinations should include heart and lung auscultation and brief neurological assessment guided by any reported

signs/symptoms/AEs (*e.g.*, evaluating subjects for potential serotonin toxicity). These examinations are to be performed by a medical assessor (physician/MD/DO).

- Slit lamp ophthalmological examination of subjects with history of lens implants will be performed by a licensed optometrist, ophthalmologist, or other suitably qualified medical assessor (physician/MD/DO) prior to the first dose of study drug (during the screening procedures or as part of the baseline assessments), at Visit 7, and at Visit 10 / early termination (after completion of efficacy assessments), to assess whether the lens has been discolored during the trial. The slit lamp examination should also be performed if a subject has cataract surgery / lens implantation at any point during his or her study participation (as soon as possible after the surgery), as well as in response to visual complaints if suggestive of lens discoloration.

- At Screening, medications administered within the last 90 days will be recorded, with the exception of anti-dementia medications, where lifetime use (as far as possible) is to be recorded. Changes in concomitant medications and any new concomitant medications will be recorded at all visits, including the telephone contact during the open-label, delayed-start phase, and reviewed by a medical assessor (physician/MD/DO). For antipsychotics, the reason for use should be documented (see Section 13.4).

Further details regarding alternate arrangements for sample collection and shipment that may be implemented due to COVID-19 are described in Section 10.2.

15.5 Other Assessments

15.5.1 MT Concentration

At Visits 2, 3, 7, and 10, blood will be collected on the same day on three occasions for determination of plasma and whole blood MT concentrations (to the extent possible, parent MT/LMT and *N*-desmethyl MT, and after the sample has had acid and heat treatment, total MT); these visits should be scheduled to occur in the morning. Samples will be collected prior to dosing (in the clinic), approximately 1 to 2 hours post-dose, and approximately 4 hours post-dose. The time of the dose given in the clinic and the time of the blood sample will be recorded. In addition, at Visits 3, 7, and 10, the time of the prior dose taken on the preceding day at home will be recorded.

At any early termination visit, if the subject has not yet discontinued study drug and is willing to take a final in-clinic dose, three blood samples will be collected as described above. If, however, the subject has already discontinued study drug or is unwilling to take a final in-clinic dose, a single blood sample only for determination of MT concentrations will be collected, irrespective of the date or time of the last dose of study drug. The date and time of the last dose must be collected and recorded.

For subjects who continue in the study off-treatment (TOTOS group), blood samples will not continue to be collected for the determination of MT concentrations.

Concentration results will not be made available to the study sites during the conduct of the study. However, results for a given subject (if available) may be provided to the DSMB if requested to aid in interpretation of a significant subject safety issue.

The collection, handling, and shipping of blood samples are described below. These are to be analyzed using validated analytical methods.

See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

15.5.1.1 Procedure for Blood Sample Collection

Blood samples (9 mL) will be collected into a suitable vacutainer (9.0 mL), as defined in the laboratory manual. A portion of the whole blood will be centrifuged under refrigeration; the separated plasma will be transferred as defined in the laboratory manual. Both the whole blood aliquot and separated plasma will be stored at *ca* -20°C until shipment to the central laboratory for storage. The complete sample collection and handling procedures to be followed can be found in the laboratory manual.

15.5.1.2 Packaging, Labeling, and Shipping of Blood Samples

The samples must be labeled with unique identification numbers; other labeling information will be detailed in the laboratory manual. Labels must remain intact and indelible throughout processing and frozen storage. Samples will be clearly distinguished from the other bioanalytical samples. Samples are to be transported in insulated containers filled with dry ice. They will be shipped to the central laboratory where they will be stored frozen and shipped in batches to the analytical laboratory.

15.5.2 Genotyping

A single blood sample will be obtained only from subjects who provide legally acceptable informed consent for genotyping evaluation of *ApoE*. The blood sample may be collected any time after eligibility for randomization and continued participation in the study has been confirmed but prior to Visit 7 (end of double-blind treatment period). A volume of approximately 2 mL is to be collected and shipped ambient to the central laboratory (Labcorp) on the day of collection. See Section 10.2 for a summary of alternate arrangements that may be implemented due to COVID-19.

Genotyping results will not be provided to the study sites or to subjects.

16 ADVERSE EVENTS AND SAFETY

16.1 Definition of AEs, Period of Observation, and Recording of AEs

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. AE recording will begin at the time the informed consent form (ICF) is signed. Thereafter, AEs will be ascertained by asking the subject (and study partner) how the subject has been since the last visit. A clinical abnormality, laboratory test value abnormality, or imaging abnormality that the investigator deems to be clinically significant should be recorded as an AE. Any abnormal laboratory test result from Screening assessments (prior to treatment) is to be added to the subject's medical history, unless deemed clinically significant by the medical assessor (MD/DO) in which case it will be reported 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 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.

New AEs reported by a subject after screen failure will not be recorded for the study. Emergent AEs up to the point of screen failure will be followed up to resolution at the discretion of the PI.

16.2 Eliciting Adverse Event Information

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 one or more of the criteria for classification as an SAE or pregnancy requiring immediate notification.

As a part of evaluating subjects for potential AEs, investigators should ask one or more questions directed to evaluating suicidal ideation and behavior. Such questions are to be part of the routine evaluation of AEs at each in-clinic visit, addressed both to subjects and to their study partners.

Follow-up of an AE, even after the final dose of study drug, is required if the AE or its sequelae persist. Follow-up should be continued beyond the scheduled final visit if needed, until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator in his / her medical judgement.

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, the relationship of the AE to study drug, action taken with regard to study drug (none, 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.

16.3 Categorizing 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
  An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

16.4 Investigator's Brochure

The Investigator's Brochure will be used as a guide to assess causality.

16.5 Assessing Causality

The investigator will make a judgement 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

16.6 Categorizing the Outcome

Outcome describes the status of the AE. The investigator will provide information regarding the subject outcome of each AE.

Note: While negligible to slight coloration of urine or feces may occur as a result of study drug, these manifestations should not be recorded as AEs.

Definitions for possible results of an AE outcome are:

- Recovered/resolved: the event has improved or the subject recuperated
- Recovering/resolving: the event is improving
- Not recovered/not resolved: the event has not improved or the subject has not recuperated
- Recovered/resolved with sequelae: the subject recuperated but retained pathological conditions directly resulting from the disease or injury
- Fatal: termination of life as a result of an AE
- Unknown: not known, not observed, not recorded, or refused

16.7 Serious Adverse Event Reporting

An SAE is defined as any event that:

- Results in death (including suicide)
- Is life-threatening
- Results in 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 study partner 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 study partner 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
- Important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of dependency or abuse

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 as to whether the event is study drug-related, *i.e.*, is 'causally' related to the study drug.

All SAEs (including any SAEs associated with COVID-19 that occur during study participation) should be reported to the Sponsor designee, Syneos Health, immediately (and not exceeding 24 hours following knowledge of the event). These should be followed by follow-up reports as soon as possible, whether or not the events are deemed study drug-related.

SAEs must be reported by entering the SAE information in the AE/SAE Section of the eCRF system. The information provided in the eCRF 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

Syneos Health Drug Safety will receive notification of the initial SAE *via* an e-mail alert generated from the eCRF system. In the event of any temporary disruption of the electronic 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 e-mail address:

safetyreporting@syneoshealth.com
Fax: +1 877 464 7787
Address:

Syneos Health
Safety/Pharmacovigilance Department
Farnborough Business Park – 1 Pinehurst Road,
Farnborough,
Hampshire, GU14 7BF
United Kingdom

SAEs that are ongoing should be followed until resolved or stabilized to a level acceptable to the investigator.

SAEs reported after screen failure will not be recorded for the study. Emergent SAEs up to the point of screen failure will be followed up to resolution at the discretion of the PI.

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 Syneos Health. 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 after the study should be communicated in writing to the Sponsor within 24 hours following knowledge of the event.

16.8 Suspected, Unexpected Serious Adverse Reactions and Emerging Safety Information

Suspected, unexpected serious adverse reactions are AEs 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.

All SUSAR reporting, whether determined following unblinding during study conduct or apparent only after the study has ended, 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.

16.9 Malignancies

All cases of malignancies, other than non-melanoma skin cancers, are to be reported to the Sponsor designee, Syneos Health, as outlined above in Section 16.7. Adverse events of malignancies other than non-melanoma skin cancers are to be reported regardless of causality or whether they meet the criteria for serious. These will be reported to Health Canada as Adverse Drug Reactions (ADRs). Expedited reporting in other countries will be consistent with the handling of SUSARs.

16.10 Reporting of 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. An event of a pregnancy will be reported to the Sponsor designee, Syneos Health, immediately (and not exceeding 24 hours following knowledge of the event), and followed by follow-up reports as soon as possible.

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 90 days 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 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 observation of any SAE, if possible. Therefore, regardless of whether or not a pregnancy is actually considered an SAE, a pregnancy form should be completed for all pregnancies.

The information provided in the eCRF should be as complete as possible, but must contain the following minimum fields:

- Subject number
- Confirmation that the subject's contact information is on file at the site
- Date of report of pregnancy
- Expected delivery date

All data related to pregnancy, pregnancy outcome, and SAEs associated with pregnancy should be recorded in a safety database maintained by personnel responsible for pharmacovigilance at Syneos Health. Pregnancies should initially be reported in the Pregnancy Notification Form, Part I and sent by e-mail to the e-mail address provided below. When the outcome of the pregnancy is known, site personnel will complete the Pregnancy Notification Form, Part II and e-mail it to the same e-mail address noted below.

Syneos Health Drug Safety will receive notification of the pregnancy *via* an e-mail alert generated from the eCRF system. In the event of any temporary disruption of the electronic system, site personnel will scan and e-mail a written report within 24 hours to the following e-mail address:

safetyreporting@syneoshealth.com
Fax: +1 877 464 7787
Address:

Syneos Health
Safety/Pharmacovigilance Department
Farnborough Business Park – 1 Pinehurst Road,
Farnborough,
Hampshire, GU14 7BF
United Kingdom

16.11 Guidance for the Handling of Adverse Events of Special Interest and Selected Test Abnormalities

The pre-specified AESIs in this study are hemolytic anemia and lens discoloration. Guidelines for the monitoring and management of the AESIs are given below along with selected test abnormalities. Clinical circumstances requiring additional evaluation of a subject and/or potential interruption or discontinuation of study drug are presented.

16.11.1 Hemolytic Anemia

When there are signs and/or symptoms of clinically evident hemolytic anemia, dosing should be interrupted. A hemolysis panel should be considered (including complete blood count with differential, reticulocyte count [including absolute reticulocyte number], lactate dehydrogenase (LDH), direct and indirect bilirubin, and haptoglobin). See Section 13.8 for guidance on vitamin B_{12}. If confirmed as related to study drug, dosing should be discontinued.

Signs of possible treatment-emergent hemolytic anemia include:
- Decrease by 20% from screening in red blood cell (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 lower haptoglobin than screening

16.11.2 Lens Discoloration

For subjects with a history of lens implants, ophthalmological examinations (slit lamp examinations) will be performed prior to the first dose of study drug (during Screening or as part of Baseline assessments), at Visit 7, and at Visit 10 / early termination as scheduled procedures. Subjects and investigators are informed of the potential for lens discoloration in the Informed Consent Form and Investigator's Brochure, respectively. If a lens discoloration is identified by slit lamp examination, this is to be recorded as an AESI in the AE eCRF; however, no specific action is required for the study drug. Slit lamp examination should also be performed if a subject has cataract surgery / lens implantation at any point during his or her study participation (as soon as possible after the surgery), as well as in response to visual complaints if suggestive of lens discoloration.

16.11.3 Other Safety Reasons Requiring Discontinuation of Study Drug

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

For any other safety concerns that may arise during treatment, the Medical Monitor or 24-hour medical contact number (see Section 4) should be contacted to discuss possible discontinuation of study drug.

16.12 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 Independent Ethics Committee/Institutional Review Board (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, IEC/IRB, and DSMB 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.

17 STATISTICAL ANALYSIS

A SAP will be finalized and signed off prior to database lock and unblinding. The SAP will provide details about the planned analysis. A brief overview of the plans for the primary analysis and selected secondary and exploratory analyses is given in the following sections. Specific ROI and SPM techniques and comparisons to previous Phase 3 data or external databases as well as Population PK analyses will be described in the SAP or a corresponding additional SAP where necessary; the SAP will provide details.

Changes to the planned analysis will be documented in the SAP prior to database lock and unblinding. Deviations from the SAP (if any) will be noted in the clinical study report.

The primary target of estimation is the difference in ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ over 52 weeks in subjects receiving the LMTM dose of 16 mg/day as compared to placebo.

The primary efficacy analyses for FDA will be performed on the Efficacy Modified Intent-to-Treat (E-MITT) which will include all randomized subjects who took at least one dose of study drug and have a baseline and a valid post-baseline efficacy assessment, and for EMA on the Intent-to-Treat (ITT) population with conservative assumptions about disease progression made for subjects who have missing post-baseline assessments. Subjects will be analyzed in the treatment group and according to the stratification variables to which they were randomized.

Changes from baseline to Week 52 on the co-primary efficacy endpoints and other modalities with repeated measures such as MRI will be analyzed using a linear mixed model for repeated measures with unstructured covariance matrix (this assumption about the covariance matrix might be relaxed if the model does not converge; the SAP will provide details). The linear mixed model will contain fixed effects for time, treatment, and a treatment-by-time interaction; additionally, the baseline value of the corresponding endpoint will be included as a covariate and the randomization stratification variables of prior usage of AChEIs and/or

memantine, MMSE split (16-19, 20-25 or 26-27) as determined at Screening, and region will be included as fixed effects in the model. ^{18}F-FDG-PET and other modalities with only one planned post-baseline assessment will be analyzed using an ANCOVA; the covariates for this model will be adjusted accordingly by removing terms with time.

Several of the analyses described below will be performed separately for the comparisons of LMTM 16 mg/day with placebo and 8 mg/day with placebo. As only the LMTM 16 mg/day and placebo comparison is a primary endpoint, the models will use two treatment levels dependent on the comparison of interest. Several analyses provided for the comparisons of LMTM 16 mg/day and placebo will be repeated for the LMTM 8 mg/day *versus* placebo group as secondary or exploratory/sensitivity endpoints. The SAP will detail which analyses are performed for which treatment groups, and in which cases the LMTM 8 mg/day with placebo comparisons will be provided for which sensitivity, subgroup, and exploratory analyses.

Further analysis on selected primary and secondary endpoints will be provided for pooled LMTM 16 mg/day and 8 mg/day arms compared to placebo. The analysis models will be identical to the 16 mg/day *versus* placebo with the exception of pooled treatment arms. The SAP will detail which analyses are repeated for the pooled 16 mg/day and 8 mg/day arms.

More details about the exact contrast statements used for these tests as well as further sensitivity analyses, additional analyses of the primary variables (such as responder analyses and subgroup analyses), and the analyses of the secondary and exploratory endpoints are described in the subsections below as well as in the SAP.

"Late" starters, *i.e.*, subjects originally randomized to placebo, will be compared to "early" starters, *i.e.*, those originally randomized to LMTM 16 mg/day or 8 mg/day (pooled, and individually for both groups as a sensitivity analysis). The last assessment prior to start of open-label treatment (pre-dose at Visit 7) will serve as the baseline assessment for these comparisons. The analyses will be based on a similar linear mixed model for repeated measures with the aim to investigate whether there is a difference in change in primary and MRI imaging endpoints dependent on LMTM treatment history. The comparison will be implemented through a non-inferiority test.

The non-inferiority margin for the primary endpoint of ADAS-cog$_{11}$ will be 2 units, motivated by the fact that these 2 units are small compared to the estimated treatment effect of > 5 units (~40% of this effect size). Margins for other endpoints which are exploratory to support a disease modifying argument will be defined in the SAP. The results will also be presented with the Visit 2 Baseline as baseline and treatment visits Week 26 and Week 52 in the open-label, delayed-start phase as Week 78 and Week 104.

17.1 Efficacy Endpoints

17.1.1 Primary Efficacy Endpoints for Double-Blind Treatment Period

- ADAS-cog$_{11}$ (LMTM 16 mg/day *versus* placebo)
- ADCS-ADL$_{23}$ (LMTM 16 mg/day *versus* placebo)

17.1.2 Secondary Efficacy Endpoints for Double-Blind Treatment Period

- Annualized rate of whole brain atrophy on brain MRI using BSI (LMTM 16 mg/day *versus* placebo)
- Difference in temporal lobe ^{18}F-FDG-PET change in SUVR normalized to pons in subjects with CDR 0.5 at Screening (LMTM 16 mg/day *versus* placebo, and LMTM 8 mg/day *versus* placebo), if a sufficient number of subjects have provided data as specified in the SAP
- ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ (LMTM 8 mg/day *versus* placebo)
- Annualized rate of temporal and parietal lobe atrophy on brain MRI using BSI (LMTM 16 mg/day *versus* placebo, and LMTM 8 mg/day *versus* placebo)

17.1.3 Secondary Endpoint for Open-Label, Delayed-Start Phase

- Difference in disease progression on the co-primary clinical endpoints and the MRI imaging endpoint for subjects who started treatment in the double-blind treatment phase and those who started treatment in the open-label, delayed-start phase (referred to as "early" and "late" LMTM starters, respectively)
    - Only ADAS-cog$_{11}$ will serve as a secondary endpoint; ADCS-ADL$_{23}$ and other imaging endpoints are exploratory with the aim to be directionally supportive

17.2 Number of Subjects and Sample Size Calculation

The target number of subjects is approximately 450 subjects enrolled in Protocol Version 5.0 and above, randomized in a ratio of 4:1:4 (at the study level) to the LMTM 16 mg/day (200 subjects), LMTM 8 mg/day (50 subjects) and placebo (200 subjects) groups; total enrollment is approximately 500 subjects. Subjects will be assigned to the MMSE severity groups based on screening MMSE score with a target of approximately 2:3:1 (MMSE 16-19, MMSE 20-25, MMSE 26-27 respectively) for those randomized to Protocol Version 5.0 and above. Subjects who drop out after randomization will not be replaced.

Sample size estimations to achieve 90% power (two-sided alpha = 0.05) to detect a difference between LMTM 16 mg/day and placebo (containing intermittent MTC as a urinary discolorant), the primary treatment group comparison in the double-blind treatment period, have been performed for the two co-primary clinical endpoints. These assume a withdrawal rate of 20% to 25% over 52 weeks. The study sample size of approximately 450 subjects (approximately 200 subjects in each treatment group, with a further 50 subjects for secondary analyses of an LMTM 8-mg/day group) is based on the ADCS-ADL$_{23}$ as a larger sample size is required to achieve the target power.

Based on an estimated decline in ADCS-ADL$_{23}$ over 52 weeks in the control arm of 7.7 units with an estimated SD of 8.5 units, the study will have >90% power (two-sided alpha=0.05) to detect a reduction in decline of 3.4 units or more. The 3.4 units are motivated by an estimated treatment effect of 5.0 ± 1.6 (mean ± standard error) units in the pooled studies TRx-237-005/ TRx-237-015.

Based on an estimated decline in ADAS-cog$_{11}$ over 52 weeks based on pooled information from Studies TRx-237-005 / TRx-237-015 in the control arm of 6.5 units with an estimated SD of 5.9 units, 200 subjects per treatment arm provide >90% power (two-sided alpha=0.05) to detect a reduction in decline of 2.6 units or more. The 2.6 units represent a conservative value as the estimated treatment effect based on pooled Studies TRx-237-005 / TRx-237-015 is 5.2 ± 1.3 (mean ± standard error) units.

With 200 subjects randomized to the primary comparison in the double-blind treatment period under Protocol Version 5.0 and above, 160 to 170 subjects per arm will enter the open-label, delayed-start phase assuming the drop-out rates mentioned above. Assuming a further 10% drop out in the delayed-start phase, the key secondary analysis to demonstrate disease modification by comparing early to late starters with a noninferiority margin of -2 ADAS-cog$_{11}$ units has approximately 80% power.

Subjects who withdraw from treatment will be encouraged to stay in the study and continue their assessments off-treatment. Subjects' withdrawal rates will be closely monitored in a blinded fashion, to monitor if sample size calculations remain correct.

17.3 Analysis Populations

The following subject populations will be used for the statistical analyses; all definitions reply on the treatment period in the double-blind phase excluding open-label assessments (population definitions will be used for the delayed-start analyses without any modifications):

- Intent-to-Treat (ITT) population will include all randomized subjects. Three subsets are defined as follows:
  - The Efficacy Modified Intent-to-Treat (E-MITT) population will include all randomized subjects who take at least one dose of the study drug and have a baseline and at least one valid post-baseline efficacy assessment in the treatment period (prior to any potential follow-up assessment).
  - An MRI Imaging Modified Intent-to-Treat (MI-MITT) population will include all randomized subjects who took at least one dose of study drug and have at least one valid baseline and at least one valid post-baseline volumetric MRI.
  - The Imaging Modified Intent-to-Treat population (PI-MITT) for ^{18}F-FDG-PET will include all randomized subjects with screening CDR 0.5 who took at least one dose of study drug and have a baseline and a valid post-baseline SUVR assessment.
- The Per Protocol (PP) population will include all subjects who are in the E-MITT and MI-MITT populations and who do not have any PP exclusionary protocol deviations or intercurrent medical events that could confound the interpretations. PP exclusionary deviations, irrespective of their classification as minor/major, and intercurrent medical events will be determined prior to treatment unblinding.
- The Safety population will include all randomized subjects who take at least one dose of study drug.

Due to the introduction of MTC spiking in the placebo arm with Protocol Version 5.0, the respective MITT populations will be restricted to subjects randomized to Protocol Versions 5.0 and above for the primary and key secondary analyses as per the SAP. The full MITT populations will be analyzed for these as a sensitivity analysis. Details will be provided in the SAP. For the ITT, respective restrictions will be applied as part of the first step in the EMA analysis (see Section 17.4.3).

17.4 Clinical Efficacy and Imaging Analysis

The various analyses planned in the study are outlined below. The SAP will be more specific and clearly state which analysis and which model will be applied to what type of data.

Subjects will be analyzed in the treatment group and stratification to which they were randomized unless stated otherwise in potential sensitivity analyses. For safety analyses, treatment assignment will be based on the treatment actually received. If a subject receives an incorrect treatment transiently, he/she will be assigned to the predominant treatment group (*i.e.,* the treatment group for which he/she received the greatest number of doses).

For E-MITT, MI-MITT, and PI-MITT analyses, only valid data will be included in the primary and secondary analyses. In subjects who have initiated treatment with an AChEI and/or memantine, assessments made after initiation of such treatment are not considered valid as they could confound the interpretation of the results and will be excluded. Such subjects and affected assessments will be identified prior to unblinding. Sensitivity analyses will be provided for the primary and selected secondary analyses including all data.

The primary and key secondary analyses will be further restricted by excluding subjects who were randomized under protocols prior to Protocol Version 5.0; this is due to the spiking with MTC in the placebo arm. Sensitivity analyses not applying this restriction will be provided.

Various imaging and clinical efficacy analyses will be handled differently for the FDA and European Medicines Agency (EMA). Summary statistics will be tabulated by visit and treatment group using observed data. ITT, E-MITT, MI-MITT, and PI-MITT population-weighted least squares means (LSM), unless otherwise stated, treatment differences, and 95% confidence intervals will also be included; the population will be determined by the corresponding model, dependent on whether the endpoint is an imaging endpoint or an efficacy endpoint. Where requested, annualized rates will be estimated based on the population-weighted LSM.

All models will include the randomization stratification variables as covariates unless otherwise stated. If the models do not converge because of too few observations for a given randomization stratification variable, the corresponding variable/variables will be removed from the model.

Various 8 mg/day analyses might be omitted if not promising based on the secondary or other analyses. These and corresponding thresholds will be defined in the SAP. In the specification of various analyses below, they are included for sake of completeness and as they might be performed.

Data listings will include all observed data for the primary and secondary endpoints.

17.4.1 Hypothesis

There are two co-primary efficacy endpoints for this trial: Baseline adjusted decline in ADAS-cog$_{11}$ and Baseline adjusted decline in ADCS-ADL$_{23}$ from Baseline at Week 52. Both

co-primary endpoints must reach significance based on the use of a two-sided test at the alpha=0.05 level of significance for LMTM to be designated as superior to placebo.

The primary analysis will be performed using the E-MITT/ITT populations as defined in Section 17.3, with the additional exclusions mentioned in Sections 17.3 and 17.4.

The global null hypotheses are as follows:

H_{01}: There is no difference between the LMTM 16 mg/day and placebo groups change in ADAS-cog_{11} from baseline to Week 52

and

H_{02}: There is no difference between the LMTM 16 mg/day and placebo groups change in ADCS-ADL_{23} from baseline to Week 52

The global null versus alternative primary efficacy hypotheses is a Union-Intersection Test which requires both co-primary endpoints to meet statistical significance at the 5% two-sided level of significance for the global null hypothesis to be rejected. Additional details will be provided in the SAP.

All secondary analyses have the same underlying null hypothesis that there is no difference in change from baseline in the quantity of interest between the LMTM 16-mg/day group, or the LMTM 8-mg/day group, and the placebo group. For association analyses, the null hypothesis is that there is no association between the variables of interest.

17.4.2 MITT (FDA) Analysis

The FDA analyses will be based on the E-MITT, MI-MITT, or PI-MITT population, with the additional restriction as per Sections 17.3 and 17.4, depending on endpoint, and will include all available valid data for each subject. No data will be imputed (unless specified in selected sensitivity/exploratory analyses). Sensitivity analyses for selected endpoints will be provided where all assessments are included.

Change from baseline in the respective efficacy/imaging parameter will be analyzed using a restricted maximum likelihood-based repeated measures linear mixed model. The model will include fixed effects for treatment group (two levels dependent on the comparison, three levels for sensitivity); nominal time; the treatment group-by-time interaction; and covariates for categorical severity, region, and prior use of AChEIs and/or memantine. The corresponding baseline parameter will be included as a covariate (continuous) as well (certain covariates in the model might be dropped if the model does not converge; see SAP for details). An unstructured covariance model will be used. The Kenward and Roger method of calculating the denominator degrees of freedom will be used for the tests of fixed effects. Treatment comparisons will be based on the modeled change from baseline at Week 52.

If there is only one scheduled post-baseline imaging or efficacy assessment, the model will be replaced by a simple linear model with fixed effects for treatment group and the randomization stratification variables and with the baseline value of the corresponding endpoint as a covariate.

For annualized rate of atrophy or decline, time will be used as a continuous variable supported by corresponding contrast analyses of time as a nominal variable.

17.4.3 ITT (EMA) Analysis

The EMA analyses will be based on the ITT population, regardless of endpoint.

Change from baseline in the respective efficacy/imaging parameter will be analyzed using a restricted maximum likelihood-based repeated measures linear mixed model or, in the case of only one scheduled post-baseline imaging or efficacy assessment, using a simple linear model (the models used are described above in Section 17.4.2). This analysis will be restricted to scheduled, on-treatment visits for subjects randomized under Protocol Version 5.0 and above (a sensitivity will be provided including data from subjects of all protocol versions). An on-treatment visit is a visit where a subject was on investigational product and not on any AChEI and/or memantine.

This provides the on-treatment effect, E, at the final time point. For each subject who withdrew from the study, the decision will be made as part of the blinded data review meeting as to whether the withdrawal was potentially treatment-related. For potentially treatment-related drop-outs, the fraction of subjects randomized to active treatment who withdrew at a given time point will be calculated. If a subject is determined to have withdrawn for non-treatment-related reasons, no further adjustment will be made as the mixed effects model correctly accounts for subjects who are missing at random.

In this intervention effect analysis, subjects who withdraw for potential treatment-related reasons are assumed to retain 100% of the treatment effect they had attained up to the point of withdrawal but do not continue to benefit from treatment afterwards. This corresponds to the estimate I = (E0*w0 + E13*w13 + E26*w26 + E39*w39) + E52*(1-w0-w13-w26-w39), where E13 is the treatment effect at week 13. W13 is defined as the fraction of subjects who withdrew for potentially treatment-related reasons, have a non-missing imaging/efficacy parameter at Week 13, and do not have any on-treatment assessments at any scheduled visit subsequent to Week 13. The other wxx are defined likewise. Wxx is calculated for the active treatment group only. W0 refers to subjects who had no measurement taken after the baseline measurement and thus E0 is zero. This analysis will be implemented as a contrast statement and the estimate I will be reported as the intervention effect.

Annualized rate of atrophy or decline will also be analyzed in a similar fashion.

17.4.4 Estimands

In general, definition of estimands in the analysis of clinical trials become increasingly important. The SAP will specify estimands to provide a more comprehensive assessment of the performance and efficacy of the drug accounting for various factors (importantly, drop-outs).

In line with the ITT analysis of Section 17.4.3, the primary estimand therefore is designed to answer the question on the treatment effect of the LMTM dose of 16 mg/day as monotherapy *versus* placebo (occasional 4 mg/day MTC) in the targeted population of subjects with probable AD and MCI-AD at Week 52, regardless of study drug discontinuation, based on the two co-primary endpoints.

This estimand is constructed in line with ICH E9 (R1) addendum. The five components defining the estimand of interest are listed below:

A. Treatment:	52 weeks of LMTM 16 mg/day or matching placebo (4 mg/day MTC) as monotherapy, regardless of adherence.
B. Population:	Subjects with probable AD or MCI-AD as described by the inclusion and exclusion criteria, randomized under Protocol Version 5.0 or higher.
C. Patient-level outcomes / variables:	Change from Baseline of the ADAS-cog_{11} and ADCS-ADL_{23} at Week 52 as co-primary outcomes.
D. Population-level summary:	Population-weighted least squares mean difference.
E. Intercurrent Events (ICE):	The following ICE have been identified which could prevent measurement of the primary outcome or change the interpretation of the measured primary outcome: 1. Withdrawal from study before completion of 52-week treatment period for non-treatment related reason 2. Withdrawal from study before completion of 52-week treatment period for treatment-related reason 3. Initiation of AChEI and/or memantine 4. Study treatment discontinuation for any reason other than initiation of AChEI and/or memantine (including discontinuation by the investigator if he/she judges that treatment is no longer appropriate, if the subject's clinical condition is worsening or for an AE, or due to study drug dose interruption that is longer / more frequent than specified in ICE #5 below) (see Section 17.4.11.4 regarding analysis of the TOTOS group) 5. A dose interruption for more than 14 consecutive days or more than two occasions of dose interruptions up to a maximum of 14 consecutive days 6. Intercurrent illnesses, or initiation of medical food or medications not allowed by protocol (which will be identified during the blinded data review meeting) 7. Study treatment non-compliance, defined as <80% or >120% taking into consideration any dose interruptions (if this cannot be estimated, it does not result automatically in a non-compliance) 8. Death before completion of 52-week treatment period 9. COVID-19 infection 10. Death due to COVID-19

The handling of ICEs is described as follows:

- **Events 1** will be handled according to a hypothetical strategy as if subjects have stayed on treatment; in a sensitivity analysis, all these subject withdrawals are assumed to be potentially treatment-related, which are then handled using the treatment policy approach from ICE #2.
- **Events 2** will be handled using a treatment policy approach reflecting Copy Incremental from Reference strategy (using data after occurrence of the ICE). Subjects who withdraw for treatment-related reasons are assumed to retain 100% of the treatment effect they had attained up to the point of withdrawal but do not continue to benefit from treatment afterwards, *i.e.*, assuming that the clinical course post ICE for either treatment group follows the placebo group. This corresponds to the estimate I = (E0*w0 + E13*w13 + E26*w26 + E39*w39) + E52*(1-w0-w13-w26-w39), where, for instance, *E13* is the treatment effect at Week 13 and *W13* is defined as the fraction of subjects who withdrew for a potential treatment-related reason, have a non-missing efficacy parameter at Week 13, and do not

have any on-treatment assessments at any scheduled visit subsequent to Week 13. The fractions are calculated within the active treatment group. *W0* refers to subjects who had no measurement taken after the baseline measurement and thus *E0* is zero. The estimate *I* will be reported as the intervention effect and will be calculated using a contrast on the LSM (see Section 17.4.3).

  - Two sensitivity analyses will be run using hypothetical strategies (not using data after occurrence of the ICE), one by imputing missing data for both treatment groups based on data seen in the placebo group, and one by imputing missing data for each treatment group based on data seen in their own group.
  - In another sensitivity analysis, the alternative assumption will be investigated, that the subjects withdrawing from treatment for treatment-related reasons do not retain any treatment effect after Baseline; the intervention effect *I* in this case is I=E*(1-w), where *E* is the treatment effect at Week 52 and *w* is the fraction of subjects within the active treatment group who withdraw for a potential treatment-related reason up to Week 52.

- **Events 3** will be handled according to the original randomized treatment group assuming they stopped treatment and did not start AChEI and/or memantine (analyzed same as ICE #2), not using data after occurrence of the ICE.
- **Events 4** will be handled according to a treatment policy strategy, using data after occurrence of the ICE. In addition, for EMA, the analysis will be carried out using the strategy as described for ICE #2 (not using data after occurrence of the ICE).
- **Events 5, 6, and 7** will be handled according to a treatment policy approach, using all data (also after occurrence of respective ICE).
- **Events 8** will be handled as treatment failure. If the subject dies prior to Week 52, the population average in decline within the placebo arm will be imputed.
- **Events 9 and 10** will be handled with a hypothetical strategy assuming COVID-19 disease would not have happened, not using data after occurrence of the ICE.

17.4.5 Handling of Missing and Incomplete Data

Missing imaging data will not be imputed; it will be assumed that the data are close to missing at random after accounting for the terms in the model for all analyses other than those described for the EMA ITT-based analyses. The EMA ITT-based analyses treat subjects for whom assessments are missing from a certain point onwards as having no treatment benefit thereafter; while the primary analysis assumes that they retained the treatment effect that they had at the point of drop-out, a sensitivity analysis treats them as having lost all treatment effect. While the primary analysis assumes that some of subjects' data might be missing at random for drop-outs, a sensitivity analysis assumes all withdrawals were treatment related. Various other sensitivity analyses, including multiple imputation, time to event, and responder analyses, will be provided to investigate the robustness of the primary and secondary analyses (see respective sections below for more detail; drop-outs are treated as non-responders or having an event of decline in these models).

Efficacy data missing for an entire outcome scale or for the majority of the scale will not be imputed unless stated otherwise. Instead, it will be assumed that the data are close to missing at random after accounting for the terms in the model. However, missing items within a subdomain or scale may be upscaled if some items of the subdomain or scale are present; the SAP will provide details of the handling of partial data for the efficacy endpoints for each scale. As automated data capturing devices are used for all efficacy assessments, the risk of missing data of this type is low. For imaging data, this type of missing data is impossible and consequently they are not subject to upscaling either.

17.4.6 Open-Label, Delayed-Start Analysis

"Late" starters, *i.e.*, subjects originally randomized to placebo, will be compared to "early" starters, *i.e.*, those originally randomized to LMTM 16 mg/day or 8 mg/day (pooled, and individually for both groups as a sensitivity analysis). The last assessment prior to start of open-label treatment (pre-dose at Visit 7) will serve as the baseline assessment for these comparisons. The analyses will be based on a similar linear mixed model for repeated measures as outlined for the FDA/EMA primary analysis (see model specification in Sections 17.4.2 and 17.4.3) with the aim to investigate whether there is a difference in change in primary and MRI imaging endpoints dependent on LMTM treatment history (certain covariates in the model might be dropped if the model does not converge; see SAP for details).

The comparison will be implemented through a non-inferiority test. The non-inferiority margin for the primary endpoint of ADAS-cog$_{11}$ will be 2 units, motivated by the fact that these 2 units are small compared to the estimated treatment effect of > 5 units (~40% of this effect size). Margins for other endpoints which are exploratory to support a disease modifying argument will be defined in the SAP.

The results will also be presented with the Visit 2 Baseline as baseline, and treatment visits Week 26 and Week 52 in the open-label, delayed-start phase as Week 78 and Week 104.

17.4.7 Dose Response Analyses

Various dose response analyses will be performed. The primary endpoints and key secondary endpoints will be analyzed using FDA/EMA primary analyses (see model specification in Sections 17.4.2 and 17.4.3) to show the functional relationship of dose and response on the various endpoints as change from baseline to Week 52. This analysis will also be provided split by MMSE groups as randomized. For CDR 0.5 subjects, the listed secondary analysis of ^{18}F-FDG-PET will be translated into a dose response curve as well.

Several of these dose response analyses are contingent on primary analyses and key secondary analyses showing a significant effect as outlined in the SAP.

17.4.8 Responder Analyses

Responder analyses will be conducted for the primary and selected secondary endpoints by dichotomizing each endpoint.

For the corresponding imaging/efficacy parameter, a responder will be defined as a subject whose change from baseline is less than or equal to a threshold "T" defined as follows (these analyses will be done separately for the LMTM 16-mg/day *versus* placebo and LMTM 8-mg/day *versus* placebo groups):

- Let LSM1 be the LSM of change from baseline for the placebo group from the respective endpoint analysis
- Let LSM2 be the LSM of change from baseline for the LMTM group from the respective endpoint analysis
- Then T = (LSM1 + LSM2)/2

Thresholds will be chosen based on the E-MITT, MI-MITT, or PI-MITT population-weighted LSMs from the respective model. Subjects who do not have a final assessment will be classified as non-responders.

For each separate LMTM group comparison *versus* placebo, the proportions of responders will be compared using the Cochran-Mantel-Haenszel test, adjusting for the randomization strata. Odds ratios and 95% confidence intervals will be presented.

For each of these analyses, if there is a significant effect of treatment on an imaging as well as another imaging or clinical efficacy parameter, the association between responders across these parameters at Week 52 will be assessed by using Pearson's chi-square test to analyze the resulting 2 × 2 table. The number and percent of subjects in each cell of the 2 × 2 table will be tabulated along with the p-value from the Pearson's chi-square test.

Responder analyses will be used to investigate associations between various endpoints. Correlation analyses will complement or replace responder-based analyses of associations in some cases.

17.4.9 Time-to-Event Analyses

Time-to-Event/Time-to-Decline analyses will be performed for a selected subset of endpoints as repeated measurements over time are needed. The distributions of time-to-decline in the key parameters will be summarized using the Kaplan-Meier method, with onset of decline defined as the first of two consecutive measurements that are worse than the baseline score, allowing for a certain margin which will be predefined in the SAP prior to database lock and unblinding; typical margins for the two primary endpoints are 1 unit. If there is no onset of decline prior to Week 52 and if Week 52 has a marked worsening as specified in the SAP for a given subject, an onset of decline will be triggered at Week 52 for that subject. Time-to-decline will be calculated as date of onset of decline – date of randomization + 1.

The time-to-decline analyses are based on visit window. One measurement per visit window is selected, including off-treatment measurements. Subjects without any decline will be censored at the date of last assessment, but if a subject missed the scheduled visit, the subject is censored at the target day of the scheduled visit. The analysis will be run for the ITT population.

Any missing efficacy/imaging value for a scheduled visit will be treated as a worsening from baseline, for that visit. Because of this convention for missing values, it is possible that the first of two consecutive measurements that are worse than the baseline score by the defined amount occurs at a missed visit. In that case, since there is no date associated with the missed visit, the time-to-decline will be calculated based on the scheduled date of the missing visit.

The Cox proportional hazards regression model with effects for treatment group (two or three levels depending on whether primary or sensitivity comparison) and the randomization stratification variables will be used to compare LMTM 8 mg/day *versus* placebo (and LMTM 16 mg/day *versus* placebo, respectively) by way of Hazard Ratio, 95% confidence interval, and p-value (for alpha 0.05). A graph of the Kaplan-Meier estimates will be provided.

There will also be versions of this analysis using actual dates.

17.4.10 Subgroup Analyses

For selected endpoints and treatment groups, subgroup analyses will be provided. These are implemented by restricting a given analysis to the corresponding subgroup or by adding interaction terms in the model with appropriate contrast statements as described in the SAP.

Subgroup analyses will be performed for the primary endpoints and selected secondary endpoints based on the E-MITT/MI-MITT/PI-MITT populations (FDA analysis) by repeating the analysis as described for the primary and secondary endpoints restricted to the subgroup. If the subgroup consists of less than 10% of subjects in observed cases, only summary statistics will be presented. The subject characteristics that will be included in this type of analysis are the following:

- Baseline diagnosis (probable AD and MCI-AD)
- MMSE (16-19, 20-25, and 26-27)
- CDR (0.5 and CDR 1 or 2 pooled)
- AChEI/memantine use (prior use and never used)
- Age group (<75 years and ≥75 years)
- Gender (male and female)
- Race (white and non-white)
- Geographic region (North America and Europe)

17.4.11 Sensitivity Analyses

Sensitivity analyses for key primary as well as secondary parameters will be conducted to assess the impact of missing data and to assess alternative models.

See Section 10.2.3 for a summary of the modifications regarding sensitivity analyses to be implemented due to COVID-19. The SAP will be more specific about the analyses conducted, including those related to COVID-19 impact assessment and will follow available regulatory guidelines.

17.4.11.1 Mis-stratification Analysis

If there are more than 5% of subjects who have been mis-stratified, then the primary analyses will be repeated using the actual status at randomization.

17.4.11.2 All Protocol Version Analysis

As outlined in Sections 17.3 and 17.4, the MITT and on-treatment populations will be restricted further in the primary analysis. A sensitivity will be provided for the respective analysis with all data from subjects or all protocol versions included (unrestricted MITT/on-treatment definitions).

17.4.11.3 Analysis of Subjects Who Started AChEI and/or Memantine

For the FDA analyses, in subjects who initiated treatment with AChEI and/or memantine at any time during the study, data after initiation of such treatment are excluded from the primary analyses as they could confound the results. Such subjects will be identified prior to

unblinding. For EMA analyses, such subjects are treated as subjects who terminated the study at the time of starting AChEI and/or memantine; a conservative post-withdrawal course is assumed for these subjects.

Data for these excluded subjects will be tabulated separately with their observed means, standard deviations, standard errors, and minimum and maximum values of selected changes in imaging and efficacy assessments. Primary reasons for initiating antidementia therapy will be provided. Furthermore, tables will be provided quantifying the number of assessments as well as time points that are impacted by these exclusions.

Sensitivity analyses will be performed including all data for these subjects. Time to event (*i.e.*, time to withdrawal in order to start AChEI and/or memantine) may also be performed if more than 10% meet this criterion; if not, the information will be tabulated.

17.4.11.4 Analysis of the Off-Treatment-On-Study (TOTOS) Subjects

Data for the TOTOS subjects will be handled in a similar fashion as described in Section 17.4.11.3. For the FDA analyses, the TOTOS subjects are included in the analyses (unless they initiated AChEI and/or memantine, in which case data after the initiation of such therapy will be excluded). For the EMA analysis, all TOTOS subjects are treated as subjects who terminated the study; a conservative post-withdrawal course is assumed for these subjects.

Data for these subjects will be tabulated separately with their observed means, standard deviations, standard errors, and minimum and maximum values of selected changes in imaging and efficacy assessments; primary reasons for withdrawal of study drug will be provided. Furthermore, tables will be provided quantifying the number of assessments as well as time points that are impacted by these exclusions.

Sensitivity analyses will be performed including all data for these subjects.

17.4.11.5 Imputation Methods

No data will be imputed in the primary and secondary analysis models unless stated otherwise. As sensitivity analyses, two methods for imputation will be explored, as described below.

17.4.11.5.1 Multiple Imputation

A multiple imputation analysis will be carried out using SAP-specified endpoints and analysis models, but will include the primary and selected secondary endpoints. The missing values will be imputed with multiple imputation methodology using PROC MI in SAS. A multivariate normal imputation model will be used by treatment group with a seed of 237039. The imputation model will have exactly the same covariates as the respective models. A total of 50 imputed datasets will be generated for this analysis. Each of the imputed datasets will be analyzed using the respective model with the same covariates. The MIANALYZE procedure in SAS will be used to combine results.

For endpoints that do not have planned multiple post-baseline assessments, additional variables such as sex, age, and other baseline values will be employed to allow appropriate multiple imputation.

17.4.11.6 Baseline Severity Rate-correction Analysis

The FDA model will include baseline value as an additive covariate. In order to determine whether baseline value influences future assessments, *i.e*., the rate of progression, a further sensitivity analysis which includes the additional term baseline*visit instead of just baseline will be conducted.

17.4.11.7 Sensitivities for Intervention Effect Analyses

Further sensitivity analyses are planned to determine the effect of withdrawals on estimation of intervention effect (as required by the EMA). These include the alternative assumption that the subjects withdrawing from treatment do not retain any treatment effect; the intervention effect I in this case is I=E*(1-w), where w is the fraction of subjects who withdraw for potential treatment-related reasons. This is implemented as a contrast statement as well. This analysis is only needed if there are more than two scheduled visits with imaging/efficacy assessments, as otherwise this analysis is identical to the EMA analysis model specified in Section 17.4.3.

An additional sensitivity analysis will assume that all subjects withdrew due to a potential treatment-related reason.

17.4.11.8 Polynomial Models

For the key efficacy/imaging assessments with more than one scheduled post-Baseline visit, maximum likelihood (rather than restricted maximum likelihood) based repeated measures models with polynomial time effects with time treated as a continuous variable (number of nominal weeks as well as actual study week defined by study day divided by 7) will be assessed. Tests of the significance of the linear, quadratic, and cubic time effects will be carried out in each treatment group. The estimated annualized change in mean values and standard errors from baseline to Week 52 will be presented.

17.4.11.9 Other Population Analyses

As a sensitivity analysis, the FDA primary analyses and potentially other pre-specified endpoints will be repeated for:

- The PP population
- The set of completers (*i.e.,* all subjects who were on-treatment at Week 52)
- All visits that are not potentially confounded by intercurrent illnesses, COVID-19, and concomitant medications as identified during the blinded data review meeting

17.5 Exploratory Analyses

A number of exploratory analyses will be undertaken, to be specified in the SAP. These could include the following (details will be provided in the SAP):

- To compare the treatment groups on the ADAS-cog$_{13}$
- To compare the treatment groups on a new composite endpoint/composite endpoints based on selected item of the Alzheimer's Disease Assessment Scale, 13-item version

(ADAS-cog$_{13}$) and the ADCS-ADL$_{23}$, analyzed at 9 months and 12 months to evaluate its usefulness for future studies (for all subjects and also separately for subjects with CDR 0.5 and CDR 1-2 at screening)

- To compare the treatment groups on the MMSE
- To compare the treatment groups on the CDR sum of boxes
- Comparison of atrophy in MRI parameters (including putamen, nucleus accumbens, and nucleus basalis) according to treatment assignment, as well as the combination of treatment assignment with previous treatment status of AChEIs and/or memantine (prior use or never used) in a subgroup analysis; the influence of the baseline volumes of putamen, nucleus accumbens, and nucleus basalis will also be investigated for selected MRI parameters. Further SPM analyses may be conducted using all available MRI volumetric data to determine regions of significant difference associated with treatment
- Comparison of decline in ^{18}F-FDG-PET SUVR normalized with respect to pons and cerebellum in temporal, parietal, and frontal lobes according to treatment assignment, as well as the combination of treatment assignment with previous treatment status of AChEIs and/or memantine (prior use or never used) in subgroup analyses
- Determination of decline in SUVR in cerebellum normalized with respect to pons according to treatment assignment, as well as the combination of treatment assignment with previous treatment status of AChEIs and/or memantine (prior use or never used) in a subgroup analysis
- Other SUVR regions of interest will also be examined including, but not restricted to, inferior temporal gyrus, angular gyrus, anterior and posterior cingulate gyrus, and cerebellum
- SPM analyses (Friston *et al*., 2007) may be conducted using all available normalized cortical ^{18}F-FDG-PET SUVR data and MRI data to determine regions of significant difference associated with treatment without assuming the location and extent of any differences
- To examine the associations of SPM approaches using all available normalized ^{18}F-FDG-PET SUVR data and volumetric MRI data with the following clinical measures:
  - ADAS-cog$_{13}$
  - ADCS-ADL$_{23}$
  - Composite Scales (selected)
- Comparisons of measures of brain MRI hyperintensities by treatment group; subgroup analyses by previous treatment status of AChEIs and/memantine (prior use or never used) will also be performed, including for the combined LMTM 8-mg/day and placebo groups
- Population pharmacokinetics (to be subject to a section in the SAP or a separate SAP and report)
- To evaluate the influence of *ApoE* genotype (in subjects who provide legally acceptable consent) on the primary and selected secondary endpoints

A number of exploratory comparisons with external data may also be performed, to be specified in the SAP. These include comparisons of LMTM 16 mg/day or LMTM 8 mg/day on the following:

- Comparison of annualized rates of atrophy in a range of brain regions (including temporal lobe and whole brain) with the estimated decline for subjects with MCI-AD and mild AD with MMSE in the range of 20-27 not receiving either of the standard

treatments for AD (AChEIs and/or memantine) from the ADNI; this will be repeated for the entire MMSE range used in this study
- To compare the primary and selected secondary imaging and efficacy endpoints at 52 weeks with pooled mild AD subjects in control groups (subjects receiving LMTM at any dose in combination with an AChEI and/or memantine) from the LMTM Phase 3 trials (Studies TRx-237-005 and TRx-237-015) with baseline MMSE in the range of 20-26; this will be repeated for the entire MMSE range used in this study
- Comparison of decline in temporal lobe ^{18}F-FDG-PET SUVR with the estimated decline for subjects with mild AD (CDR 0.5 at Screening) not receiving either of the standard treatments for AD (AChEIs and/or memantine) from the ADNI
- Accounting for and using historic data more generally such as placebo decline or treatment effects as priors to inform the analyses of this study.

17.6 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics and medical history will be summarized in tables. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. The tabular summaries will present the numbers and percentages of subjects with abnormalities in a given MedDRA System Organ Classification (SOC).

Recently used medications and concomitant medications will be coded using the 01March 2017 version of the WHO drug dictionary. Tabulations will be prepared of all drugs used concomitantly (relative to the first dose of study drug) 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 in each treatment group using each concomitant medication. Separate tabulation will be made of on-treatment changes in antipsychotic medications (to be identified by blinded review), together with the reason(s) for such change.

Further information indicating years spent in full-time education and its level before the age of 26 years is to be collected. In addition, main occupation during working life is to be provided (see Section 28.3); main occupation will be coded using the Standard Occupational Classification, 2010, Volume 2 The Coding Index, UK Office for National Statistics. These have been found to be useful proxies for cognitive reserve (Staff *et al*., 2004). Exploratory analyses will be described in the SAP.

All data, including study eligibility and screening data (including reason for exclusion), will be listed.

Subjects who are mis-stratified at the time of randomization will be flagged in the listing.

17.7 Safety Analysis

Various safety analyses will be conducted for this study. Details will be provided in the SAP. The planned safety analyses, including tabulations by treatment group, include:
- A quantification of the extent of drug exposure
- Various analyses of AEs (using MedDRA Version 20.1)
  - TEAEs, including by relationship and intensity
  - TEAEs that result in interruption or discontinuation of study drug
  - Selected subsets of TEAEs (referred to as TauRx AE Groupings)

  - Subgroup analyses
  - Time-to-event analyses of TEAEs
  - SAEs and serious adverse reactions
  - Malignancies other than non-melanoma skin cancers
- Clinical laboratory evaluations
- Vital sign analysis
- Physical and neurological examinations

All safety data will be listed.

17.8 Other Data

Total duration of exposure and mean and modal daily dose per subject (including "dose equivalent" for subjects randomized to placebo), will be summarized descriptively by treatment group. Mean, modal, and maximum dose will also be summarized over selected exposure intervals. In addition, tabular summaries of the proportions of subjects with dose interruptions will be prepared for each treatment group. Listings will encompass dosing, drug accountability, and compliance (percentage of tablets taken relative to intended number); any doses that are other than that randomized will be flagged.

The plasma MT and whole blood concentrations (parent MT/LMT, *N*-desmethyl MT, and total MT concentrations, as available) will be listed. The results of population PK and exposure-response analyses will be provided in a separate report.

ApoE genotype will be listed for each subject who consents to this determination. Use of these data in exploratory analyses will be described in the SAP.

17.9 Interim Analysis

No interim futility or efficacy analysis is planned prior to the completion of the double-blind treatment period in which treatment groups will be compared.

Recruitment and discontinuations will, however, be continuously monitored in a blinded fashion to ensure that the sample size calculations remain appropriate. The sample sizes may be increased but not decreased; thresholds will be defined in an interim monitoring SAP. Specifically:

- Should the overall dropout for the duration of the study be projected to exceed 25%, then the number of subjects to be enrolled may be increased in order to power an analysis at 52 weeks.
- The assumed SD for the change from baseline to Week 52 in the primary endpoints may be re-estimated at some point during the study's recruitment period and the sample size required to provide 90% power for the primary endpoints will be re-estimated.
- The balance between the three different MMSE stratification groups is determined to be approximately 2:3:1 (MMSE 16-19, 20-25, and 26-27) for those randomized to Protocol Version 5.0 and above. This value will be closely monitored and controlled at study level. Should the balance be deviating from the desired balance, then the number of subjects to be enrolled may be increased in order to rebalance the design enriching the MMSE groups that are underrepresented.

- As indicated in Section 10.2, COVID-19 can have a significant effect on the number of assessments available for analysis. Quality and subitems of assessments can also be impacted, leaving the primary analysis underpowered. The interim monitoring SAP will provide details regarding how this will be assessed prior to any analysis being conducted and will also outline approaches that are to be followed given pre-determined thresholds.

As noted in Section 10.7, an analysis of the primary efficacy endpoints will be undertaken when the last subject completes the final visit in the double-blind treatment period.. If the null hypotheses presented in Section 17.4.1 are rejected, complete safety and efficacy analysis of the data from the double-blind treatment period will be undertaken and an interim study report prepared. The complete Clinical Study Report will be prepared upon completion of the entire study as defined in Section 10.7.

18 REGULATORY AND ETHICS

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 and with the principles contained in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP)[7] and with applicable country and local regulatory requirements and laws. All deviations identified at or by the site will be reported to the study monitor. See Section 10.2 regarding the Sponsor's ongoing consideration of updates to guidances and requirements due to COVID-19 to ensure continued protection of subject safety, subject rights, trial integrity, and compliance.

The Sponsor's designee(s) 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's designee(s) will forward any protocol amendments to the regulatory authority and will ensure that SAEs are reported, and that progress reports and details of any serious protocol violations are provided as required.

Each regulatory authority will be informed should the study be terminated early consistent with local requirements.

18.1 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's designee, Syneos Health, 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

[7] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [homepage on the Internet]. E6(R2): Good Clinical Practice: Consolidated Guideline (or ICH E6(R1) in those jurisdictions where ICH E6(R2) is not yet implemented by the regulatory authorities)

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 the submission of a protocol amendment to the regulatory authority. In the event of a substantial amendment, prior regulatory approval is required for implementation.

18.2 Serious Breaches

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 or delegated party in accordance with TauRx Standard Operating Procedures (SOPs).

18.3 Informed Consent

It is the responsibility of the PI or SI to obtain informed consent from each subject (or his/her LAR who is permitted to provide consent in accordance with local legislation) and study partner(s) participating in this study. At all study sites, the PI or SI who obtains informed consent must be a physician (such as a neurologist, psychiatrist) or other medically qualified person (MD/DO).

Subjects and/or their LAR(s) must give written (signed and personally dated) informed consent prior to study entry and before any study specific procedures are undertaken. The identified study partner(s) for each subject also must provide written consent to his/her own participation as outlined below. Where there is a change of study partner, the new study partner 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 LARs will be required to sign the ICF as required by national and/or local 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 signs of significant distress.

Informed consent can be obtained only after it is confirmed that the subject has a likely diagnosis of probable AD or MCI-AD and the aims, methods, anticipated benefits, and known potential hazards of the study have been explained to and discussed with the potential subject and study partner(s) by the investigator. As subjects are not allowed to receive approved AD medication while in the study, they will be informed of the benefits and risks of discontinuing and/or not initiating such therapy, as pertinent. If a subject decides to discontinue AD medication in order to enter the study, a letter will be sent to his/her primary care physician informing him/her of the subject's decision.

A subject information sheet, providing a written summary of all relevant information, will be given to the potential subject and study partner(s) prior to written informed consent being obtained. The study partner(s) will also be given an information sheet. The information sheets 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 study partner(s) are aware of this. The investigator will explain to the potential subject and study partner(s) 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 will not impinge on the future management of the subject. The potential subject and study partner(s) 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 includes sites in North America and Europe, two geographic regions that maintain descriptions of clinical studies on the internet. As required by the FDA, 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.

Separate consent may be required by the previous imaging center for transfer of prior amyloid PET scan data to the imaging core laboratory for later confirmation of positive amyloid status.

18.4 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 PI 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 PI 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 SIs and other appropriately qualified persons to whom duties have been delegated
- Supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site
- 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

TauRx and the appointed DSMB will constantly evaluate the risk threshold of this particular study by assessing the safety profile 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 AEs at each visit in accordance with the schedule of assessments, and have the right to interrupt or discontinue study drug for safety reasons as described in Section 11.4.

The burden/distress associated with participation in this study is addressed in the subject information sheet. 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.

19 CONFIDENTIALITY AND DATA PROTECTION

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

The investigator must strictly maintain the confidentiality of subjects in the trial. For all documents and materials submitted to TauRx, its designee, or any electronic system (for example, eCRFs, samples, specimens, and other documents), the investigator must refer to subjects by an identification code. The investigator must keep a separate local log of subject codes, names, and addresses for all subjects, including those that were screened but not enrolled. This local log must never be uploaded to the electronic Trial Master File (eTMF).

Collecting, processing of, and / or transferring data outside the European Economic Area will meet the requirements of EU Directive 2016/679 (General Data Protection Regulation), with appropriate transparency notices included in informed consent documentation. In the United States, data will be protected consistent with Health Insurance Portability and Accountability Act.

Confidentiality of the records identifying each subject shall 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.

For the avoidance of doubt, this protocol does not define or describe any data protection obligations. These will be dealt with in relevant vendor contracts and subject-facing documentation in compliance with relevant local law.

20 STORED SAMPLES AND IMAGING DATA

20.1 Biosamples

TauRx is interested in identifying biomarkers that correlate to a drug's mechanism of action or the disease state under study. Finding appropriate biomarkers can give clinicians a clearer understanding of the most appropriate patients for a particular drug and the most appropriate dose for those patients, offering the potential for improved clinical outcomes.

Storage of samples of plasma and whole blood for possible future research related to determination of potential biomarker predictors of LMTM response or surrogates of treatment response is a mandatory part of this study, unless country-specific laws and regulations prohibit this storage. The samples obtained for genetic testing and the remainder of the samples not used for MT concentration determination as described in Section 15.5 will be stored. Stored samples will retain the subject identifier and, therefore, will not be stored indefinitely. Samples will be stored for a maximum of 8 years after the last subject visit for the study; any sample remaining at that time will be destroyed. Because of the exploratory nature of these analyses and because the results should not change medical management, neither subjects nor investigators will receive the test results.

TauRx's research procedures dictate that a research plan be prepared before conducting any secondary (future) research on stored samples. The research plan would include objectives of the research, scientific rationale for the research, a clear indication that the research is being conducted as secondary research, how alternative authorization to use and disclose the data from secondary research is to be obtained, and how the results are intended to be used. For this study, future research could include, but need not be limited to, measurement of plasma markers of tau and other protein species, genetic and epigenetic markers which might be predictors of LMTM response, or potential surrogate markers of treatment response. Analysis of these data could provide an important, minimally invasive biomarker that would guide future decisions by clinicians and researchers.

20.2 Imaging Data

Additional exploratory analyses are to be undertaken of the blinded ^{18}F-FDG-PET and MRI data generated as part of this study. The analyses will be for scientific research and quality control purposes which are separate from the study objectives. A separate plan will capture standard procedures and a data transfer agreement will detail the requirements for data to be transferred to the imaging center performing the analyses. Data analyses will be conducted in line with required data protection requirements, will not reveal potentially sensitive information about the study or its participants, and will not lead to potential unblinding of study data. The transfer and use of these data will be described in the informed consent form.

21 QUALITY ASSURANCE AND CLINICAL MONITORING

21.1 Standard 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.

QA audits will be conducted on critical phases during the clinical and reporting phases of the study. These audits will be carried out by QA personnel, independent of the staff involved in the study, according to relevant SOPs.

Clinical monitoring, both primary and secondary, will be performed by trained clinical research personnel. Clinical monitoring is an integral part of controlling and securing of data integrity and subject safety. The first monitoring visit will be scheduled appropriately after the first subject is screened at a site depending on factors that could impact on data reliability, some of which are mentioned below. The average monitoring frequency will be described in a CMP and will depend on a number of factors, including subject screening and recruitment rates, site performance, and quality adherence. Regulatory recommendations and guidelines will be followed. Detailed expected monitoring activity will be described in the CMP, which will be modified on an ongoing basis to ensure subject safety and data integrity.

The monitor will ensure compliance with the protocol, adherence to regulatory and ICH obligations, accurate reporting of AEs, maintenance of trial records including drug accountability records, and correct administration of study procedures including supply and storage of study materials. ICFs will be reviewed to verify that they are correctly signed and dated by the subject and study partner and the medically qualified PI or SI. At each monitoring visit, subject data will be reviewed and verified against the medical records.

The monitor will require direct access to laboratory test results and other records needed to verify entries on the eCRF.

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.

Quality review of data and/or trial documentation may be carried out by or on behalf of the Sponsor at any stage. Audits of study sites and/or trial processes may be carried out at any stage.

21.2 COVID-19 Risk Assessment

Due to the impact of COVID-19 on this study, the Sponsor has conducted risk assessments to identify the potential risk levels and impacts of COVID-19, as well as associated mitigating actions for a number of clinical study aspects, including: direct-to-subject study drug shipments, missed study visits and/or clinical assessments, handling of missed post-baseline study data, remote site initiation visits, remote monitoring visits, and remote clinical assessments (*e.g.*, remote ADAS-cog$_{13}$). Vendors have also conducted risk assessments associated with their services to this study. Risk assessment and management are ongoing processes for this study; all risks and mitigations are regularly reviewed and managed, and the Sponsor will continue to ensure that additional risk assessments are carried out and documented, in particular for any potential impact due to COVID-19, as the situation develops and as regulatory guidances are updated.

A summary of alternate arrangements to clinical monitoring that may be implemented due to COVID-19 is provided in Section 10.2.2.

22 DOCUMENTATION

The following documents must be provided before or at site initiation:

- 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/IRB approval
- Approved subject and study partner information sheets, ICF, and advertisement for recruitment (if any)
- eCRFs
- Confidentiality agreement(s)
- Financial disclosure
- Signed *curricula vitae* for personnel who have signed the authorized delegation log (including PI, all SIs, and designated assistants)
- Authorized signature log/delegation list
- Investigator's Brochure with signed and dated Investigator's 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)
- Imaging center agreement (if any)
- SAE forms

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. The eCRF may serve as the primary collection medium for any data (to be agreed with the investigator and documented in the Source Document Agreement). Each enrolled subject must have an eCRF completed and this must be reviewed and approved by the investigator.

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.

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 25 years after the end of the clinical trial or for the period of time specified by local law for the preservation of hospital subject documents, whichever is the longest. No study documents should be destroyed without prior written agreement between TauRx and the investigator. Should the site wish to assign the study records to another party, or move them to another location, TauRx must be informed.

The study eTMF will be maintained as specified by ICH GCP. The eTMF shall be archived for a minimum of 25 years after the end of the clinical trial in a way that ensures that it is readily available, upon request, to the regulatory authorities.

23 PUBLICATION

Since this is a multicenter 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 his/her work conducted under this protocol after 12 months from a New Drug Application 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.

24 INDEMNITY, INSURANCE, AND COMPENSATION

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

25 ADMINISTRATIVE AND FINANCIAL AGREEMENT

Agreed costs for each participating study site will be met by TauRx. 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 TauRx or its designee before the initiation of the trial. Each PI and SI must also sign a Form FDA 3455 or its equivalent to disclose any financial arrangements or interests.

Subjects will be reimbursed by TauRx, through the investigator, for reasonable travel costs to and from the study site and accommodation in certain circumstances by prior agreement with the Sponsor.

26 STUDY ADMINISTRATION

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

Vendors 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 SAEs; to provide services for laboratory, imaging, and PK analysis; to package and distribute the clinical trial supplies; and to provide QA support and services.

Calibration certification for the following equipment maintained by the site and used to generate study data will be confirmed: ECG machines, refrigerated centrifuges, and pharmacy temperature loggers.

27 REFERENCES

Aduhelm FDA Drug Approval Package, Office of Neurology's Summary Review Memorandum. June 2021.

Al-Hilaly YK, Pollack SJ, Vadukul D, *et al.*: Alzheimer's disease-like paired helical filament assembly from truncated tau protein is independent of disulphide cross-linking. J Mol Biol 2017;429:3650-65.

Al-Hilaly YK, Pollack SJ, Rickard JE, *et al.*: Cysteine-independent inhibition of Alzheimer's disease-like paired helical filament assembly by leuco-methylthioninium (LMT). J Mol Biol 2018; https://doi.org/10.1016/j.jmb.2018.08.010.

Albert MS, DeKosky ST, Dickson D, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3):270-9.

Baddeley TC, McCaffrey JM, Storey JM, *et al*. Complex disposition of methylthioninium redox forms determines efficacy in tau aggregation inhibitor therapy for Alzheimer's disease. J Pharmacol Exp Ther 2015; 352(1):110-18.

Berg L, Miller JP, Storandt M, *et al.* Mild senile dementia of the Alzheimer type: 2. Longitudinal assessment. Ann Neurol 1988; 23(5):477-84.

Bierer LM, Hof PR, Purohit DP, *et al*. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch Neurol 1995; 52(1):81-8.

Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database of Systematic Reviews, Issue 3, 2004. Article No. CD001190.

Bowie P, Branton T, Holmes J. Should the Mini Mental State Examination be used to monitor dementia treatments? Lancet 1999; 354(9189):1527-8.

Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991; 82(4): 239-59.

Courtney C, Farrell D, Gray R, et al. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): Randomised double-blind trial. *Lancet*. 2004;363:2105-15

Fillenbaum GG, Peterson B, Morris JC. Estimating the validity of the Clinical Dementia Rating Scale: the CERAD experience. Aging (Milano) 1996; 8(6):379-85.

Fitzpatrick AWP, Falcon B, He S, *et al.*: Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 2017; 547:185-90.

Folstein MF, Folstein SE, McHugh PR. “Mini-mental State”: A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3):189-98.

Friston K, Ashburner J, Kiebel S, *et al*. (eds) *Statistical Parametric Mapping: The analysis of functional brain images*. 1st ed. Amsterdam: Academic Press; 2007.

Galasko D, Bennett D, Sano M, *et al.* An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11(Suppl 2):S33-9.

Galasko D, Schmitt F, Thomas R, *et al.* Detailed assessment of activities of daily living in moderate to severe Alzheimer's disease. J Int Neuropsychol Soc 2005; 11(4):446-53.

Gauthier S, Feldman HH, Schneider LS, *et al*. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer’s disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. Lancet 2016; 388:2873-84.

Hughes CP, Berg L, Danziger WL, *et al.* A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140:566-72.

Lockhart SN, Baker SL, Okamura N, *et al*. Dynamic PET measures of tau accumulation in cognitively normal older adults and Alzheimer’s disease patients measured using ^{18}F THK-5351. PLoS One 2016; 11(6):e0158460.

McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011; 7(3):263-9.

Mohs RC, Knopman D, Petersen RC, *et al*. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11(Suppl 2):S13–21.

Morris JC, McKeel DW Jr, Fulling K, *et al.* Validation of clinical diagnostic criteria for Alzheimer's disease. Ann Neurol 1988; 24(1):17-22.

Morris JC, Ernesto C, Schafer K, *et al.* Clinical Dementia Rating training and reliability in multicenter studies: the Alzheimer's Disease Cooperative Study experience. Neurology 1997; 48(6):1508-10.

Mukaetova-Ladinska EB, Garcia-Siera F, Hurt J, *et al*. Staging of cytoskeletal and β-amyloid changes in human isocortex reveals biphasic synaptic protein response during progression of Alzheimer's disease. Am J Pathol 2000; 157(2):623-36.

National Institute for Clinical Excellence (NICE) Technology Appraisal Guidance No 19. Guidance for the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer’s disease 2001, London: NICE.

Olin J, Schneider L. Galantamine for dementia due to Alzheimer's disease. Cochrane Database of Systematic Reviews, Issue 3, 2002, article No. CD001747.

Pontecorvo MJ, Devous MD, Sr., Navitsky M, *et al.* Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain 2017; 140:748-63.

Reisberg B, Doody R, Stöffler A, *et al*. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348(14):1333-41.

Riedel G, Klein J, Niewiadomska G, et al. Mechanisms of anticholinesterase interference with tau aggregation inhibitor activity in tau-transgenic mouse model. Curr Alzheimer Res. 2020;17(3):285-296.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141(11):1356-64.

Schelter BO, Shiells H, Baddeley TC, *et al*. Concentration-dependent activity of hydromethylthionine on cognitive decline and brain atrophy in mild to moderate Alzheimer's disease. J Alzheimers Dis 2019;72(3):931-46

Schneider LS, Dagerman KS, Higgins JP, *et al*. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol 2011; 68(8):991-8.

Staff RT1, Murray AD, Deary IJ, *et al*. What provides cerebral reserve? Brain 2004; 127(Pt 5):1191-9.

Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: A comprehensive review. J Am Geriatr Soc 1992; 40(9):922-35.

Wilcock GK, Gauthier S, Frisoni GB, *et al*. Potential of low dose leuco-methylthioninium bis(hydromethanesulphonate) (LMTM) monotherapy for treatment of mild Alzheimer's disease: Cohort analysis as modified primary outcome in a Phase III clinical trial. J Alzheimer's dis 2018; 61:435-57.

Wischik CM, Lai RY, Harrington CR. Modelling prion-like processing of tau protein in Alzheimer's disease for pharmaceutical development. In: Brain Microtubule Associated Proteins: Modifications in Disease. Eds. Avila J, Brandt R, Kosik KS 1997. Amsterdam: Harwood Academic Publishers, 185-241.

Wischik CM, Novak M, Edwards PC, *et al.*: Structural characterization of the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci USA 1988a; 85:4884-8.

Wischik CM, Novak M, Thøgersen HC, *et al.*: Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer disease. Proc Natl Acad Sci USA 1988b; 85:4506-10.

Wischik CM, Staff RT, Wischik DJ, *et al*. Tau aggregation inhibition therapy: an exploratory Phase 2 study in mild or moderate Alzheimer's disease. J Alzheimer's Dis 2015; 44(2):705-20.

Xia CJ, Makaretz SJ, Caso C, *et al*. Association of in vivo [^{18}F] tau PET imaging results with cortical atrophy and symptoms in typical and atypical Alzheimer disease. JAM Neurol 2017; 74:427-36.

28 APPENDICES

28.1 Disallowed Treatments and Windows

28.1.1 Disallowed Medical Food / Medications Beginning 90 Days Before Baseline and During the Study

Medical food
Souvenaid®

Antipsychotic
Clozapine

Antiepileptic drugs
Carbamazepine
Primidone
Valproate

Anti-malarial drugs
Dapsone
Primaquine and related antimalarials

Anesthetics
Benzocaine or other local anesthetics used chronically

Investigational product for cognition (unless confirmed to have been randomized to placebo)

28.1.2 Disallowed Medications Beginning 60 Days Before Baseline and During the Study

Alzheimer's disease drugs
Donepezil
Galantamine
Rivastigmine
Memantine

28.1.3 Disallowed Treatments Beginning 28 Days Before Baseline and During the Study

Investigational drug (other than for cognition), biologic, device, or medical food

28.2 Study Blood Assessments

Please see schedule of assessments for timing of blood sample collections.

Clinical Chemistry

Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Phosphorus
Glucose
Blood urea nitrogen
Creatinine
Indirect bilirubin
Direct bilirubin
Total bilirubin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Gamma-glutamyl transferase
Lactate dehydrogenase

Hematology

Red blood cell (RBC) count
Hemoglobin
Hematocrit
MCV, MCH, MCHC
RBC distribution width
Platelet count
White blood cell (WBC) count
WBC Differential (% and absolute)
• Neutrophils
• Eosinophils
• Basophils
• Lymphocytes
• Monocytes
Reticulocytes (absolute and relative)

Other Tests

Serum Pregnancy test
Vitamin B_{12} / Folate
Haptoglobin
Thyroid Stimulating Hormone (TSH)
Glucose-6-Phosphate Dehydrogenase (G6PD)
ApoE (in subjects who consent for this)
Blood sample for MT concentration

28.3 Education / Occupation

28.3.1 Education

Q: How many years did you spend in full time education before the age of 26?
(integer) _ years

Q: How would you best describe your level of education?

1. Elementary
2. Some high school / secondary
3. Completed high school / secondary
4. Some post high school / secondary education
5. College education graduate
6. Post graduate education (including high professional qualification)

28.3.2 Occupation

Q: What was your main occupation during your working life?
(text)

(Responses will be coded using The Standard Operational Classification, 2010, Volume 2 The Coding Index, UK Office for National Statistics)

28.4 Summary of Changes to the Protocol

28.4.1 Protocol Version 2.0

The protocol for study TRx-237-039 (Version 1.0 dated 23 Aug 2017) has been revised (Version 2.0) to clarify the assessments that will be made at various visits as follows:

- The blood will be collected during Visit 2 and Visit 3 (not at Visit 2 *or* Visit 3).
- A spelling error was corrected (dimethyl to desmethyl).
- Clarification was made that the *time of dose* from the previous day will be collected.
- A redundant paragraph was removed.
- Specifications for procedure of blood collection were removed from the protocol as these details will be presented in the laboratory manual.
- The Appendices were renumbered and the table of contents updated.
- Minor edits, such as expansion of abbreviations, were made.

The sections affected by these changes are detailed below.

Summary of Changes	Affected Section(s) in Revised Protocol (Version 2.0)
Targeted examinations will be performed pre-dose and approximately 3 hours after administration of first dose of study drug (Visit 2); these are to be repeated as needed for subjects who remain in the clinic longer than 4 hours. Thereafter, targeted examinations are to be performed at each subsequent visit or upon early termination.	• Synopsis, Safety and tolerability • Table 10-1 Schedule of Assessments, foot note 'f' • Section 15.2, Bullet #7
Added the following missing bullet to the Synopsis: TSH, vitamin B_{12}, folate, haptoglobin and G6PD will be measured at Screening only. Standard clinical laboratory testing, including hematology, blood chemistry, will be performed at Screening and each visit thereafter including an early termination, if applicable. A blood sample for a serum pregnancy test will be collected for all women of childbearing potential at Screening and at each subsequent visit, or upon early termination.	• Synopsis, Safety and tolerability
Several updates were made to the various statistical analyses planned	• Section 17.8 including subsections
The blood will be collected during Visit 2 and Visit 3 (not at Visit 2 *or* Visit 3)	• Table 10-1 Schedule of Assessments, foot note 'q'
A redundant bullet was removed	• Synopsis, Safety and Tolerability • Section 15.2
Spelling changed from dimethyl to desmethyl	• Synopsis, safety and tolerability, Bullet #5 • Section 15.2 Bullet #5 • Section 15.5.2, line 2

Summary of Changes	Affected Section(s) in Revised Protocol (Version 2.0)
The *time of dose* from the previous day will be collected	• Table 10-1 Schedule of Assessments, foot note 'q' • Section 15.4.1 Paragraph 1
The volume of whole blood, centrifuge speed and the number and type of blood collection tubes were removed	• Section 15.4.1.1
The Appendices were renumbered and the Table of contents updated	• Table of Contents • Appendices 30.3 and 30.3.1

28.4.2 Protocol Version 2.1

The protocol for study TRx-237-039 (Version 2.0 dated 31 Aug 2017) was updated to make administrative changes to provide the latest contact details of the Sponsor and the Sponsor's personnel, and the details of the Central Laboratory.

Summary of Changes	Affected Section(s) in Revised Protocol (Version 2.1)
The address and phone numbers of the Sponsor and the Sponsor's personnel was updated.	• Cover page • Section 3 Protocol Approval • Section 4 Responsible Personnel
Version number was changed from 2.0 to 2.1 and date of the protocol was changed from 31 Aug 2017 to 25 Oct 2017.	• Cover page • Headers • Footers • Section 5 Investigator Signature Sheet
The Central Laboratory name, address and phone numbers were added.	• Section 4 Responsible Personnel

28.4.3 Protocol Version 3.0

The protocol for Study TRx-237-039 (Version 2.1 dated 25 October 2017) was updated to modify the study design to a 39-week treatment period (from 26 weeks) in subjects with early AD (*i.e.*, by the inclusion of subjects with MCI-AD in addition to mild AD). As a result of the addition of a cognitive/functional Composite Scale (to be finalized prior to database lock and unblinding) and a third treatment arm (LMTM 16 mg/day), the sample size has been increased to approximately 375 subjects (from 180 subjects). Numerous changes have been made to the protocol to clarify and/or specify the timing and sequence of assessments.

A summary of the key changes and primary affected sections is provided below (as the Synopsis is affected by the majority of the changes, it is not listed).

Administrative changes have also been made, such as adding the EudraCT number issued for this study (2017-003558-17); updating references to the 2013 (current) version of the Declaration of Helsinki, the ICH Integrated Addendum to ICH E6(R2) Guidelines for GCP, and GDPR; and updating parties and contact information for responsible parties in Section 4. Additional statistical analyses, including of derived endpoints (such as the Composite Scale) and the higher treatment group, are now described. While a brief summary of planned statistical analyses of primary and secondary endpoints is described and a list of possible exploratory analyses is included, these will be finalized in a Statistical Analysis Plan prior to database lock and unblinding. These are not described below but are enumerated in a separate detailed summary of changes document.

Summary of Changes	Primary Affected Sections in Revised Protocol (Version 3.0)
Background	
The recently adopted United States Abbreviated Names of hydromethylthionine (LMT) and hydromethylthionine mesylate (LMTM, drug substance) have been added	Section 8.1.1 Investigational Product Section 12.1.1 Active Ingredient
Nonclinical and clinical data have been updated to be reflective of most current version of Investigator's Brochure (v. 20.0); references have been updated as pertinent	Section 8.1.2 Nonclinical Data Section 8.1.3 Clinical Data
Objectives	
A new clinical efficacy scale has been added as a gated primary objective; this Composite Scale is to be derived from cognitive/functional items selected from the ADAS-cog$_{11}$ and ADCS-ADL$_{23}$	Section 8.2 Rationale Section 9.1 Primary Objectives Section 15.3.3 Composite Scale Section 17 Statistical Analysis Section 17.1.2 Primary Efficacy Endpoint Section 17.2 Number of Subjects and Sample Size Calculation Section 17.4.1 Hypothesis Section 17.4.7 Subgroup Analyses Section 17.4.8.4.1 Multiple Imputation Section 17.5 Exploratory Analyses
The secondary clinical endpoint has been changed from the ADAS-cog$_{11}$ to the ADAS-cog$_{13}$ as potentially more sensitive to change in subjects with milder disease	Section 9.2 Secondary Objectives 10.4.2.2 Clinical Efficacy Assessments 15.3.1 ADAS-cog 17.1.4 Other Secondary Endpoints 17.5 Exploratory Analyses

Summary of Changes	Primary Affected Sections in Revised Protocol (Version 3.0)
The sequence of the secondary objectives has been modified and the examination of associations between the ^{18}F-FDG-PET regions of interest and the Composite Scale and the examination of associations between brain MRI endpoints and ADAS-cog$_{13}$, ADCS-ADL$_{23}$, and the Composite Scale have been added. Comparison of the LMTM 16 mg/day and placebo groups has also been added.	Section 9.2 Secondary Objectives Section 17.1.3 Secondary Imaging Endpoints Section 17.1.4 Other Secondary Endpoints
Exploratory analyses and exploratory analyses that are comparisons with external data are now listed only in the Statistical Analysis section.	Section 9.3 (*Section removed*) Section 9.4 (*Section removed*) Section 17.5 Exploratory Analyses
Study Design	
The duration of the study has been increased from 6 to 9 months; the numbers of visits, schedules of safety and efficacy assessments, and statistical analyses have also been updated accordingly.	Section 10.1 General Description Section 10.3 Duration Section 10.4.2 Baseline and Post-randomization Assessments Section 10.4.2.1 Imaging Efficacy Assessments Section 10.4.2.2 Clinical Efficacy Assessments Section 10.4.2.3 Safety Assessments Section 12.2 Study Regimens Section 15.2.3 Imaging Methods for Efficacy Section 15.3 Clinical Assessments and Raters Section 15.4 Safety Assessment and Procedures Section 17 Statistical Analysis
Total study duration for an individual subject has been increased from 36 weeks to up to 54 weeks, including a Screening period of up to 15 weeks (105 days) and a Treatment period of 39 weeks, which is updated throughout the protocol. As a result, the total duration of the overall study has been increased to at least 24 months, depending on recruitment rate.	Section 10.1 General Description Section 10.3 Duration
A third treatment arm, LMTM 16 mg/day, has been added and the total sample size increased from 180 subjects (90 each randomized to placebo and LMTM 8 mg/day) to 375 subjects (150 each randomized to placebo and LMTM 8 mg/day and 75 randomized to LMTM 16 mg/day). As many as 900 subjects may be screened (increased from 360).	Section 10.1 General Description 10.2 Study Population 17.2 Number of Subjects and Sample Size Calculation
The follow-up telephone contact, previously scheduled to occur 4 weeks after the last dose of study drug, has been deleted; the protocol clarifies that investigators are to follow any unresolved adverse events to resolution or acceptable stabilization consistent with their medical judgment.	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments Section 10.4.2.3 Safety Assessments Section 11.4 Discontinuations / Withdrawals Section 15.4 Safety Assessment and Procedures Section 16.2 Eliciting Adverse Event Information Section 16.7 Serious Adverse Event Reporting
Patient Population (Inclusion and Exclusion Criteria)	
The patient population has been expanded to include subjects with mild cognitive impairment due to Alzheimer's disease (MCI-AD), such that the study is now being performed in subjects with early Alzheimer's disease (AD) (inclusive of both mild AD and MCI-AD)	Section 8.2 Rationale Section 9 Objectives Section 10.1 General Description Section 10.2 Study Population Section 10.4.1.1 Diagnostic and Cognitive Eligibility Assessments Section 11.1 Inclusion Criteria

Summary of Changes	Primary Affected Sections in Revised Protocol (Version 3.0)
Subjects must be able to give their own consent; consent by a caregiver on behalf of the subject is no longer allowed	Section 9.2 Secondary Objectives Section 10.4.1 Screening Assessments Section 10.4.2 Baseline and Post-randomization Assessments Section 10.4.3 Other Assessments Section 11.1 Inclusion Criteria Section 15.5.3 Genotyping Section 18.3 Informed Consent
A PET scan positive for amyloid is now required for eligibility (either by prior documentation or undertaken for the study)	Section 10.1 General Description Section 10.2 Study Population Section 10.4.1 Screening Assessments Section 10.4.1.1 Diagnostic and Cognitive Eligibility Assessments Section 11.1 Inclusion Criteria Section 10.4.1 Screening Assessments Section 15.1 Demographic Data/Medical History Section 15.2.1 General Considerations Section 15.2.3.1 ^{18}F-FDG-PET Section 18.3 Informed Consent
The acceptable disease severity based on MMSE has been expanded from 20-25 to 20-27; randomization will now be stratified based on a MMSE of 20-25 and 26-27 (in a 2:1 ratio, monitored and controlled at the site level and capped as needed at the study level)	Section 10.1 General Description Section 10.2 Study Population Section 11.1 Inclusion Criteria Section 11.3 Re-screening Section 12.3 Randomization Section 17.4.7 Subgroup Analyses
Screening Global CDR score of 0.5 now has a further requirement that subjects have a score of >0 in one of the functional domains (Community Affairs, Home and Hobbies, or Personal Care)	Section 10.2 Study Population Section 11.1 Inclusion Criteria Section 11.3 Re-screening
Subjects taking an AChEI and/or memantine at Screening may now be enrolled, provided they are willing to discontinue such medication; the screening period in such subjects has been expanded to 15 weeks to allow for the requisite eligibility assessments prior to the discontinuation of such medication (at least 60 days before Baseline ^{18}F-FDG-PET); if subjects discontinue these medications, a letter is to be sent to the primary care physicians to inform them of this decision	Section 10.1 General Description Section 10.4.1 Screening Assessments Section 10.4.1.1 Diagnostic and Cognitive Eligibility Assessments Section 10.4.2 Baseline and Post-randomization Assessments Section 11.1 Inclusion Criteria Section 13.1 AChEI and/or Memantine
As a result of the increased sample size, at least 100 sites may be required (increased from 60) and sites from geographical regions outside of North America and Europe may also be sought	Section 10.1 General Description Section 10.2 Study Population Section 12.3 Randomization Section 17.4.7 Subgroup Analyses
Additional exclusion criteria: • Any physical disability that would prevent completion of study procedures or assessments (with examples provided) • Use of Souvenaid® within the 90 days prior to Baseline	Section 11.2 Exclusion Criteria

Summary of Changes	Primary Affected Sections in Revised Protocol (Version 3.0)
Modifications of exclusion criteria include: • Moderate to severe sleep apnea, even if adequately controlled (previously, subjects who were controlled were accepted) • Carbamazepine is not allowed (previously, use for treatment of restless legs was permitted) • G6PD deficiency has been defined based on WHO classification (<60% of normal, *i.e.*, <6.1 U/g Hgb) • Use of olanzapine is no longer exclusionary (the only disallowed antipsychotic is clozapine) • Need for a cardiology consult in subjects with left bundle branch block has been removed • The acceptable window for prior use of an investigational product for cognition has been reduced to 90 days (from 120 days) prior to Baseline (rather than Screening)	Section 11.2 Exclusion Criteria Appendix 28.1
Study Drug	
With the addition of a third treatment arm, all subjects will now receive four tablets daily, two in the morning and two in the evening, to maintain the study blind.	12.2 Study Regimens
The study drug wallet now contains 28 tablets (rather than 14 tablets)	12.4 Packaging, Labeling, and Storage
Assessments	
Information regarding education and main occupation will now be collected at Screening	Section 15.1 Demographic Data / Medical History Section 17.6 Demographic and Baseline Characteristics Appendix 28.3 Education / Occupation
In subjects with extended Screening, medical assessments for eligibility may need to be repeated if initial assessments were more than 42 days prior to Baseline	Section 10.4.1 Screening Assessments Section 10.4.1.2 Other Medical Screening Assessments
Brain MRI hyperintensities will now be quantified	Section 10.4.2.1 Imaging Efficacy Assessments Section 15.2.3.2 MRI Section 17.5 Exploratory Analyses
MMSE and CDR sum of boxes (which are obtained at Screening) will now also be assessed after 39 weeks, or upon early completion of the study	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments Section 10.4.2.2 Clinical Efficacy Assessments Section 15.3 Clinical Assessments and Raters Section 17.5 Exploratory Analyses
Whole blood will also be assessed for MT, *N*-desmethyl MT, and total MT concentrations (in addition to plasma)	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments Section 15.5.1 MT Concentration Section 15.5.1.1 Procedure for Blood Sample Collection Section 17.8 Other Data
A urine sample will be collected at the final visit (following all safety and efficacy assessments) for determination of color by the central laboratory; results will not be reported to the site	Section 10.1 General Description Section 10.4.3 Other Assessments Section 15.5.2 Urine Color Section 17.8 Other Data
Other	
Malignancies (with the exception of non-melanoma skin cancers) are to be to be reported as ADRs to Health Canada	Section 16.9 Malignancies Section 17.7 Safety Analysis

Summary of Changes	Primary Affected Sections in Revised Protocol (Version 3.0)
Stored samples may be kept for up to 8 years for future, as yet unspecified, analyses; consent to such storage is mandatory for participation in the study	Section 20 Stored Samples

28.4.4 Protocol Version 4.0

The protocol for Study TRx-237-039 (Version 3.0 dated 31 May 2018) has been updated to include administrative changes, as the responsible party for study management, monitoring, and pharmacovigilance has changed (previously PAREXEL International, now Syneos Health). Additional modifications and clarifications have been incorporated with respect to the Sponsor contact details, objectives and statistical analyses, background, study population, informed consent, study assessments, documentation, data protection, and study administration.

A summary of the key changes and affected sections is provided below.

Summary of Changes	Affected Sections in Revised Protocol (Version 4.0)
Sponsor Information	
The contact details for the Sponsor have been clarified to indicate that the company headquarters are in Singapore, while the operational location is in the United Kingdom.	Cover page
Compliance Statement	
Compliance statement regarding ICH GCP further clarified to include ICH E6(R1) in those jurisdictions where ICH E6(R2) is not yet implemented by the regulatory authorities. Reference to the Declaration of Helsinki has been clarified to refer to the current applicable version.	Section 2 GCP Compliance Statement Section 5 Investigator Signature Sheet Section 18 Regulatory and Ethics
Responsible Personnel	
Changes have been made to include updated contact information for the Global Project Manager, North America Medical Monitor, Europe Medical Monitor, and Pharmacovigilance, as the responsible party is now Syneos Health (previously PAREXEL International); the procedures for safety and regulatory/ethics reporting have been updated accordingly. Additional telephone numbers have been added to the list of DSSL 24-hour Medical Contacts, as the study will also be conducted in Italy and Spain. The vendor for recruitment services (ThreeWire) has been removed.	Section 4 Responsible Personnel Section 16.7 Serious Adverse Event Reporting Section 16.9 Malignancies Section 16.10 Reporting of Pregnancy Section 18 Regulatory and Ethics Section 18.1 Approval of the Protocol and Amendments
Objectives and Statistical Analyses	
The evaluation of the outcomes described in the Primary and Secondary Objectives for LMTM 16 mg/day and placebo has been clarified in Objective Nos. 6 and 12, and an evaluation of the outcomes of selected endpoints for pooled doses of LMTM 8 mg/day and 16 mg/day compared to placebo has been added as Objective No. 13. The various LMTM 8 mg/day as well as LMTM 16 mg/day and pooled comparisons to placebo are described in the SAP.	Synopsis Section 9.2 Secondary Objectives Section 17 Statistical Analysis
Background	
A new reference has been added regarding cysteine-independent inhibition of Alzheimer's disease-like paired helical filament assembly by leuco-methylthioninium (Al-Hilaly *et al*., 2018).	Section 8.1.1 Investigational Product Section 27 References
The summary of PK data from studies in subjects with renal and hepatic impairment has been clarified; results have been added from a completed study in healthy older volunteers.	Section 8.1.3.1 Pharmacokinetics

Summary of Changes	Affected Sections in Revised Protocol (Version 4.0)
Study Population	
Up to approximately 1500 subjects may be screened for the study (increased from 900).	Section 10.2 Study Population
Informed Consent	
Clarification that at all study sites, the PI or SI who obtains informed consent must be a physician (such as a neurologist, psychiatrist) or other medically qualified person.	Section 10.4.1 Screening Assessments Section 18.3 Informed Consent Section 21 Quality Assurance and Clinical Monitoring
Study Assessments	
Clarification that the initial ophthalmological examination for subjects with lens implants will be performed prior to the first dose of study drug (during the Screening procedures or as part of the Baseline assessments), rather than being limited to Screening.	Synopsis Section 10.1 General Description Section 10.4.1 Screening Assessments Section 10.4.1.2 Other Medical Screening Assessments Section 10.4.2 Baseline and Post-randomization Assessments Section 10.4.2.3 Safety Assessments Section 15.4 Safety Assessments and Procedures
Baseline characteristics to be collected include smoking history and history of lens implantation.	Section 15.1 Demographic Data/Medical History
Additional instruction for investigators assessing AEs during the study includes asking one or more questions to evaluate suicidal ideation and behavior at each in-clinic visit, as recommended by the U.S. FDA. Questions are to be addressed to both subjects and their study partners.	Section 16.2 Eliciting Adverse Event Information
Clarification provided that lens discoloration reported during ophthalmological examination is to be reported as an SAE.	Section 16.7 Serious Adverse Event Reporting
Medical history and adverse events will be coded using MedDRA Version 20.1.	Section 17.6 Demographic and Baseline Characteristics
Direct bilirubin and alkaline phosphatase have been added to clinical chemistry laboratory assessments.	Section 28.2 Study Blood Assessments
Documentation	
Further details regarding archiving and management of the eTMF are provided. The requirements for document retention and archiving have been clarified to refer to a minimum of 25 years after the end of the clinical trial.	Section 7 Abbreviations Section 22 Documentation
Clarification that all deviations identified at or by the site will be reported to the study monitor, and deviations from the SAP (if any) will be noted in the clinical study report.	Section 17 Statistical Analysis Section 18 Regulatory and Ethics
Data Protection	
Clarification that data protection obligations are not defined in the protocol, but rather are to be described in vendor contracts and subject-facing documentation (*e.g.*, in appropriate transparency notices included in informed consent documentation) in compliance with relevant local laws.	Section 19 Confidentiality and Data Protection
Study Administration	
Reference to pipettes has been removed from calibration certification, as the pipettes provided in the laboratory kits are disposable.	Section 26 Study Administration

28.4.5 Protocol Version 4.1

The protocol for Study TRx-237-039 (Version 4.0 dated 24 August 2018) has been revised in this administrative amendment to include an additional Sponsor signatory for Medical Oversight, and to remove references to specific personnel for Medical Monitoring representation in North America and Europe. The most current Medical Monitoring contact information is now provided by cross-reference to the Site Contact List in the Investigator Site File.

A summary of the changes and affected sections is provided below.

Summary of Changes	Affected Sections in Revised Protocol (Version 4.1)
Protocol Signatories	
An additional Sponsor signatory has been added for TauRx Medical Oversight.	Section 3 Protocol Approval
Responsible Personnel	
Specific names and contact information have been removed for personnel responsible for medical monitoring (*i.e.*, the North America Medical Monitor and Europe Medical Monitor). The most current contact information is now provided by cross-reference to the Site Contact List in the Investigator Site File.	Section 4 Responsible Personnel

28.4.6 Protocol Version 5.0

The protocol for study TRx-237-039 (Version 4.1 dated 9 November 2018) has been revised primarily to include the following modifications:

- The study design now includes two phases, including the double-blind treatment period (now 12 months, extended from 9 months) with subjects randomized to LMTM 16 mg/day, LMTM 8 mg/day, or placebo, followed by an open-label, delayed-start treatment period with LMTM 16 mg/day for an additional 52 weeks; study visits and schedules of assessments have been modified accordingly

- The study population now includes subjects with early to mild-moderate AD (previously only early AD), and the number of randomized subjects has been increased to approximately 450 subjects (previously 375 subjects)

- The primary objectives for the double-blind treatment period now pertain to comparing LMTM 16 mg/day with placebo for the co-primary endpoints of ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ (difference in temporal lobe ^{18}F-FDG-PET change in SUVR and the Composite Scale are no longer primary objectives), and for assessing safety and tolerability; secondary objectives have been modified to include comparisons of LMTM 16 mg/day with placebo in whole brain atrophy as measured by MRI, to restrict the ^{18}F-FDG-PET endpoints to subjects with CDR 0.5 at Screening, and to compare the LMTM dose of 8 mg/day for selected endpoints

Modifications have also been made to administrative information, criteria for subject enrollment and eligibility for the EAP, study drug supplies for the placebo group (now including a urinary discolorant to maintain blinding during the double-blind treatment period), and study assessments. A summary of the key changes and primary affected sections is provided below (as the Synopsis is affected by the majority of the changes, it is not listed).

Minor revisions have also been incorporated for clarity; these are not described below but are enumerated in a separate detailed summary of changes document.

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
Administrative	
The GCP compliance statement has been modified to indicate that the study will be conducted in compliance with the principles contained in the Declaration of Helsinki, rather than include reference to a specific version.	Section 2 GCP Compliance Statement Section 5 Investigator Signature Sheet Section 18 Regulatory and Ethics
The statistician for the study has been changed to Bjoern Schelter, PhD (Data Analytics and Biostatistics Lead for TauRx).	Section 3 Protocol Approval
The TauRx Global Project Leads for this study are now Sotereos Gates and Alison Walker (previously Sean Neville).	Section 4 Responsible Personnel
A Coordinating Investigator, Serge Gauthier, C.M., C.Q., MD, FRCPC, is now identified.	Section 4 Responsible Personnel
The current 24-hour medical contact (DSSL) information is also provided by cross-reference to the Site Contact List in the Investigator Site File.	Section 4 Responsible Personnel

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
For image hypersensitivities, Aberdeen Biomedical Imaging Centre has been removed as the data output will be provided by BioClinica, Inc.	Section 4 Responsible Personnel
Study Population	
The protocol now includes subjects with early to mild-moderate AD rather than only those with early AD. MMSE and CDR severity scores at Screening have been modified to reflect this change (*i.e.*, MMSE 16 to 27 [inclusive] and Global CDR 0.5 to 2 [if 0.5, including a score of >0 in one of the functional domains]). An additional stratification level for MMSE severity (*i.e.*, 16-19) has been added, with a target of approximately 2:3:1 for MMSE scores of 16-19, 20-25, and 26-27, respectively.	Cover Page Section 10.1 General Description Section 10.2 Study Population Section 11.1 Inclusion Criteria Section 11.3 Re-screening Section 12.3 Randomization Section 17 Statistical Analysis Section 17.2 Number of Subjects and Sample Size Calculation
The study will be conducted in approximately 150 study sites in North America and Europe (previously planned to be at least 100 study sites in North America, Europe, and Rest of World). Approximately 2000 subjects (previously up to 1500 subjects) may be screened.	Section 10.2 Study Population Section 12.3 Randomization Section 17.4.9 Subgroup Analyses
Clarification provided that, at Screening, an interview and examination by the investigator are required to ensure subjects have a likely diagnosis of AD or MCI-AD prior to being offered consent forms. It is further specified that the accuracy of the diagnosis is to be confirmed independently by the diagnosing physician at the site.	Section 10.4.1 Screening Assessments Section 11.1 Inclusion Criteria
Treatment Groups	
The primary treatment group comparison is now LMTM 16 mg/day *versus* placebo, with secondary comparison of subjects receiving 8 mg/day *versus* placebo. The rationale for revising primary LMTM dosing to 16 mg/day (using plasma concentration thresholds based upon a population PK model) and for adding the open-label, delayed-start treatment phase is described. Safety margins for nonclinical data were updated to reflect the 16 mg/day dose. Supportive data regarding reduction in treatment effects of LMTM by pretreatment with an AChEI or memantine are also described.	Section 8.1.2 Nonclinical Data Section 8.2 Rationale Section 9.1 Primary Objectives Section 9.2.1 Double-blind Treatment Period Section 10.1 General Description Section 12.2 Study Regimens
The number of randomized subjects has been increased to approximately 450 subjects (previously 375 subjects), with a ratio of 4:1:4 (at the study level) to LMTM 16 mg/day (200 subjects), LMTM 8 mg/day (50 subjects), and placebo (200 subjects).	Section 10.1 General Description Section 10.2 Study Population Section 12.2 Study Regimens Section 12.3 Randomization Section 17.2 Number of Subjects and Sample Size Calculation
Study Design	
The study design has been modified to occur in two phases. The randomized, double-blind, placebo-controlled portion is now a 12-month (extended from 9-month) study, including five (rather than four) post-randomization visits (Visits 3 through 7). Following completion of the double-blind treatment period, subjects will continue open-label treatment with LMTM 16 mg/day for an additional 52 weeks, representing a modified delayed start of treatment; the open-label, delayed-start phase will include three treatment visits (Visit 8 [telephone contact], Visit 9, and Visit 10). Prior treatment assignment will not be unblinded; however, upon completion of the initial 52-week, double-blind, placebo-controlled treatment period, the database will be	Cover Page Section 8.2 Rationale Section 9 Objectives Section 10.1 General Description Section 10.3 Duration Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 12.2 Study Regimens Section 12.5 Dispensing Section 12.6 Compliance Section 12.8 Breaking the Blind for the Double-Blind Treatment Period

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
locked and unblinded for analysis. Individual subject treatment assignment will not be divulged to subjects or individuals involved in the conduct of the ongoing open-label, treatment phase (except in cases of medical situations where it is deemed essential in order to provide appropriate care). Access to the randomization list has also been clarified.	Section 13 Concomitant Medications and Subject Restrictions Section 17.1.3 Secondary Endpoint for Open-Label, Delayed-Start Phase Section 17.4.1 Hypothesis Section 17.4.5 Open-Label, Delayed-Start Analysis
Total duration of participation for an individual subject is now up to 120 weeks (rather than 54 weeks), including a Screening period of up to 16 weeks, a double-blind treatment period of 52 weeks, and a further open-label, delayed-start phase of 52 weeks. Overall study duration is now anticipated to be at least 40 months (rather than 24 months), depending on recruitment.	Section 10.1 General Description Section 10.3 Duration
Subject Enrollment and Withdrawal	
The protocol now states that, in the case of subjects with reduced decision-making capacity, legally acceptable representative(s), consistent with national law, may provide (and withdraw) written informed consent.	Section 7 Abbreviations Section 10.4.1 Screening Assessments Section 11.1 Inclusion Criteria Section 11.4.2 Handling of Study Discontinuation / Withdrawal Section 18.3 Informed Consent
Clarification that subjects are not to be treated with an AChEI and/or memantine within the 60 days prior to Baseline assessments, rather than only Baseline ^{18}F-FDG-PET as previously stated.	Section 10.1 General Description Section 10.4.1 Screening Assessments Section 11.1 Inclusion Criteria Section 13.1 AChEI and/or Memantine
Re-screening of a subject is allowed to a newly specified maximum of two re-screening occasions. An additional acceptable instance for re-screening has been added for subjects with Hgb below the lower limit of laboratory normal; such subjects may be re-consented and re-screened after appropriate management at the discretion of the TauRx Medical lead. Any other criterion not included the list would require approval by TauRx.	Section 11.3 Re-Screening
Criteria for significant head injury no longer specifies a specific duration of associated loss of consciousness.	Section 11.2 Exclusion Criterion #3
Criteria for epilepsy now specifies that a single prior seizure >6 months prior to Screening is considered acceptable.	Section 11.2 Exclusion Criterion #4
Determination of whether or not a Screening Hgb value below age/sex appropriate lower limit of normal is exclusionary now includes discussion with the Medical Monitor, with final decision at the discretion of the Medical Oversight Lead.	Section 11.2 Exclusion Criterion #12
Subjects with moderate to severe sleep apnea are to be excluded if the apnea is currently, rather than previously, diagnosed; the definition of moderate to severe apnea is now included (*e.g.*, requiring oxygen supplementation).	Section 11.2 Exclusion Criterion #15
Clarified that active hepatitis or primary biliary cirrhosis; or active HTLV-III, LAV, mutants/derivatives of such, or conditions associated with AIDS or similar, are exclusionary.	Section 11.2 Exclusion Criterion #16
Further definitions have been added for exclusions regarding cancer diagnosis *(e.g.*, new diagnosis within past 2 years, or previous [>2 years] diagnosis requiring any intervention or treatment within past 2 years).	Section 11.2 Exclusion Criterion #17
Subjects who complete the study and receive treatment with LMTM up to and including the last open-label visit may be eligible for the EAP (and once entered into the EAP, are required to remain off AChEIs and/or memantine). Patients	Section 10.2 Study Population Section 10.6 Definition of End of Study Section 11.4.1 Handling of Subjects who Discontinue Study Drug

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
who discontinue treatment permanently in this study will not be eligible for the EAP.	Section 12.2.2 Dose Interruption
Study Drug	
The study title now refers to the investigational study drug by its USAN. In addition to hydromethylthionine mesylate being the USAN, clarification is provided that it is also the INN.	Cover Page Section 8 Background and Rationale for the Study Section 8.1.1 Investigational Product Section 12.1.1 Active Ingredient
The drug supplies for the placebo group will include tablets containing a urinary discolorant, MTC, 4 mg. To prevent inadvertent unblinding due to urinary discoloration, subjects randomized to placebo may receive a 4-mg tablet of MTC as one of the four tablets to be taken daily (the remainder being placebo tablets), in order to maintain the treatment blind.	Section 8.1.1 Investigational Product Section 8.2 Rationale Section 12.2 Study Regimens
Additional drug dispensing visits now include Visits 6 and 7 during double-blind treatment, as well as Visit 9 of the open-label, delayed-start phase, at which time the number of tablets dispensed will be recorded and the complete study drug kit will be returned. Subject compliance with study drug now will also occur at Visits 6 and 7 during the double-blind treatment period, at Visits 9 and 10 during the open-label, delayed-start phase, and during the telephone contact (Visit 8).	Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 12.2 Study Regimens Section 12.5 Dispensing Section 12.6 Compliance
Imaging Assessments	
^{18}F-FDG-PET imaging is now to be performed only in AD subjects with CDR 0.5; imaging is to occur at Baseline and at end of double-blind treatment, *i.e.*, Visit 7/Week 52 (or early termination). For purposes of establishing the Baseline assessment, ^{18}F-FDG-PET images are to be obtained prior to Visit 2 and at least 60 days after the last dose of AChEI and/or memantine.	Section 9.2.1 Double-blind Treatment Period Section 10.1 General Description Section 10.4.1 Screening Assessments Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.1 Imaging Efficacy Assessments in Double-Blind Treatment Period Section 13.4 Drugs Used to Manage Behavioral Disturbance Section 13.5 Other Medications Section 15.3.1 General Considerations Section 15.3.3.1 ^{18}F-FDG-PET Section 17.1.2 Secondary Efficacy Endpoints for Double-Blind Treatment Period Section 17.3 Analysis Populations Section 17.4.6 Dose Response Analyses
Additional volumetric brain MRIs and cognitive / functional assessments (ADAS-cog$_{13}$ and ADCS-ADL$_{23}$) are to be conducted at Visit 7/Week 52, as well as after the additional 26 and 52 weeks of open-label treatment (Visit 9/Week 78 and Visit 10/Week 104), or upon early termination in the case of the ADAS-cog$_{13}$ and ADCS-ADL$_{23}$. As pertains to early termination and MRI scans, no additional scan is required if the subject's last scan was performed < 90 days prior to the early termination date for either the double-blind treatment period or open-label treatment period.	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.1 Imaging Efficacy Assessments in Double-Blind Treatment Period Section 10.4.2.2 Clinical Efficacy Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.4.3.1 Imaging Efficacy Assessments in the Open-Label, Delayed-Start Phase Section 15.3.3.2 MRI
The estimated total radiation exposure to subjects from the amyloid PET scan procedure (if not performed previously) is now provided.	Section 15.3.1 General Considerations
Clinical Efficacy Assessments	
At Screening, the CDR assessment is only to be performed if the subject meets the MMSE inclusion criteria, and if the	Section 10.1 General Description

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
subject does not qualify with either of these scales, no further assessments are to be made and the subject will be considered a screen failure. For enrolled and randomized subjects, the MMSE and CDR sum of boxes (as exploratory clinical efficacy assessments) are to be administered at Visit 7 and at the final open-label, delayed-start visit (Visit 10), or upon early termination.	Section 10.4.1.1 Diagnostic and Cognitive Eligibility Assessments Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.2 Clinical Efficacy Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.4.3.2 Clinical Efficacy Assessments in the Open-Label, Delayed-Start Phase Section 15.2.2 Instruments Section 17.5 Exploratory Analyses
Efficacy rater requirements, allocation, and the order of assessments by visit have been clarified. The CDR and MMSE are now further described in the protocol with additional references included.	Section 15.2 Assessment of Efficacy *(and all subsections)* Section 27 References
Safety Assessments	
Safety assessments are to occur at each clinic visit during double-blind treatment, with additional assessments after 26 and 52 weeks of open-label treatment (Visit 9/Week 78 and Visit 10/Week 104), and as needed to follow up on an AE. A telephone contact has been added to record AEs and changes in concomitant medications after 4 weeks in the open-label, delayed-start phase (Visit 8/Week 56). All safety assessments are to be performed by an independent qualified assessor not involved in efficacy measures, with certain assessments now specified to be conducted and/or reviewed by a medical assessor (physician/MD/DO), including targeted physical and neurological examinations, clinical laboratory and ECG results, and AEs and concomitant medications.	Section 10.1 General Description Section 10.4.1.2 Other Medical Screening Assessments Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.3 Safety Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.4.3.3 Safety Assessments in the Open-Label, Delayed-Start Phase Section 13 Concomitant Medications and Subject Restrictions Section 15.4 Safety Assessments and Procedures
Additional ophthalmological examinations in subjects with lens implants are to occur at Visits 7 and 10 (or early termination) to assess for potential lens discoloration. It is now specified that the examinations are to be conducted by an ophthalmologist, optometrist, or other suitably qualified medical assessor (physician/MD/DO).	Section 10.1 General Description Section 10.4.1 Screening Assessments Section 10.4.1.2 Other Medical Screening Assessments Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.3 Safety Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.4.3.3 Safety Assessments in the Open-Label, Delayed-Start Phase Section 15.4 Safety Assessments and Procedures
Targeted physical examinations, to be performed by a medical assessor, are now specified to include, at a minimum, heart and lung auscultation and brief neurological assessment guided by any reported signs/symptoms/AEs (*e.g.*, evaluating for potential serotonin toxicity).	Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 15.4 Safety Assessments and Procedures
For women of childbearing potential, it is now specified that the return visit to the clinic for pregnancy testing is to occur within 3 months of last exposure to study drug in the event of delayed menstruation.	Section 10.1 General Description Section 13.7 Contraceptive Measures Section 16.10 Reporting of Pregnancy
New AEs and SAEs reported by a subject after screen failure will not be recorded for the study. Emergent AEs and SAEs up to the point of screen failure will be followed up to resolution at the discretion of the PI.	Section 16.1 Definition of AEs, Period of Observation, and Recording of AEs Section 16.7 Serious Adverse Event Reporting

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
Other Assessments	
In addition to study visits that are to occur in the morning for Visits 2 and 3 to allow for in-clinic dosing and PK blood sampling, the protocol now specifies that in-clinic dosing and PK sampling are also to occur at morning appointments for Visit 7 (after 52 weeks on study drug) and Visit 10 (after 104 weeks of study drug). Subjects are to be instructed not to take their morning dose at home.	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.4 Other Assessments in Double-Blind Treatment Period Section 10.4.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.4.3.4 Other Assessments in Open-Label, Delayed-Start Phase Section 12.2 Study Regimens Section 15.5.1 MT Concentration
A urine sample will no longer be collected for color determination by the central laboratory.	Section 10.1 General Description Section 10.4.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.4.2.4 Other Assessments in Double-Blind Treatment Period Section 15.5.2 Urine Color *(deleted)*
Blood samples for determination of plasma and whole blood MT concentrations will now be 9-mL blood samples collected in 9-mL vacutainers (previously 8-mL).	Section 15.5.1.1 Procedure for Blood Sample Collection
Objectives and Endpoints / Statistical Analyses	
The primary objectives now pertain to the double-blind treatment period only, comparing LMTM 16 mg/day with placebo for the co-primary endpoints of ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ (difference in temporal lobe ^{18}F-FDG-PET change in SUVR and the Composite Scale are no longer primary objectives), and for assessing safety and tolerability. Secondary objectives have been modified for the double-blind treatment phase to include comparisons of LMTM 16 mg/day with placebo in whole brain atrophy as measured by MRI, to restrict the ^{18}F-FDG-PET endpoints to subjects with CDR 0.5 at Screening, and to compare the LMTM dose of 8 mg/day for selected endpoints. Brain MRI remains as a secondary efficacy endpoint, with clarification that it will also be used to confirm a lack of treatment unblinding.	Section 9.1 Primary Objectives Section 9.2 Secondary Objectives Section 9.2.1 Double-blind Treatment Period Section 9.2.2 Open-Label, Delayed-Start Phase Section 15.3.1 General Considerations Section 17 Statistical Analysis Section 17.1.1 Primary Efficacy Endpoints for Double-Blind Treatment Period Section 17.1.2 Secondary Efficacy Endpoints for Double-Blind Treatment Period Section 17.4.1 Hypothesis
The Composite Scale will now be based on items selected from the ADAS-cog$_{13}$, rather than the ADAS-cog$_{11}$, and on selected items from the ADCS-ADL$_{23}$, with analysis at 9 months and 12 months during double-blind treatment to evaluate usefulness for future studies and is included in the exploratory analyses.	Section 15.2.2.1 ADAS-cog Section 15.2.2.2 ADCS-ADL$_{23}$ Section 15.2.2.3 Composite Scale
Two open-label, delayed-start phase objectives have been added: determination if there is a difference in disease progression on the co-primary clinical endpoints and MRI imaging endpoint for subjects who started treatment in the double-blind phase and those who started in the open-label, delayed-start phase (*i.e.*, "early" and "late" LMTM starters, respectively), and assessment of safety and tolerability of LMTM given for up to 104 weeks. Additional statistical analysis for the open-label phase has been defined.	Section 9.2.2 Open-Label, Delayed-Start Phase Section 17 Statistical Analysis Section 17.1.3 Secondary Endpoint for Open-Label, Delayed-Start Phase
Sample size estimations and study power to determine treatment effect have been revised based upon changes to primary treatment group, study population, co-primary clinical endpoints, and length of the double-blind treatment period of the study. Sample size estimations have also been	Section 17.2 Number of Subjects and Sample Size Calculation

Summary of Changes	Affected Sections in Revised Protocol (Version 5.0)
added for the open-label, delayed-start treatment period of the study.	
Clarification is provided that the primary efficacy analyses for FDA will be based on the E-MITT, MI-MITT, or I-MITT population (depending on endpoint), and for EMA on the ITT population. The co-primary efficacy endpoints and MRI will be analyzed using a linear mixed model for repeated measures with unstructured covariance matrix, and ^{18}F-FDG-PET analyzed using an ANCOVA, with covariates for this model adjusted accordingly.	Section 17 Statistical Analysis Section 17.4 Clinical Efficacy and Imaging Analysis Section 17.4.2 FDA Analysis
Evaluation of the influence of ApoE genotype (in subjects who provide legally acceptable consent) on the primary and selected secondary endpoints is now an exploratory endpoint (previously a secondary endpoint).	Section 9.2 Secondary Objectives Section 17.1.2 Secondary Efficacy Endpoints for Double-Blind Treatment Period Section 17.5 Exploratory Analyses
No interim futility or efficacy analysis is planned in which treatment groups will be compared. Recruitment and discontinuations will, however, be continuously monitored in a blinded fashion and projections on future dropouts calculated. In addition, a blinded interim analysis to re-estimate the assumed SD for the change from Baseline to Week 52 in the primary endpoints may be carried out at some point during the study's recruitment period.	Section 17.9 Interim Analysis

28.4.7 Protocol Version 5.1

The protocol for Study TRx-237-039 (Version 5.0 dated 9 July 2019) has been revised primarily to include modifications to the exclusion criterion regarding hematological abnormalities (reverting to the original criterion), clarifications to background information for the study drug and the efficacy objectives/statistical analyses, as well as updates to responsible personnel. A summary of the key changes and affected sections is provided below.

Additional revisions are editorial and are intended to correct typographical errors or add further clarification.

Summary of Changes	Affected Sections in Revised Protocol (Version 5.1)
Responsible Personnel	
Charles River Laboratories Edinburgh Ltd has been added to responsible personnel for analysis of MT concentrations (cross-validation purposes only).	Section 4 Responsible Personnel
Subject Enrollment and Withdrawal	
The provision for discussion of potentially exclusionary low screening Hgb values with the Medical Monitor has been removed; Hgb values below age/sex appropriate lower limit of the central laboratory normal range are once again exclusionary regardless of etiology.	Synopsis Section 11.2 Exclusion Criterion #12 Section 11.3 Re-screening
Study Drug	
Clarification has been added that the increased incidences of pancreatic islet cell adenoma and adenoma or carcinoma (combined) in male rats, reported in a 2-year carcinogenicity study performed by the National Toxicology Program, were attributed to MTC by FDA (as interpreted by the FDA Executive Carcinogenicity Assessment Committee).	Section 8.1.2 Nonclinical Data
Clarification has been added that the magnitude of concentration-dependent treatment effects was reduced when LMTM was given to subjects who were concurrently using (rather than prior use of) AChEIs and/or memantine.	Section 8.1.3.3 Efficacy
Objectives and Endpoints / Statistical Analyses	
To correct a typographical error in the synopsis regarding the first secondary endpoint (the comparison of the LMTM dose of 16 mg/day with the placebo group in annualized rate of whole brain atrophy, rather than temporal and parietal lobe atrophy).	Synopsis
To clarify the exploratory analysis for comparison of decline in temporal lobe ^{18}F-FDG-PET SUVR with the estimated decline for subjects with mild AD (CDR 0.5); reference to the MMSE range has been removed. The analyses will be further described and clarified in the SAP.	Section 17.5 Exploratory Analyses

28.4.8 Protocol Version 6.0

The protocol for Study TRx-237-039 (Version 5.1 dated 05 February 2020) has been revised to incorporate modifications to the study conduct and monitoring, guidance for continued data collection and analysis, and ongoing risk assessment due to the COVID-19 Public Health Emergency. In addition, the total number of subjects to be randomized has increased, and updates have been incorporated for contact information for responsible personnel, as well as modifications and/or clarifications to investigator responsibilities, study assessments, and statistical analyses. Reference to a separate plan has been included for additional analyses to be undertaken of the blinded ^{18}F-FDG-PET and MRI data for scientific research and quality control purposes. A summary of the key changes and affected sections is provided below.

Additional revisions are editorial and are intended to correct typographical errors and editorial inconsistencies as well as to add clarification.

Summary of Changes	Affected Sections in Revised Protocol (Version 6.0)
Changes due to COVID-19 Public Health Emergency	
The post-Baseline visits for safety, PK, and genotyping blood sample collection as well as efficacy assessments may be completed in-clinic at the site, in the home, or at other safe, suitable alternative location if deemed necessary to protect subjects due to COVID-19. Acceptable procedures for safety and efficacy assessments, blood sample collection, shipment, and analysis are described. Study visit windows may be further extended at the discretion of the Sponsor when justification is provided.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 10.5.3 Assessments in the Open-Label, Delayed-Start Phase Section 13.7 Contraceptive Measures Section 15.4 Safety Assessments and Procedures Section 15.5.1 MT Concentration Section 16.7 Serious Adverse Event Reporting
Alternative arrangements for dispensing study drug supplies may be permitted if deemed necessary to protect subjects due to COVID-19. Requirements for obtaining subject consent consistent with local and national requirements, maintaining the specified study drug storage conditions, and handling, accountability, and compliance monitoring will be addressed and documented.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 12.2 Study Regimens Section 12.5 Dispensing
If a subject is undergoing screening assessments and cannot have assessments performed due to COVID-19, the subject should be put on screening pause until such times as COVID-19 impacts have ceased.	Synopsis Section 10.2.1 Changes to Study Conduct Section 10.5.1.1 Diagnostic and Cognitive Eligibility Assessments Section 11.3 Re-screening
The Sponsor may approve subject randomization without a brain ^{18}F-FDG-PET scan if the scan cannot be performed due to COVID-19.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 10.5.1 Screening Assessments Section 10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period
All MRI scans are to be performed at approved MRI centers using approved scanners; no alternative scanners will be accepted; there is to be no change in scanner for a given subject over the course of the study. Guidance will be provided for scheduled MRI visits at approved imaging centers that may be closed due to COVID-19, including acceptable windows outside of the scheduled visit window during which MRI scans can still be performed and would be accepted for analysis.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 15.3.1 General Considerations Section 15.3.3.2 MRI
All ^{18}F-FDG-PET scans are to be performed at approved PET centers using approved scanners; there is to be no	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct

Summary of Changes	Affected Sections in Revised Protocol (Version 6.0)
change in scanner for a given subject over the course of the study.	Section 15.3.1 General Considerations
The ADAS-cog$_{13}$ may also be performed by videoconference and the MMSE, ADCS-ADL$_{23}$, and CDR may be performed by speakerphone. The remote efficacy scale assessments are now described in the protocol.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 15.2.2 Instruments
Clarification is now provided that multiple study partners participating only as caregivers will be permitted for a given subject, either simultaneously or as replacements for previous study partners, with no specified maximum. A maximum total of two study partners participating as informants (*i.e.*, one replacement) would normally be permitted for a given subject; however, up to a total of four study partners (*i.e.*, three replacements) are permitted if circumstances change due to COVID-19. Information obtained from study partners participating as informants will be appropriately identified to distinguish each informant in the event that a given subject has more than one study partner providing data for analysis.	Synopsis Section 10.1 General Description Section 10.2.1 Changes to Study Conduct Section 10.5.1 Screening Assessments Section 10.5.1.1 Diagnostic and Cognitive Eligibility Assessments Section 11.4.2 Handling of Study Discontinuation / Withdrawal Section 11.4.3 Replacements Section 15.2.1 Raters
For PK blood sample collection at Visit 2, Visit 3, Visit 7, and Visit 10, the third sample to be collected approximately 4 hours after the dose is not required if the visit occurs in the home.	Synopsis Section 10.2.1 Changes to Study Conduct Section 10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.5.2.4 Other Assessments in Double-Blind Treatment Period Section 10.5.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.5.3.4 Other Assessments in Open-Label, Delayed-Start Phase Section 15.5.1 MT Concentration
Sections have been added describing the Sponsor's ongoing risk assessment regarding the impact of COVID-19 on this study, including guidance for continued data collection and potential changes in site and remote monitoring procedures, as well as changes to statistical analyses.	Synopsis Section 10.2 Changes Implemented Due to COVID-19 Section 10.2.1 Changes to Study Conduct Section 10.2.2 Changes to Study Monitoring Section 10.2.3 Changes to Statistical Analyses Section 17.4.11 Sensitivity Analyses Section 17.9 Interim Analysis Section 18 Regulatory and Ethics Section 21.2 COVID-19 Risk Assessment *(new)*
Responsible Personnel	
A DSSL 24-hour medical contact telephone number has been added for France.	Section 4 Responsible Personnel
Investigator responsibilities include supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.	Section 18.4 Investigator Responsibilities
Study Population	
The number of randomized subjects has been increased: a sufficient number of subjects will be recruited such that approximately 500 subjects are enrolled; beginning with Version 5.0, approximately 450 subjects are to be enrolled and randomized in a 4:1:4 ratio (at the study level) to the LMTM 16-mg/day, LMTM 8-mg/day, and placebo groups. The inclusion criterion for an MMSE score of 16-27 (inclusive) at Screening will be subject to stratification requirements.	Synopsis Section 10.1 General Description Section 10.3 Study Population Section 11.1 Inclusion Criteria Section 12.2 Study Regimens Section 12.3 Randomization Section 17.2 Number of Subjects and Sample Size Calculation

Summary of Changes	Affected Sections in Revised Protocol (Version 6.0)
Imaging	
If subjects have an acceptable MRI scan or PET scan (the latter only in subjects who have a screening CDR of 0.5) already completed during the original Screening window, the scan does not require repetition.	Section 10.2.1 Changes to Study Conduct Section 10.5.1.1 Diagnostic and Cognitive Eligibility Assessments Section 11.3 Re-screening Section 15.3.3.1 ^{18}F-FDG-PET
Reference is included to a separate plan and data transfer agreement that will capture standard procedures for additional exploratory analyses to be undertaken to characterize the blinded ^{18}F-FDG-PET and MRI data for scientific research and quality control purposes, which are separate from the study objectives.	Section 20.2 Imaging Data *(new)*
Added consistent wording regarding baseline ^{18}F-FDG-PET scan in subjects who have a screening CDR of 0.5.	Synopsis Section 10.1 General Description Section 10.5.2.1 Imaging Efficacy Assessments in Double-Blind Treatment Period Section 11.3 Re-screening Section 13.1 AChEI and/or Memantine Section 15.3.3.1 ^{18}F-FDG-PET
Safety	
Permanent discontinuation due to decreased creatinine clearance is only required in subjects if renal concerns arise.	Section 11.4.1 Handling of Subjects Who Discontinue Study Drug Section 16.11.2 Other Safety Reasons Requiring Discontinuation of Study Drug
Any abnormal laboratory test result from Screening assessments (prior to treatment) is to be added to the subject's medical history, unless deemed clinically significant by the medical assessor (MD/DO) in which case it will be recorded as an AE.	Section 15.4 Safety Assessments and Procedures Section 16.1 Definition of AEs, Period of Observation, and Recording of AEs
Other Assessments	
Guidance is now provided regarding collection of blood samples at early termination visits for determination of MT concentrations.	Synopsis Section 10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.5.2.4 Other Assessments in Double-Blind Treatment Period Section 10.5.3 Assessments in the Open-Label, Delayed-Start Phase Section 10.5.3.4 Other Assessments in Open-Label, Delayed-Start Phase Section 15.5.1 MT Concentration
Statistical Analyses	
The secondary efficacy endpoints to compare the difference in temporal lobe ^{18}F-FDG-PET change in SUVR normalized to pons in subjects with CDR 0.5 at Screening (LMTM 16 mg/day *versus* placebo, and LMTM 8 mg/day *versus* placebo) will now only be analyzed if a predefined threshold is reached for a sufficient number of subjects providing data as specified in the SAP.	Synopsis Section 9.2.1 Double-Blind Treatment Period Section 17.1.2 Secondary Efficacy Endpoints for Double-Blind Treatment Period

Summary of Changes	Affected Sections in Revised Protocol (Version 6.0)
Upon completion of the initial 52-week, double-blind, placebo-controlled treatment period, the database will be locked and unblinded for analysis, and an interim report will be prepared describing the complete efficacy and safety analyses of the double-blind phase; individual subject prior treatment assignment will not be divulged to subjects or individuals involved in the operational conduct of the ongoing open-label, treatment phase.	Section 10.1 General Description Section 10.7 Definition of End of Study Section 12.8 Breaking the Blind for Double-Blind Treatment Period Section 17.9 Interim Analysis
Due to the introduction of MTC spiking in the placebo arm with Protocol Version 5.0, the respective MITT populations will be restricted to subjects randomized to Protocol Versions 5.0 and above for the primary and key secondary analyses as per the SAP. The full MITT populations will be analyzed for these as a sensitivity analysis. Details will be provided in the SAP.	Section 17.3 Analysis Populations Section 17.4 Clinical Efficacy and Imaging Analysis
It is now indicated that the SAP will specify estimands to provide a more comprehensive assessment of the performance and efficacy of the drug accounting for various factors (importantly, drop-outs).	Section 17.4.4 Estimands
The last observation carried forward (LOCF) imputation has been removed from the statistical analyses.	Section 17.4.11.6 Last Observation Carried Forward (LOCF) Imputation *(deleted)*

28.4.9 Protocol Version 7.0

The protocol for Study TRx-237-039 (Version 6.0 dated 09 October 2020) has been revised to incorporate changes to responsible personnel; updates to the background information to reflect the most current version of the Investigator's Brochure; clarification of assessments and drug dispensing for Visit 7 of double-blind treatment (also Baseline/Day 1 of open-label phase); addition of lens discoloration as an AESI and further instruction regarding timing of slit lamp examinations; clarification that MT concentration sampling will not continue for the off-treatment on-study (TOTOS) group; and further description of composite scores and endpoints. Additional statistical analysis updates include sensitivity and subgroup analyses, and further detail provided for primary endpoints, all in response to potential impacts of COVID-19; the primary efficacy hypotheses have been clarified; and the primary estimand and five components of interest are now described.

A summary of the key changes and affected sections is provided below.

Additional revisions are editorial and are intended to correct typographical errors and editorial inconsistencies as well as to add clarification.

Summary of Changes	Affected Sections in Revised Protocol (Version 7.0)
Signatories / Responsible Personnel	
Modified address for Sponsor Medical Oversight signatory.	Section 3 Protocol Approval
The Global Project Manager has been changed to Marty Perry, with corresponding telephone numbers and email address added.	Section 4 Responsible Personnel
The 24-hour Medical Contact has been changed from DSSL to Emergency Scientific and Medical Services Global (ESMS Global).	Section 4 Responsible Personnel
The Central Laboratory has been changed from Covance, Inc. to Labcorp Central Laboratory Services (e.g., Labcorp Central Laboratory Services LP in the Americas and Labcorp Central Laboratory Services S.à r.l in Europe).	Section 4 Responsible Personnel Section 10.2.1 Changes to Study Conduct Section 10.5.1 Screening Assessments Section 15.5.2 Genotyping
Certara USA, Inc. is now responsible for Statistical Analysis of Pharmacokinetic Data rather than the Institute for Clinical Pharmacodynamics, with corresponding addresses and telephone number added for Certara's New Jersey and Amsterdam locations.	Section 4 Responsible Personnel
The data management and statistics responsible personnel have now been divided, with Synteract, Inc. continuing to be responsible for data management and Cytel Inc. now responsible for statistics (corresponding address and telephone number added for Cytel Inc.).	Section 4 Responsible Personnel Section 12.8 Breaking the Blind for Double-Blind Treatment Period
Background	
The background information has been updated to be reflective of the most current version of the Investigator's Brochure (Version 23.0), including updates to nonclinical and clinical data as well as the study drug terminology. The discussion of drugs currently available to treat AD has been updated to include the recent FDA accelerated approval of Aduhelm (aducanumab).	Synopsis Section 8 Background and Rationale for the Study Section 8.1.1 Investigational Product Section 8.1.2 Nonclinical Data Section 8.1.3.1 Pharmacokinetics Section 8.1.3.3 Efficacy Section 8.1.3.4 Safety Section 8.2 Rationale Section 12.1.1 Active Ingredient Section 13.2 Drugs with Serotonergic Potential

Summary of Changes	Affected Sections in Revised Protocol (Version 7.0)
	Section 13.3 CYP and P-gp Substrates Section 13.6 Dietary Tyramine Section 13.8 Folate and Vitamin B_{12} Section 15.5.1 MT Concentration Section 17.8 Other Data Section 27 References
Study Visits and Drug Dispensing	
Clarification provided that Visit 7 of the double-blind treatment period is also Baseline/Day 1 of the open-label phase. The in-clinic dose of study drug at Visit 7 is to be taken from a newly dispensed open-label study drug kit, after pre-dose assessments have been completed. The pre-dose and post-dose assessments to be performed at Visit 7 have also been clarified.	Synopsis Section 10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.5.3 Assessments in the Open-Label, Delayed-Start Phase Section 12.2 Study Regimens Section 12.5 Dispensing Section 15.2.1 Raters Section 17 Statistical Analyses Section 17.4.6 Open-Label, Delayed-Start Analysis
Efficacy	
Composite Scores (and additional Composite Endpoints [if any]) derived from the ADAS-cog_{13} and the ADCS-ADL_{23} will be defined in the SAP prior to sign off and database lock/unblinding, with at least one designed to be sensitive to early stages of the disease as well as one that is less/not impacted by COVID-19.	Synopsis Section 15.2.2 Instruments Section 15.2.2.3 Composite Scale(s) Section 17.5 Exploratory Analyses
Safety	
Clarification that slit lamp ophthalmological examinations in subjects with history of lens implants are to be performed prior to the first dose of study drug (Screening/Baseline), at Visit 7, and at Visit 10/early termination to check for lens discoloration. In addition, this examination is now to be performed if subjects have cataract surgery/lens implantation at any point during study participation (as soon as possible after the surgery), as well as in response to visual complaints if suggestive of lens discoloration.	Synopsis Section 15.4 Safety Assessments and Procedures Section 16.11.2 Lens Discoloration
A new section added for lens discoloration, which is now a pre-specified AESI (in addition to hemolytic anemia). If a lens discoloration is identified by slit lamp examination, it is to be recorded as an AESI in the AE eCRF; however, no specific action is required for study drug. Lens discoloration has been removed from the list of examples of SAEs that are not life-threatening, as it should be reported as an AESI unless SAE reporting criteria are later met.	Section 16.7 Serious Adverse Event Reporting Section 16.11 Guidance for the Handling of Adverse Events of Special Interest and Selected Test Abnormalities Section 16.11.2 Lens Discoloration
Clarification that adverse events of malignancies other than non-melanoma skin cancers are to be reported to Syneos Health (regardless of causality or whether they meet the criteria for serious).	Section 16.9 Malignancies Section 17.7 Safety Analysis
Other Assessments	
For MT concentration sampling, if a subject has discontinued study drug but continues to attend study visits off-treatment (the TOTOS group), blood samples will not continue to be collected for measurement of MT concentrations.	Synopsis Section 10.5.2 Baseline and Post-randomization Assessments in Double-Blind Treatment Period Section 10.5.3 Assessments in the Open-Label, Delayed-Start Phase Section 11.4.1 Handling of Subjects Who Discontinue Study Drug

Summary of Changes	Affected Sections in Revised Protocol (Version 7.0)
	Section 15.5.1 MT Concentration
Statistical Analyses	
Further detail provided that if >5% of all assessments (over all subjects and visits) of a given primary endpoint are impacted by COVID-19 (based on the eCRF COVID-19 Impact Assessment), the impacted assessment will be excluded and upscaled when the respective primary endpoint is analyzed.	Section 10.2.3 Changes to Statistical Analyses
Other sensitivity analyses were added and include: subgroup analysis of endpoint ascertainment (in-clinic, remote) with subjects assigned to the subgroup with most visits done, excluding (in-clinic) Baseline and Week 52 visits; analysis of ADAS-cog$_{11}$ to include only subset of items (for all visits) which are administered remotely by telephone or video call; analysis of ADCS-ADL$_{23}$ to exclude items affected by COVID-19 restrictions; and analysis of composite scale designed as COVID-19 impact free joint score, to include items selected from ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ that are not expected to be impacted by COVID-19.	Section 10.2.3 Changes to Statistical Analyses
Clarification provided that the two co-primary endpoints are Baseline adjusted decline in ADAS-cog$_{11}$ and Baseline adjusted decline in ADCS-ADL$_{23}$ from Baseline at Week 52.	Section 17.4.1 Hypothesis
The primary efficacy hypotheses have been clarified, with the global null versus alternative as a Union-Intersection Test requiring both co-primary endpoints to meet statistical significance at the 5% two-sided level of significance for the global null hypothesis to be rejected.	Section 17.4.1 Hypothesis
For the ITT (EMA) analysis, no data will be imputed, unless specified in selected sensitivity/exploratory endpoints.	Section 17.4.3 ITT (EMA) Analysis
The Estimands section has been expanded, with the primary estimand now defined and constructed in line with ICH E9 (R1) addendum. The five components for the estimand of interest are as follows: treatment, population, patient-level outcomes/variables, population-level summary, and intercurrent events (ICE).	Section 17.4.4 Estimands

28.4.10 Protocol Version 7.1

Summary of Changes	Affected Sections in Revised Protocol (Version 7.1)
Signatories / Responsible Personnel	
The Global Project Manager has been changed to Marta Medina, with corresponding telephone numbers and email address added.	Section 4 Responsible Personnel
Bjoern Schelter job title has been updated from Data analytics and Biostatistic lead to Chief Analytics Officer	Section 3 Protocol Approval
Vendor Bioclinica removed for Magnetic Resonance Imaging (MRI); suitably qualified vendor added	Section 4 Responsible Personnel
Study Design	
Removed sentence- an interim report will be prepared describing the complete efficacy and safety analyses of the double blind phase.	Section 10.1 General Description
Study Assessments	
Aberdeen Biomedical Imaging centre removed as vendor. Removed sentence any further processing by central reader will be documented in SAP and replaced with Details of analysis conducted will be reported in a separate report.	Section 15.3.3.1 ^{18}F-FDG-PET Section 15.3.3.2 MRI