STATISTICAL ANALYSIS PLAN: 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: 07-JUN-2023

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

STATISTICAL ANALYSIS PLAN

(Double-Blind and Open-Label Extension Phase)

Protocol 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

Protocol Number: **(Version Date)**	TRx-237-039 (7.0) 28-JUL-2021 (UK: 19-AUG-2021)
Name of Test Drug:	Hydromethylthionine Mesylate (HMTM) previously referred to as LMTM, TRx0237
Phase:	3
Methodology:	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
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Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

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Document Date: 07 June 2023

Document Version: 3.0

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Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

SIGNATURE PAGE

Protocol Title:	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
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Protocol Number:	TRx-237-039
SAP Document Date/Version:	07 June 2023/v3.0
Cytel, Inc. Author: [redacted] **Senior Biostatistician**	Signature:_____ Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the Clinical Study Report (CSR).

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

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MODIFICATION HISTORY

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
			Initial issuance of document
V 1.0	27-AUG-2021	[redacted]	First signed version
V 2.0	01-MAY-2022	[redacted]	Implementing protocol v7.0 and v7.0 UK. Incorporating information from SAP review meeting and BDRM. Specifying SPM analysis.
V 3.0	07-JUN-2023	[redacted]	Update of section Statistical Analyses of Open-Label Treatment Phase (including TLF shells). Adding Biomarker Analysis section (including TLF shells). Differentiation between subjects receiving only true placebo and subjects receiving at least one dose of MTC. Additional (post hoc) analyses.

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

TABLE OF CONTENTS

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

LIST OF IN-TEXT TABLES

Table **Page**

ABBREVIATIONS

Abbreviation	Definition
AChEI	Acetylcholinesterase Inhibitor
AD	Alzheimer's Disease
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
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ApoE(4)	Apolipoprotein E(4) genotype
ASL	Arterial Spin Labeling
AST	Aspartate Aminotransferase
BDRM	Blinded Data Review Meeting
BSI	Boundary Shift Integral
CBF	Cerebral Blood Flow
CDR	Clinical Dementia Rating
CDR-SOB	Clinical Dementia Rating – Sum Of Boxes
Cmax,ss	Maximal concentration during steady state
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019 Public Health Emergency
CRF	Case Report Form
CSR	Clinical Study Report
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

Abbreviation	**Definition**
EMA	European Medicines Agency
E-MITT	Efficacy Modified Intention-To-Treat
EOT	End Of Treatment
ET	Early Termination
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
^{18}F-FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FWE	Familywise Error Rate
G6PD	Glucose-6-Phosphate Dehydrogenase
GFAP	Glial Fibrillary Acidic Protein (biomarker)
GGT	Gamma-Glutamyl Transferase
GLM	General Linear Models
HMTM	Hydromethylthionine Mesylate
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intention-To-Treat
LOQ	Limit Of Quantification
LSM	Least Squares Mean
MAOI	Monoamine Oxidase Inhibitor
MAR	Missing At Random
MCI-AD	Mild Cognitive Impairment due to AD
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MI-MITT	MRI Imaging Modified Intention-To-Treat
ML	Maximum Likelihood
MMRM	Mixed effect Model with Repeated Measurement
MMSE	Mini-Mental State Examination

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

Abbreviation	**Definition**
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MT	Methylthioninium
MTC	Methylthioninium Chloride
NfL	Neurofilament Light (biomarker)
OL	Open-Label
PCS	Potentially Clinically Significant
PK	Pharmacokinetic
PET	Positron Emission Tomography
PI	Principal Investigator
PI-MITT	PET Imaging Modified Intention-To-Treat
PT	Preferred Term
P-tau181	Tau phosphorylated at residue 181 (biomarker)
P-tau231	Tau phosphorylated at residue 231 (biomarker)
rCBF	Regional Cerebral Blood Flow
REML	Restricted Maximum Likelihood
ROI	Region Of Interest
RTF	Rich Text Format
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS®	Statistical Analysis System
SD	Standard Deviation
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SPM	Statistical Parametric Maps
SSRI	Selective Serotonin Reuptake Inhibitor
SUVR	Standardized Uptake Value Ratio
TC	Telephone Contact

Abbreviation	**Definition**
TCA	Tricyclic Antidepressant
TEAE	Treatment Emergent Adverse Event
TICV	Total Intracranial Volume
TLV	Total Lesion Volume
TOTOS	The Off Treatment On Study (subjects)
TSH	Transmissible Spongiform Encephalopathy
T-tau	Total tau (biomarker)
UK	United Kingdom
VBM	Voxel Based Morphometry
vMRI	Volumetric Magnetic Resonance Imaging
WBC	White Blood Cell

Sponsor:	TauRx Therapeutics Ltd.		
Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

An unmet need exists to develop new medications for Alzheimer's Disease (AD) that more directly modify the underlying disease pathology and offer longer-term and greater efficacy. HMTM (hydromethylthionine mesylate), 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 HMTM in AD.

Results from two phase 3 studies of HMTM on AD subjects (TRx-237-005, TRx-237-015) suggest that HMTM 8 mg/day given as monotherapy may be effective in delaying progression of mild to moderate AD on co-primary clinical efficacy endpoints, ADAS-cog_{11} and ADCS-ADL_{23}, and also on magnetic resonance imaging (MRI) measures of progression of brain atrophy and ^{18}F-FDG-PET (^{18}F-fluorodeoxyglucose positron emission tomography) measures of impairment in neuronal metabolic function, and that there is no added benefit to using doses substantially higher than 8 mg/day. Recent population pharmacokinetic (PK) studies have confirmed that there are concentration-response relationships for cognitive and neuroimaging outcomes at the 8 mg/day dose. This is seen whether HMTM is taken alone or as add-on to symptomatic treatments. In a within-cohort meta-analysis of both studies, HMTM 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 when HMTM was given to subjects who were concurrently using acetylcholinesterase inhibitors (AChEIs) and/or memantine. The reduction in treatment effects of HMTM 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.

In the continued development of HMTM, 16 mg/day has been chosen as the primary target dose. This was based on a population PK-response model that was applied to data from the earlier Phase 3 studies. The clearance of parent Methylthioninium (MT) is most significantly associated with renal function, suggesting that the most important predictor of whether or not a subject achieves a parent MT Cmax,ss above the threshold is creatinine clearance. At a dose of 8 mg/day, approximately 60% of subjects would be expected to have plasma concentrations above the threshold concentration that was identified with pharmacologic activity whereas at a dose of 16 mg/day, all subjects would. In order to provide some degree of urinary discoloration in what as originally a "true" placebo control group, a small amount of methylthioninium chloride (MTC), 4 mg, was introduced to placebo treatment kits (one tablet on two intermittent occasions twice per week, i.e., 8 mg/week). This amount of MTC had been anticipated to be without activity, consistent with results of a prior Phase 2 trial and estimated plasma

half-life. For this reason, this treatment arm is referred to herein (and in tables, listings, and figures) as "control" rather than "placebo".

This document describes the plan for the full statistical analyses and reporting of study TRx-237-039, which in its current version is a randomized, double-blind, controlled, three-arm, 12-month, safety and efficacy study of HMTM monotherapy in subjects with AD followed by a 12-month open-label treatment. Results of the analyses described in this Statistical Analysis Plan (SAP) will be included in the Clinical Study Report (CSR).

The planned analyses identified in this SAP will be included in regulatory submissions and future manuscripts. Any post-hoc or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP, will be clearly identified in the CSR.

This SAP is primarily based on the protocol version 7.0 from 28-JUL-2021 and version 7.0 UK from 19-AUG-2021. Key decisions based on earlier versions are acknowledged where appropriate.

The statistical analysis of pharmacokinetic data will be described in a separate SAP (responsible: Certara USA, Inc.; 100 Overlook Center, Suite 101; Princeton, NJ 08540; United States), but will be included/referenced in the CSR.

1.2. Objectives of Statistical Analysis

The primary objectives of the study TRx-237-039 are to evaluate the efficacy and safety of HMTM (16 mg/day) over up to two years of treatment, depending on the initially randomized treatment group, compared to the control arm.

This SAP is designed to outline the methods to be used in the analysis of study data to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation, are provided.

1.3. Study Protocol Versions

The following table shows an overview of the differences in duration, population, sample size and randomization ratios, and planned doses groups between the study protocol versions.

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Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

Table 1 Protocol evolution

	Version 2.1	Version 3.0 – 4.1	Version ≥5.0
Duration of study	6 months (double-blind)	9 months (double-blind)	12 months (double-blind) + 12 months (open-label)
Population	Mild AD (MMSE 20-25)	MCI-AD, or mild AD (MMSE 20-27) PET positive for amyloid	MCI-AD, mild AD, or moderate AD (MMSE 16-27) PET positive for amyloid
Target enrollment (randomization ratio according to doses below)	180 (1:1)	375 (2:2:1)	500 (≥v5.0: 450) (1:4:4)
Planned doses (sample size)	HMTM 8 mg/day (N=90) Placebo (N=90)	HMTM 8 mg/day (N=150) Placebo (N=150) HMTM 16 mg/day (N=75)	HMTM 8 mg/day (N=50) Placebo/MTC (N=200) HMTM 16 mg/day (N=200)

The primary efficacy analysis is performed based on the subjects randomized under protocol version 5.0 or higher, in which some MTC tablets were introduced to placebo treatment kits (on average twice per week spiking) as urinary discolorant to maintain the treatment blinding. In a sensitivity analysis, all randomized subjects are analyzed. Safety assessment will be performed based on all randomized subjects as well.

1.4. UK Versions of Study Protocol

The protocol (version 5.1, 05-FEB-2020) was adapted in response to requests made by the Medicines & Healthcare products Regulatory Agency (MHRA), after the inclusion of moderate AD subjects with protocol version 5.0.

The resulting first UK-specific version is protocol 5.2 UK (02-MAR-2020), which requires that subjects be either treatment naïve or to have already discontinued prior treatment with AChEI and/or memantine due to intolerance, lack of efficacy, or recommendation by the primary care provider prior to giving consent to participate in the study. The other major change is to require that the first visit in the newly

added open-label delayed-start period (after 2 weeks, V8) be an in-clinic visit rather than a telephone contact given that some subjects will be receiving HMTM treatment for the first time.

For all subsequent UK versions, no additional country specific changes were implemented.

1.5. Interim Analysis

An early efficacy analysis is planned prior to the completion of the study.

The initial 52-week, double-blind, controlled treatment phase is completed when the last subject completes the final visit in the double-blind treatment phase (Week 52 visit, V7, pre-dose procedures). Then, the database will be partially locked and unblinded for analysis (see following Section 1.6). Treatment assignment will not be divulged to subjects or individuals involved in the operational conduct on-site of the ongoing open-label treatment phase. For further information regarding unblinding, see Section 2.7.

The complete CSR will be prepared upon completion of the entire study.

COVID-19 related changes to the study are documented as specified in the versions 6.0 and 6.0 UK or later versions of the protocol. During the study, the impact of COVID-19 on the study was closely monitored by the Sponsor as per a separate analysis plan (iSAP, v1.0, 28-MAY-2021) in relation to drop-out rates and site reported (in Medidata RAVE) impact on assessments and endpoints. No adjustments to the study design, sample size or conduct were made as a result of this monitoring.

1.6. Database Locks

For future references, all data from data snapshots and database locks, which are described below, will be saved and are not to be changed.

To perform the analysis of the double-blind treatment phase, a data snapshot will be done after all outstanding queries concerning double-blind treatment phase data are resolved. All case report forms (CRFs) will be approved by the Principal Investigator (PI). After that, double-blind treatment phase data must not be edited or added, except for updating data related to safety, which can be found in CRFs including but not limited to Medical History, Concomitant Medications, Procedures, Study Drug Interruption Log and Serious Adverse Events (SAEs). For the analysis of the double-blind treatment phase, the following data will be included:

- All (efficacy) data until the last visit of the double-blind treatment phase,
- Eye exam, if it was performed until the end of the Week 52 protocol-specified visit window,
- Any further (safety) data up until the receipt of the first dose of the open-label treatment phase drug, and

- Data of imaging parameters (MRI, ^{18}F-FDG-PET) assessed within 14 days after first dose of the open-label treatment phase drug.

After the last subject visit of the open-label treatment phase, the database will be locked in accordance with the Database Lock Plan. Data from previously locked CRFs will be checked to capture any potential changes in data, by comparing SDTM and/or ADaM datasets, and/or re-running the analysis of the double-blind treatment phase based on the final database lock data; discrepancies will be listed. For the analysis of the open-label treatment phase, all data until the end of the study will be included. Full listings will be re-run including data from the double-blind and open-label treatment phases.

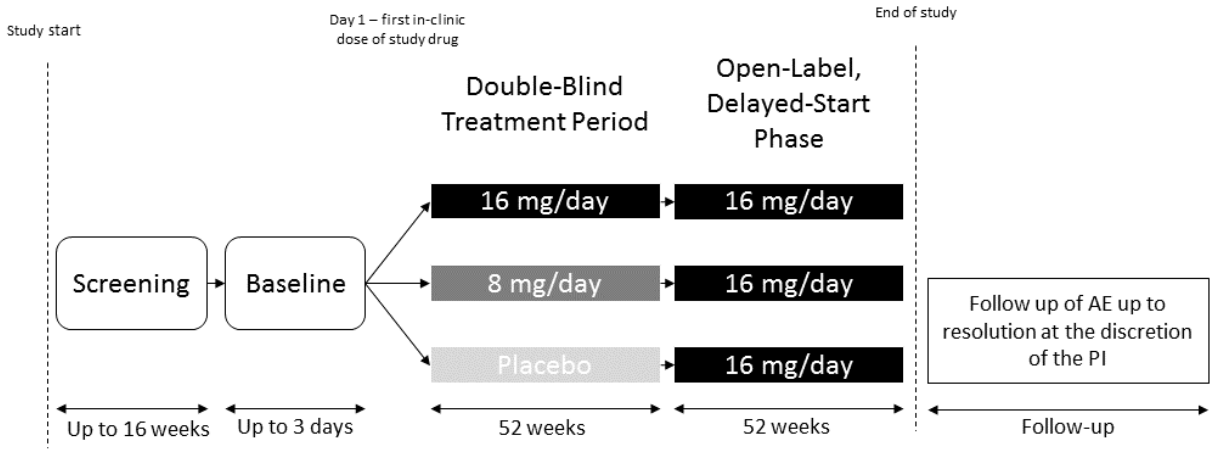
2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a two-phase outpatient study of HMTM administered as monotherapy in approximately 500 subjects (450 under protocol version 5.0 or higher) with early to mild-moderate AD: a randomized, double-blind, controlled, 52-week treatment phase followed by a 52-week open-label treatment phase that represents a modified delayed start of treatment. Subjects[a] for whom legally acceptable informed consent was obtained and who were found eligible on the basis of Screening evaluations, were randomly assigned at Baseline to receive either HMTM 16 mg/day, HMTM 8 mg/day, or control (i.e., placebo/MTC) (4:1:4, at the study level); as noted earlier, the drug supplies for the control group included tablets containing a urinary discolorant (MTC), 4 mg, dosed at an average frequency of two tablets per week. The primary treatment group comparison during the double-blind treatment phase is between HMTM 16 mg/day and control. Following completion of the 52-week treatment phase, all subjects (regardless of randomized treatment assignment or response) will continue open-label treatment with HMTM 16 mg/day for a further 52 weeks.

[a] Not receiving concomitant AChEI and/or memantine (required for patients in the UK) or otherwise receiving concomitant AChEI and/or memantine at the time of signing informed consent and agreeing to discontinue them before randomization (see Section 2.2).

Figure 1 Schematic of study design (Protocol version 5.0+)



2.2. Screening Period

The Screening period is to be up to 9 weeks for subjects not receiving an AChEI and/or memantine at the time of signing the consent (Initial Screening Visit, Visit 1). For subjects 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 Clinical Dementia Rating (CDR) of 0.5). Signing of the initial informed consent form (ICF) is assigned to the screening period irrespective of when it occurred.

The Screening period could be extended for COVID-19 related reasons as specified in the versions 6.0 and 6.0 UK, or later versions of the protocol.

For re-screened subjects, information from the previous screenings will be included and is flagged in the subject data listings. In case of screening data being used for analysis, the latest available screening information, including previous screenings, will be used.

2.3. Double-Blind Treatment Phase (Week 0 up to Week 52)

Five post-Baseline visits are scheduled during the double-blind treatment phase (Visit 3 (Week 4): safety, and Visits 4, 5, 6, and 7 (Week 13, 26, 39, and 52): efficacy, imaging, and safety, see Table 2).

Unscheduled visits may occur as needed for assessment, or upon early termination. In addition, subjects are to be followed as needed for the resolution or stabilization of an AE, including following the last dose, consistent with the Investigator's medical judgement.

The Baseline value is defined as the last non-missing value prior to first dose of study drug or value obtained on the same day of the first dose of study drug. In case of pre- and post-dose assessments at the Baseline visit, the pre-dose value will be used as the Baseline assessment. If no assignment to pre-/post-dose is possible algorithmically, it will be treated as pre-dose unless specified otherwise during the Blinded Data Review Meeting (BDRM).

2.4. Open-Label Treatment Phase (Week 52 up to Week 104)

During the open-label treatment phase, three visits are scheduled in-clinic unless otherwise noted: Visit 8 at 56 weeks (telephone contact only for all but UK sites), Visit 9 at 78 weeks, and Visit 10 at 104 weeks. The last non-missing value/assessment prior to first dose of the open-label treatment phase serves as the Baseline visit for the open-label treatment phase, but subjects with a missing Week 52 efficacy endpoint are excluded from the respective non-inferiority PPv5-OL population (see Section 3.1.2).

2.5. Changes of Study Conduct due to COVID-19

The protocol was revised to version 6.0 and 6.0 UK to incorporate modifications to the study conduct and monitoring, guidance for continued data collection and analysis, and ongoing risk assessment due to the Coronavirus Disease 2019 Public Health Emergency (COVID-19). Key assessments deciding the eligibility of subjects as well as Baseline, Week 52, Week 56 for UK sites, and early termination assessments must be done on-site and cannot be assessed remotely. Other visits can be done remotely as per the agreed risk assessments and data collection plans.

Since ^{18}F-FDG-PET was not needed to determine study eligibility and is not the primary efficacy imaging, the Sponsor may have approved subject randomization without a brain ^{18}F-FDG-PET scan if the scan could not be performed due to COVID-19. For imaging (MRI, ^{18}F-FDG-PET), alternative scanners will only be accepted if data comparability is confirmed and ensured prior to assessments being made; every effort was made to avoid any change in scanner for a given site and subject over the course of the study. If a Baseline ^{18}F-FDG-PET scan could not be done due to lack of imaging facility, a follow-up ^{18}F-FDG-PET scan was not required.

If a subject underwent Screening assessments but could not have protocol-required assessments performed due to COVID-19, the subject could be put on screening pause until such times as COVID-19 impacts had ceased (abstention from treatment with an AChEI and/or memantine should have been retained).

The planned in-clinic post-Baseline visits (except Week 52 visit), including blood samples for safety laboratory assessments as well as optional genotyping, may have been completed at home, or at other safe, suitable alternative location if deemed necessary to protect subjects due to COVID-19.

Study visit windows may have been extended beyond the allowed +/- 14 days at the discretion of the Sponsor when justification was provided and unless two planned study visits did not fall into the same visit window as per Sections 5.5 / 6.5.

Efficacy scales may have also been performed remotely, if approved by the Sponsor in advance on a case-by-case basis.

Dose interruption not triggered by the site clinician because of COVID-19 might be allowed for more than 14 days at the discretion of the Sponsor.

2.6. Randomization Methodology

With protocol version 5.0 (see Table 1), subjects who satisfied all eligibility criteria were randomized to one of three study regimens HMTM 16 mg/day, HMTM 8 mg/day, or control (4:1:4, at the study- rather than site-level). Randomization was stratified by (**bold** level will be used as reference category in statistical analyses, if needed and results are not population weighted):

- Severity (three levels: Mini-Mental State Examination (MMSE) **16-19 (moderate)**, 20-25 (mild), or 26-27 (MCI-AD)),
- Prior use of standard AD treatment (two levels: AChEI/memantine or **none**), and
- Region (two levels: North America or **Europe**).

Global enrollment across the whole study was managed such that subjects were assigned to the Screening MMSE severity groups with a target of approximately 2:3:1 (MMSE 16-19, MMSE 20-25, and MMSE 26-27, respectively) for those randomized under protocol version 5.0 and above. Each stratum was closed when the target enrollment was achieved.

If not indicated otherwise, any analysis or summary that groups subjects by prior use of AChEI and/or memantine, is inclusive of those with a prior history of such use and those who withdrew usage for the purposes of this study (such as lack of efficacy). When data are analyzed descriptively, discontinuation of AChEI and/or memantine before entering the study and discontinuation of AChEI and/or memantine for purposes of study participation (after entering the study) will be differentiated.

If a subject consented to protocol version 2.1 and did not reconsent to a later protocol version, the stratification information provided by the site is considered correct with respect to prior use of AChEI and/or memantine, unless there is specific information in the CRF that contradicts that. In earlier version of the protocol (v2.1), there was no stratum for MMSE as the inclusion criterion was to have an MMSE of 20-25; for all these subjects the stratum will be imputed as MMSE 20-25.

2.7. Stopping Rules and Unblinding

The randomization list for the double-blind treatment phase is maintained within the Randomization and Trial Supply Management system (RTSM, hosted by Clario previously known as BioClinica) and in secure locations by individuals who are not directly involved in the conduct of the study. The blind for an individual subject should not be broken during conduct of the study except in the case of a medical emergency for which it is deemed essential to know which treatment the subject has received during the double-blind treatment phase to provide appropriate care. Then, the Investigator may unblind a specific subject and determine the identity of treatment using the RTSM System. This will be achieved via a “peek blind” function within this 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. For any such affected subject, study drug will be discontinued, and the subject will be followed until resolution or stabilization of the event and then discontinued from study.

After the initial 52-week, double-blind, controlled treatment phase is completed, a data snapshot will be done (see Section 1.6) and unblinded for analysis. It will be an interim lock, because some electronic case report form (eCRF) pages might need to be reopened to allow for resolution of AEs for instance; a version of all raw data for the analysis of the double-blind treatment phase will be stored; prior to the final database lock of the study, a comparison with the stored data from the interim lock will be

performed and changes will be identified/followed-up. Treatment assignment will not be divulged to subjects or individuals involved in the operational conduct on-site of the ongoing open-label treatment phase.

The study is monitored for safety by a blinded Data and Safety Monitoring Board (DSMB) throughout its duration. At any time, the DSMB may recommend that the study may continue, with or without modifications, or be terminated due to safety concerns. The DSMB may also request to receive additional data unblinded to the subject level in response to identified safety concerns.

Further information about blinded and unblinded personnel during the conduct of the study is given in the document *Study Blind Maintenance Plan for TRx-237-039* (current version 3.0, 27-OCT-2022) – a Sponsor controlled document.

2.8. Study Procedures

The schedule of assessments for double-blind and open-label treatment phase, as outlined in the study protocol, is provided in Table 2 and Table 3, respectively.

Table 2 Schedule of Assessments for double-blind treatment phase

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Protocol:	TRx-237-039		
Document Version No.:	3.0	**Document Date:**	07-JUN-2023

Visit Name	**Screening**	**Baseline**		**Double-Blind Treatment Phase**				
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7 (or ET)**
Weeks Relative to Baseline	**≥ -9 weeks**	**-**		**4 weeks**	**13 weeks**	**26 weeks**	**39 weeks**	**52 weeks**
		(+3)						
Allowable Time Window in Days		**Pre-Dose**	**Post-Dose**	**(±3)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Likely diagnosis of probable AD or MCI-AD, and confirmation	X							
Informed consent by Subject (and/or LAR) and Study Partner(s)	X							
Demographics	X							
Medical history and concomitant medication review	X							
12-lead electrocardiogram	X							
Amyloid PET scan	X							
^{18}F-FDG-PET	X							X
Randomization		X						
MRI	X				X	X	X	X
ADAS-cog$_{13}$ and ADCS-ADL$_{23}$		X			X	X	X	X
AE/Concomitant Medication Recording/Review		X	X	X	X	X	X	X
Physical/Neurological Examinations	X							
Targeted Physical/Neurological Examinations		X	X	X	X	X	X	X
Ophthalmological Examination	X	X						X

Visit Name	**Screening**	**Baseline**		**Double-Blind Treatment Phase**				
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7 (or ET)**
Weeks Relative to Baseline	**≥ -9 weeks**	**-**		**4 weeks**	**13 weeks**	**26 weeks**	**39 weeks**	**52 weeks**
		(+3)						
Allowable Time Window in Days		**Pre-Dose**	**Post-Dose**	**(±3)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Clinical Laboratory testing	X	X		X	X	X	X	X
Pregnancy Testing	X	X		X	X	X	X	X
Blood Pressure, Pulse, Body Weight	X	X	X	X	X	X	X	X
Study Drug Dispensing		X			X	X	X	X
Study Drug Compliance Assessment				X	X	X	X	X
Blood Sample for MT Concentration		X	X	X				X
Blood Sample for Genotyping (optional)		X						
MMSE	X							X
CDR	X							X

Table 3 Schedule of Assessments for continued open-label treatment phase

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

[a] Onsite for UK sites, and telephone contact (TC) for non-UK sites. Scheduled onsite assessment for UK sites only.

2.9. Efficacy, Pharmacokinetic, Safety, and Other Variables

2.9.1. Efficacy Variables

2.9.1.1. Primary Efficacy Variables

Primary efficacy variables are (assessed at Baseline, 13, 26, 39, 52, 78, and 104 weeks, or early termination):

- ADAS-cog_{11}
- ADCS-ADL_{23}

The **ADAS-cog_{11}** is the cognitive subscale of the ADAS, originally proposed with 11 items (domains: memory, praxis, orientation, and language), resulting in scores that range from 0 to 70, with higher numbers indicating greater impairment. For the ADAS-cog_{13} two additional items have been added (in domain Memory: Delayed Word Recall, and as a new domain Attention: Number Cancellation) to provide additional sensitivity to change in cognition at earlier stages of the disease, resulting in a maximal score of 85 (see Appendix 12.2). As the original ADAS-cog_{11} was used in the earlier Phase 3 studies (TRx-237-005, TRx-237-015), that score will be derived from the assessment of the ADAS-cog_{13} for the primary analyses. ADAS-cog_{13} will be analyzed as an explorative efficacy variable.

The **ADCS-ADL_{23}** includes 23 items describing the performance of activities of daily living (ADL) by AD subjects with scores ranging from 0 to 78 and higher numbers indicating lesser impairment.

2.9.1.2. Secondary Efficacy Variables

Secondary efficacy variables are:

- Brain MRI evaluated for whole brain volume and temporoparietal lobe volume (assessed at Screening, 13, 26, 39, 52, 78, and 104 weeks, or early termination).
- Brain ^{18}F-FDG-PET evaluated for temporal lobe, in Standardized Uptake Value Ratio (SUVR) normalized to pons in subjects with CDR of 0.5 (assessed at Screening and 52 weeks, or early termination).

Change in MRI volumetric parameters and change in ^{18}F-FDG-PET SUVR parameters are quantified by imaging core laboratories (MRI: Clario previously known as BioClinica, ^{18}F-FDG-PET: Invicro).

If documented volumes are split into left and right area, these two values will be averaged to get the total value. For the MRI temporoparietal lobe volume, temporal lobe volume and parietal lobe volume will be averaged also.

For the open-label treatment phase, 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.

Table 4 MRI and ^{18}F-FDG-PET parameters and their raw data pendants

	Parameter	Raw data variable(s)
MRI	Whole brain	BILATERAL WHOLE BRAIN
	Temporoparietal lobe	LEFT TEMPORAL LOBE RIGHT TEMPORAL LOBE LEFT PARIETAL LOBE RIGHT PARIETAL LOBE
	Lateral ventricular	VENTRICLES
	Hippocampal	LEFT HIPPOCAMPUS RIGHT HIPPOCAMPUS
	Putamen	LEFT PUTAMEN RIGHT PUTAMEN
	Nucleus accumbens	LEFT ACCUMBENS AREA RIGHT ACCUMBENS AREA
	Nucleus basalis	NUCLEUS BASALIS
	Total lesion volume	WHITEMATTER HYPOINTENSITIES
^{18}F-FDG-PET	Temporal lobe	TEMPORAL_CORTEX_L TEMPORAL_CORTEX_R
	Parietal lobe	PARIETAL_CORTEX_L PARIETAL_CORTEX_R
	Frontal lobe	FRONTAL_CORTEX_L FRONTAL_CORTEX_R
	Cerebellum	MEAN_CEREBELLUM_GRAY
	Anterior cingulate gyrus	ANTERIOR_CINGULUM_L ANTERIOR_CINGULUM_R

	Parameter	Raw data variable(s)
	Posterior cingulate gyrus	POSTERIOR_CINGULUM_L POSTERIOR_CINGULUM_R

2.9.1.3. Exploratory Efficacy Variables

Exploratory efficacy variables are:

- MMSE (assessed at Screening and 52 weeks, or early termination)
- CDR (levels: 0.5, 1, 2, 3) and CDR – Sum Of Boxes (CDR-SOB) (range: 0 to 18) (assessed at Screening, 52, and 104 weeks, or early termination)
- ADAS-cog_{13} (assessed at Baseline pre-dose, 13, 26, 39, 52, 78, and 104 weeks, or early termination).
- Composite Scale (analyzed at 39 and 52 weeks).
  The Composite Scale is the sum of cognitive subdomains from ADAS-cog_{11} (Word Recall [score: 10], Constructional Praxis [5], Orientation [8], Spoken Language Ability [5], and Comprehension [5]) and functional items from ADCS-ADL_{23} (Use of telephone [5], Keeping appointments [3], Cooking and preparation of meals [4], and Cleaning dishes [3]), resulting in a maximum possible score of 48 (higher score indicates less impairment). Since a higher score for ADAS-cog_{11} indicates more impairment (less impairment for ADCS-ADL_{23}), the values of ADAS-cog_{11} will be transformed (maximal score minus actual score) before summarizing both assessments.
- COVID-19 Composite Scale (see Sections 12.2.1, and 12.2.2)
- Brain MRI evaluated for lateral ventricular, hippocampal, putamen, nucleus accumbens, nucleus basalis, and further region of interest (ROI) volumes
- Brain ^{18}F-FDG-PET evaluated for temporal lobe in SUVR normalized to cerebellum, and parietal lobe, and frontal lobe, both in SUVR normalized to pons and normalized to cerebellum in subjects with CDR of 0.5 (assessed at Screening and 52 weeks, or early termination). In addition, further parameters to evaluate are cerebellum in SUVR normalized to pons; and anterior and posterior cingulate gyrus in SUVR normalized to pons and normalized to cerebellum.

2.9.2. Pharmacokinetic Variables

Plasma MT and whole blood concentrations (parent MT, *N*-desmethyl MT, and total MT, to the extent possible) are determined at Baseline, Week 4, Week 52, and Week 104, or early termination. Samples are collected prior to dosing (in clinic), approximately 1 to 2 hours post-dose and approximately 4 hours

post-dose. At the early termination visit, a single blood sample is collected only for determination of MT concentrations, if the subject had already discontinued study drug or was unwilling to take a final in-clinic dose.

The statistical analysis of PK data performed by Certara USA, Inc., is not within the scope of this SAP and will be described in a separate document.

2.9.3. Safety Variables

Safety assessments performed during the study include the following:

- **Blood pressure** and **pulse** measured at Screening, Baseline pre-dose and approximately 2 hours post-dose, 4, 13, 26, 39, 52, 78, and 104 weeks, or early termination
- **Weight** measured at Screening, 4, 13, 26, 39, 52, 78, and 104 weeks, or early termination
- Standard **clinical laboratory** testing, including **hematology** and **blood (serum) chemistry**, performed at Screening, 4, 13, 26, 39, 52, 78, and 104 weeks, or early termination

  TSH, vitamin B12, folate, haptoglobin, and G6PD measured at Screening; a thyroid panel may be obtained in response to an elevated TSH. Additional testing as needed in response to an AE.
- Blood sample for a **serum pregnancy test** at Screening, 4, 13, 26, 39, 52, 78, and 104 weeks, or early termination, and up to 3 months after last dose of study drug; in women of childbearing potential, such women should be encouraged to return to the clinic or request serum pregnancy testing in the event of a delayed menstrual period to rule out possible pregnancy.
- **Targeted physical and neurological examinations** performed pre-dose and approximately 3 hours after administration of the first dose of study drug (Baseline). Thereafter, performed at 4, 13, 26, 39, 52, 78, and 104 weeks, or 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).
- **Ophthalmological examination** of subjects with history of lens implants performed prior to the first dose of study drug and at Week 52 and Week 104, to assess whether the lens has been discolored during the trial.
- Recording of **medications** administered within the last 90 days before Screening. Except 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.
- **AEs** recorded from the time the informed consent was signed 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 adverse events (TEAE).

2.9.4. **Other Variables**

Other assessments are:

- A single blood sample for Apolipoprotein E gene (*ApoE*) obtained from subjects who provide legally acceptable informed consent, collected at any time after eligibility for randomization and continued participation in the study has been confirmed but prior to Week 52.
- Other biomarkers will be analyzed as well. Their analysis is pre-specified in the separate Research Plan "TRx-237-039_Secondary Research Plan_Plasma Biomarker Analysis_v2.2_16Mar23". The analysis to be performed is described in more detail in Section 7 of this SAP.
- MRI arterial spin labelling parameters will be provided in a subject data listing.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data.

3.1.1. Double-Blind Populations

Intention-to-Treat (ITT) Population: all randomized subjects. Subjects are analyzed as randomized.

Efficacy Modified Intention-to-Treat (E-MITT) Population: all ITT subjects who received at least one dose of study drug and have a Baseline and at least one *valid* post-Baseline efficacy assessment (either ADAS-cog$_{11}$ or ADCS-ADL$_{23}$). Subjects are analyzed as randomized.

MRI Imaging Modified Intention-to-Treat (MI-MITT) Population: all ITT subjects who received at least one dose of study drug and have a Baseline and at least one *valid* post-Baseline volumetric MRI (either whole brain or temporoparietal lobe). Subjects are analyzed as randomized.

PET Imaging Modified Intention-to-Treat (PI-MITT) Population: all ITT subjects with screening CDR of 0.5 and who received at least one dose of study drug and have a Baseline and at least one *valid* post-Baseline SUVR assessment (temporal lobe). If data is available from subjects with a CDR > 0.5, these subjects will not be included in this population. Subjects are analyzed as randomized.

Per Protocol (PP) Population: all subjects who are in the E-MITT and MI-MITT population, without any important protocol deviation (see Section 3.2) that would deem the subject exclusionary from the PP Population (as per BDRM decision) or intercurrent medical events that could confound the interpretations. Subjects are analyzed as randomized. **Important here refers to a classification that is decided during BDRM based on the original protocol deviation classification as major/minor and their impact on key (efficacy/safety) outcomes of this study. The original classification as major/minor will be provided as well.**

A valid value means that the assessment was not affected by prior initiation of an AChEI and/or memantine.

Safety Population: all subjects who received at least one dose of study drug. Subjects are analyzed as treated. If a subject received different doses, the predominant treatment group (based on the number of doses) will be assigned.

v5-Populations: If the above-mentioned populations (ITT, E-MITT, MI-MITT, PI-MITT, PP, Safety) are restricted to subjects randomized under study protocol version 5.0 or higher, which are the primary efficacy analysis populations, the population names are: ITTv5, E-MITTv5, MI-MITTv5, PI-MITTv5, PPv5, and Safetyv5.

Pharmacokinetic (PK) Population: all subjects who were administered at least one dose of study drug and have at least one analyzable post-dose PK sample.

The analysis of estimands is based on the ITT population. For the FDA, the modified endpoint specific ITT populations (MITTs) will be analyzed. The Safety population is the primary population for the analysis of safety endpoints.

Two population trackers will be generated and will be provided to Cytel for the use in the analyses. The first as a result of the double-blind treatment phase BDRM, and the second as a result of the open-label treatment phase Data Review Meeting (DRM). These trackers will specify if subjects are included or need to be excluded from certain populations (e.g., TOTOS, PP, PP-OL). The population tracker from the BDRM will also specify if dropouts are potentially related to treatment.

3.1.2. Open-Label Populations

The following subject populations will be evaluated and used for presentation and analysis of the open-label data:

Intention-to-Treat Open-Label (ITT-OL) Population: all randomized subjects who received at least one dose of study drug from the open-label treatment phase or continued off-treatment during the open-label treatment phase (e.g., TOTOS subjects from the double-blind treatment phase). Subjects are analyzed as randomized.

Per Protocol Open-Label (PP-OL) Population: all randomized subjects who received at least one dose of study drug from the open-label treatment phase and without any important protocol deviation during the open-label treatment phase. Subjects are analyzed as randomized.

Safety Open-Label (Safety-OL) Population: all subjects who received at least one dose of study drug from the open-label treatment phase. Subjects are analyzed as treated.

Pharmacokinetic Open-Label (PK-OL) Population: all subjects who were administered at least one dose of study drug from the open-label treatment phase and have a subsequent analyzable open-label treatment phase PK sample.

v5-Populations: If the above-mentioned populations (e.g., ITT, and PP) are restricted to subjects randomized under study protocol version 5.0 or higher, which are the primary efficacy analysis populations, the population names are: ITTv5-OL, and PPv5-OL.

3.1.3. HMTM Treatment Phase Population

Safety HMTM (Safety-HMTM) Population: all subjects with at least one dose of HMTM study drug. This means that control subjects (who received placebo and/or MTC 8 mg/week) not participating in the open-label treatment phase will be excluded. Subjects are analyzed as treated.

3.2. Protocol Deviations

The Sponsor, or designee, will be responsible for producing the final protocol deviations file and for determining what kind of deviations will be considered important and which of these require the

subject to be excluded from the PP population. This file will include a description of the protocol deviation, will provide the information regarding previous classification (minor/major), will provide the classification into important/non-important done by the Sponsor, and will be finalized prior to unblinding of the double-blind treatment phase. The level of detail and information provided will allow full traceability.

All protocol deviations will be presented in a subject data listing (by Synteract, the vendor of the RAVE EDC clinical database; as well as via a Sponsor protocol deviation Log, which includes the manual generated protocol deviations that cannot be assigned to a specific subject data point). This listing will be presented pooled (COVID-19 and non-COVID-19 related protocol deviations) and separate for COVID-19- and non-COVID-19-related protocol deviations.

Summaries by categorization (important/non-important) and type (or code) will be provided by treatment phase. This will be done pooled and separate for COVID-19- and non-COVID-19-related protocol deviations. Also, one version will count all protocol deviations and one version will count only the overall unique deviations (when one deviation is resulting in subsequent ones).

Some examples for protocol deviations are:

- Protocol deviations related to Inclusion/Exclusion criteria (ineligible subject randomized to the study)
- Randomization/drug dispensation errors (incorrect kit dispensed to a subject)
- Use of “prohibited” concomitant treatments (e.g., AChEI or memantine)
- Non-compliance regarding study drug intake or endpoints assessment
- Baseline or Week 52 visit are not done in-clinic, but remotely
- Out of window assessments

4. STATISTICAL METHODS

4.1. General Methods

All outputs will be incorporated into Rich Text Format (RTF) files, sorted, and labeled according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, Screening, Baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, lower quartile (Q1), upper quartile (Q3), standard deviation, minimum and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier Methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles (if available) with associated two-sided 95% confidence intervals (Hall-Wellner Bands), as well as percent of censored observations.

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the two-sided, 0.05 level of significance.

4.2. Data Conventions

Mean, median, standard deviation, standard error, Q1 and Q3 will be presented with one more decimal place compared to the raw data, and minimum and maximum will be presented with the same number of decimal places as the raw data. Percentages will be presented with one decimal place.

Wherever a calendar date is presented in a listing, the corresponding Study Day will be included, with Study Day defined as:

- date – first dose date + 1, where date >= first dose date
- date – first dose date, where date < first dose date

For listings including day 1 data with assessments collected prior to and after first study drug, a flag will be included for pre-dose assessments.

The following conversion factors will be used to convert days to months or years where applicable:

- 1 month = 30.4375 days
- 1 year = 365.25 days
- 1 week = 7 days

Additional data handling rules are as follows:

- Age (years) = year of informed consent – year of birth
- Weight values recorded in pounds will be converted to kilograms using the following formula: kilograms = pounds/2.2046
- Height values recorded in inches will be converted to centimeters using the following formula: centimeters = inches*2.54
- Temperature recorded in Fahrenheit to Celsius: 1 °C = (°F – 32)/1.8
- Duration on study (weeks) = (Last visit date – randomization date + 1) / 7
- Duration on treatment (weeks) = (Last dose date – first dose date + 1) / 7
- (Absolute) Change from Baseline = Value at the time point – Baseline value
- Relative Change from Baseline = (Value at the time point – Baseline value) / Baseline value * 100

To calculate descriptive / inferential statistics for laboratory values containing values below/above the limit of quantification, the following general rule of thumb will be applied: each laboratory value below/above the limit of quantification will be imputed numerically to the nearest value below/above the limit, respecting the same number of decimal places than numerical values (e.g., if the number of decimal places=0, subtract/add 1 to the limit of quantification (LOQ); if the number of decimal places=1, subtract/add 0.1 to the LOQ, etc.). Is the LOQ already the lowest value larger than zero, the LOQ will be imputed numerically to the nearest value below the limit with one more decimal place (e.g., if the LOQ is 1, subtract 0.1 from the LOQ: 0.9). The subject data listings will not show the imputed value, but that the value is below or above the limit of quantification.

Partial dates will be reviewed and imputed (where possible) after the BDRM and before unblinding, potentially resulting in an Excel file, which will be provided to Cytel for the use in the analysis. Remaining cases (if existing), which are required for calculation, or cases for which no additional information is provided after the BDRM or if no file has been generated will be handled as follows:

<u>Start dates</u>

- For missing start day only: Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the first date of dosing, then the partial date will be imputed to equal the first date of dosing (unless the known end date lies before the first date of dosing, when imputing the incomplete start date).
- For missing start day and month: Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the first date of dosing, then the partial date will be imputed to equal the first date of dosing (unless the known end date lies before the first date of dosing, when imputing the incomplete start date).

<u>Stop dates</u>

- For missing stop day only: Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31) or the last day of study contact if earlier.
- For missing stop day and month: Day and month will be imputed as the last day of the year (i.e., 31 December) or the last day of study contact if earlier.

4.3. Computing Environment

Statistical analyses will be performed using SAS® statistical software (Version 9.4 or higher), unless otherwise noted. Medical History and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Recently used medications and concomitant medications will be coded using the World Health Organization (WHO) Drug version from 01MAR2017.

In addition, main occupation during working life is to be provided, which will be coded using the Standard Occupational Classification, 2010, Volume 2 The Coding Index, UK Office for National Statistics.

More coding details are described in the Data Management Plan.

4.4. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdraw from the study were not to be replaced.

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 (with protocol version 7.0 and 7.0 UK). These subjects will be classified as “the off-treatment-on-study” (TOTOS) group. A subgroup of TOTOS are the subjects with antidementia therapy initiation (AchEI and/or memantine) after informed consent.

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. If this is exceeded, study drug would need to be discontinued; however, the subject will be encouraged to continue study participation off-treatment (TOTOS). If subjects stopped the dosing without the Investigator’s approval, they could get back on treatment.

For each subject who withdraws from the study, the decision will be made as part of the BDRM if the withdrawal is potentially treatment-related. For potentially treatment-related dropouts, the fraction of subjects who withdrew at a given time point will be calculated for each treatment group. In addition, a table and figure of the Kaplan-Meier estimator of time to potential treatment-related withdrawal will be given.

A separate listing of the subjects with antidementia therapy initiation will be provided, including the reason if available. Furthermore, listings will be provided for the efficacy endpoints showing all assessments and assessments which are impacted by antidementia therapy initiation being flagged.

4.5. Missing, Unused, and Spurious Data

In the estimand approach multiple imputation will be applied in hypothetical strategies (see Section 5.9.1). In the MITT analysis multiple imputed data are included as a sensitivity analysis.

4.5.1. Upscaling

Upscaling will be applied in the presence of missing and/or non-valid data, as long as there are sufficient data available.

According to Section 2.5 efficacy scales may have been performed remotely. Based on the document *TRx-237-039: Impact of Remote Administration of Efficacy Scales* the following items are not possible to assess remotely:

- ADAS-cog$_{13}$: All but Orientation. All others, except Ideational Praxis, Number Cancellation, and Commands (sub-subdomains 3 and 4), are possible, when assessment is done by video call. For ADAS-cog$_{11}$ without Ideational Praxis and Commands the maximal achievable total score is 60.
- MMSE: Naming, Comprehension, Reading, Writing, Drawing (may possible, when assessment is done by video call).

For ADSC-ADL$_{23}$ the following items are affected by COVID-19 restrictions:

- Travel, Shopping, Keeping appointments, Left alone, Talk about current events, and Pastime (hobby or game). The maximal achievable total score of the remaining items is 58.

When these items are excluded in the COVID-19 sensitivity analysis, the remaining items will be upscaled as described.

For the end of treatment value (see Section 5.9.1.3), the last available upscaled on-treatment value will be used for analysis.

4.5.1.1. ADAS-cog$_{11}$ and ADAS-cog$_{13}$

The ADAS-cog$_{11}$ / ADAS-cog$_{13}$ total score is the sum of four / five domain scores (see Appendix 12.2.1).

The Word Recall subscore will be calculated as the mean of the non-missing scores from the three trials, rounded to 2 decimal places. The other subscores are obtained directly from the CRF page.

Within a given domain, there may be some missing subscores. If the sum of the maximum possible score of the non-missing items *m* is greater or equal to one half (50%) of the maximum possible score

for the domain *t*, the domain score will be scaled up using the formula: *t*s/m*, with *s* being the score of the non-missing subscores.

Otherwise, the domain score will be missing. If any domain score is missing, the ADAS-cog_{11} / ADAS-cog_{13} total score will be missing.

4.5.1.2. ADCS-ADL_{23}

For ADCS-ADL_{23}, it is possible to answer items with "Don't Know". If not more than four items are answered that way, the items are not missing and will count as 0. Upscaling of the other missing values is then done as follows:

Let *m* be the maximal obtainable score of the non-missing items (including "Don't Know"), and *s* the score of the non-missing items (including "Don't Know"). If m/78 is < 2/3, then the total score is set to missing, otherwise upscaling will be performed using the formula: *78*s/m*.

In case of more than four items answered with "Don't Know", the Total score is not provided by the data vendor. Therefore, a more complex upscaling algorithm will be applied to calculate the Total score. Since it cannot be decided, which four "Don't Know" items will count as 0 and which not, the mean of the maximal obtainable scores of the items answered with "Don't Know" is used in the following upscaling rule:

Let *x* be the mean of the maximal obtainable scores of the items answered with "Don't Know", m_2 the maximal obtainable score of the non-missing items (excluding "Don't Know") plus *4*x*, and *s* the score of the non-missing items (excluding "Don't Know") (plus *4*0*).

If $m_2/78$ is < 2/3, then the total score is set to missing, otherwise upscaling will be performed using the formula: $78*s/m_2$.

4.5.1.3. MMSE, CDR-SOB

The following rule is true for MMSE, and CDR-SOB.

Let *t* be the maximal score (MMSE: 30, CDR-SOB: 18), *m* the maximal obtainable score of the non-missing items, and *s* the score of the non-missing items. If m/t is < 2/3, then the total score is set to missing, otherwise upscaling will be performed using the formula: *t*s/m*.

4.5.1.4. Composite Scale and COVID-19 Composite Scale

For the two composite scales, upscaling will be performed analogously to the algorithm as described above (see Sections 4.5.1.1 and 4.5.1.2), restricted to the respective composite scale subscores/ items. If one of the two scales is missing, the respective composite scale missing.

4.5.2. Multiple Imputation

Upscaling will be performed prior to the use of multiple imputation.

Multiple imputation will be performed only for the double-blind treatment phase data of the two co-primary endpoints and the secondary endpoint MRI whole brain volume.

Missing values will be imputed multiple times to account for the uncertainty about the true values to impute. A multivariate imputation by fully conditional specification (FCS) methods will be used, which handles arbitrary missing patterns. This will be applied using the FCS statement in the MI procedure in SAS®.

The imputation model uses the same fixed factors and covariates as in the respective analysis models, unless specified otherwise.

The seed of **237039** was pre-specified in the study protocol and must be used in the final run. A total of 50 imputed datasets will be generated.

For the MITT populations data after multiple imputation are analyzed in a sensitivity analysis. The imputation model will not include the treatment indicator.

Sample SAS code (will be fully validated at the analysis stage):

*PROC MI DATA=dataset SEED=**237039** NIMPUTE=50 OUT=datami;*

CLASS visit severity region prioruse;

FCS REG(adascog11 = visit severity region prioruse adascog11bl);

FCS REG(adcsadl23 = visit severity region prioruse adcsadl23bl);

FCS REG(mriwbv = visit severity region prioruse mriwbvbl);

VAR visit severity region prioruse adascog11bl adcsadl23bl mriwbvbl adascog11 adcsadl23 mriwbv;

RUN;

Imputed values will not be edited to fit their respective definition area, since they are not equivalent to observed data and serve only to help estimating covariances between variables.

In sensitivity analyses of the primary estimand (see Section 5.9.1.1) the following two strategies will be followed, as summarized in Section 4.5.2.1 and 4.5.2.2:

4.5.2.1. Imputing missing data for both treatment groups based on data seen in control group

Outcomes are imputed for all treatment groups as if they would have continued on the control, which assumes the statistical behavior of control- and HMTM-treated subjects is the statistical behavior of control-treated subjects.

This will be implemented by the MNAR statement, which imputes missing values by using the pattern-mixture model approach:

Sample SAS code (will be fully validated at the analysis stage):

*PROC MI DATA=dataset SEED=**237039** NIMPUTE=50 OUT=datami;*

CLASS visit severity region prioruse;

FCS REG(adascog11 = visit severity region prioruse adascog11bl);

FCS REG(adcsadl23 = visit severity region prioruse adcsadl23bl);

FCS REG(mriwbv = visit severity region prioruse mriwbvbl);

MNAR MODEL (adascog11 / MODELOBS=(treatment='control'));

MNAR MODEL (adcsadl23 / MODELOBS=(treatment='control'));

MNAR MODEL (mriwbv / MODELOBS=(treatment='control'));

VAR visit severity region prioruse adascog11bl adcsadl23bl mriwbvbl adascog11 adcsadl23 mriwbv;

RUN;

4.5.2.2. Imputing missing data for each treatment group based on data seen in their own group

Outcomes are imputed assuming that subjects would follow their initial treatment (rather than switching to control after discontinuation), conditional on baseline and pre-withdrawal data included in the analysis. Therefore, the treatment arm will be included in the imputation model.

Sample SAS code (will be fully validated at the analysis stage):

*PROC MI DATA=dataset SEED=**237039** NIMPUTE=50 OUT=datami;*

CLASS visit severity region prioruse treatment;

FCS REG(adascog11 = visit severity region prioruse adascog11bl treatment);

FCS REG(adcsadl23 = visit severity region prioruse adcsadl23bl treatment);

FCS REG(mriwbv = visit severity region prioruse mriwbvbl treatment);

VAR visit severity region prioruse treatment adascog11bl adcsadl23bl mriwbvbl adascog11 adcsadl23 mriwbv;

RUN;

4.5.2.3. Analysis of multiple imputed data

Each of the 50 imputed datasets will be analyzed as done for the non-multiple imputed data, by adding the BY _IMPUTATION_ statement. Afterwards, these 50 results will be combined using standard Rubin's combination rules. Since the analyses results are assumed to be normally distributed no additional transformation will be necessary.

PROC MIANALYZE PARMS (CLASSVAR=FULL) = mxparms;

CLASS treatment visit severity region prioruse;

MODELEFFECTS treatment|visit severity region prioruse scorebl;

BY parameter;

ODS OUTPUT PARAMETERESTIMATES=mimxparms;

RUN;

4.6. Control Group Labeling

With protocol version 5 on, drug supplies for the control group included tablets containing a urinary discolorant (MTC), 4 mg, dosed at an average frequency of two tablets per week (see Sections 1.3 and 2.1). This means, that most of the subjects randomized to placebo/control received at least one dose of MTC. The sponsor will provide an Excel file to Cytel, which will list the subjects who received placebo only and subjects who transitioned from placebo to MTC 8 mg/week. All other control group subjects will have received MTC 8 mg/week.

In the analysis, a few tables will present subjects who received placebo only separately from subjects who received at least one dose of MTC, which is then highlighted in the respective section of this SAP. In this case, the following treatment group labels will be used: "Placebo Only" and "MTC 8 mg/week".

For other analyses in which subjects randomized under a protocol version before version 5 are included (e.g., ITT population, see Section 3.1.1), the label for the control group will be "Placebo and/or MTC 8 mg/week", and for the analyses in which subjects randomized under a protocol version before version 5 are not included (e.g., ITTv5 population), the label for the control group will be "MTC 8 mg/week".

In the subject data listings control group subjects will be labeled as "Placebo Only" and "MTC 8 mg/week", respectively.

4.7. Subject Data Listings

Subject data listings of all documented data of interest will be provided (see efficacy, safety, and exploratory analysis sections).

For the efficacy endpoints the following listings will be prepared: one showing the total score of the scales (ADAS-cog$_{11}$, ADAS-cog$_{13}$, ADCS-ADL$_{23}$, Composite Scale, and COVID-19 Composite Scale), one showing the MRI parameters and another one showing the ^{18}F-FDG-PET parameters. These listings will be accompanied by:

- the information under which protocol version the subject has been randomized,
- a flag for subjects who are excluded from the respective MITT population,
- a flag for assessments that are not potentially confounded by intercurrent illnesses, COVID-19, and concomitant medications (which includes assessments after initiation of an AchEI and/or memantine) as identified during the BDRM,
- a flag for "off treatment" assessments that are after 14 days after the withdrawal of study treatment, or after 14 days after the beginning of a dose interruption and before the restart of study drug intake,
- a flag if the assessment was done remotely,
- the upscaled value,
- a flag indicating a response, and
- a flag indicating a decline.

In addition, for the scales, the individual items and any computed subdomains/ scores etc. will be listed. If feasible, ADAS-cog$_{11}$ and ADAS-cog$_{13}$ can be listed together. For MMSE and CDR separate listings will be provided, too.

Further subject data listings are described in their respective sections (e.g., subject disposition).

4.8. Summary Statistics

To complete the efficacy analysis, which is described in the following sections, summary statistics will be tabulated by visit and treatment group using observed data (after upscaling is applied); for the absolute values, and the change from Baseline, based on the respective analysis populations. This will be repeated for subjects with treatment initiation of AchEI and/or memantine (post-hoc, if sample size is sufficiently high), and for withdrawals from study treatment but remaining in the study (TOTOS, see Section 4.4), separately, for selected primary and secondary endpoints (ADAS-cog$_{11}$, ADCS-ADL$_{23}$, MRI whole brain volume, ^{18}F-FDG-PET temporal lobe). If the number of subjects with treatment initiation of AchEI and/or memantine is less than five, a separate subject data listing is enough. Summary statistics for sensitivity analysis will be done post-hoc, if of interest.

If applicable, the absolute values, change from Baseline, and treatment difference (with its 95% confidence intervals), between the HMTM active group(s) and control, based on the least squares

means (LSM) from the corresponding MMRM or ANCOVA model, will be presented by visit (e.g., see Section 5.9.2.1).

The number and percentage of affected (missing or likely impacted) assessments by COVID-19 will be summarized by endpoint and visit, and further by treatment group and overall, using the information from the respective eCRF *Covid-19 Impact Assessment*. From this eCRF the reason(s) why the study visit was affected, e.g., *Subject unable to attend clinic visit*, will be analyzed in the same way. The denominator is the number of subjects who were still on study for the respective visit.

5. STATISTICAL ANALYSIS OF DOUBLE-BLIND TREATMENT PHASE

In the following, *decline* is defined as a change into the direction of greater impairment. An *on-treatment visit*, and their corresponding assessments, is defined as a visit where a subject was on investigational product (within the last 14 days) and not on any AchEI and/or memantine (except short-term use). This means, in case of a longer dose interruption a visit can be off-treatment if the subject was not on-treatment within the last 14 days of the visit.

5.1. Primary Efficacy Analysis

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. Repeated measurements on these endpoints scheduled at Weeks 13, 26, 39, and 52 will be treated using a mixed effects model (see Section 5.9). Suppose $\mu_{ADAS\text{-}cog11,T}$ and $\mu_{ADCS\text{-}ADL23,T}$ are the means of decline at Week 52 for the treated arm and $\mu_{ADAS\text{-}cog11,C}$ and $\mu_{ADCS\text{-}ADL23,C}$ are the corresponding means for the control arm, then the global null and the alternative primary efficacy hypotheses can be written as:

H_0: $\mu_{ADAS\text{-}cog11,T} = \mu_{ADAS\text{-}cog11,C}$ OR $\mu_{ADCS\text{-}ADL23,T} = \mu_{ADCS\text{-}ADL23,C}$; versus

H_1: $\mu_{ADAS\text{-}cog11,T} \neq \mu_{ADAS\text{-}cog11,C}$ AND $\mu_{ADCS\text{-}ADL23,T} \neq \mu_{ADCS\text{-}ADL23,C}$.

Thus, the global null versus alternative is a Union-Intersection Test (UIT) 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.

5.2. Multiple Comparisons/Multiplicity

In the double-blind treatment phase, the primary comparison is between HMTM 16 mg/day and control, based on subjects randomized under study protocol version 5.0 or higher.

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 HMTM 16 mg/day to be designated as superior to control. This is because the global null hypothesis is only rejected if and only if the null hypothesis for each of the two co-primary endpoints are rejected. Furthermore, since the efficacy endpoints are primarily analyzed based on two different analysis populations (ITTv5, and the respective MITTv5), the pre-defined sequence is MITTv5 before ITTv5. ITT and MITT populations will be analyzed in the framework of sensitivity analyses.

Therefore, no multiplicity adjustment is necessary.

5.3. Sample Size Justification

Sample size estimations to achieve 90% power (two-sided alpha = 0.05) to detect a difference between HMTM 16 mg/day and true placebo 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 – here restricted to subjects randomized under protocol version 5.0 or higher as this is the primary analysis population – of approximately 450 subjects (approximately 200 subjects in each treatment group, with a further 50 subjects for secondary analyses of an HMTM 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 approximately 93.2% 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 approximately 96.7% 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.

5.4. Protocol Deviations

Protocol deviations from the double-blind treatment phase will be analyzed as described in Section 3.2.

5.5. Visit Windows

Since data might be documented under a wrong label (as a wrong visit) within the EDC system, all data will be (re-)assigned to a visit according to the column *Intervals for analysis* in Table 5.

Furthermore, if a subject has multiple values for a parameter within a visit window, the “worst” value will be used for that visit window summary (see Appendix 12.3), for efficacy endpoints the closest to the scheduled visit will be used (if two have the same distance from the scheduled visit the later one will be used, and if two have the same day, the Sponsor will provide a file, which identifies the value to be used in the analysis). For the double-blind treatment phase, priority at Week 52 is given to assessments that took place before initiation of the open-label treatment in case there are multiple values for them within the visit window.

As an exception, for the analysis of the double-blind treatment phase, a delayed Week 52 ^{18}F-FDG-PET or MRI assessment will be included in the double-blind treatment phase even if it has been done within 14 days after first dose of the open-label treatment phase drug. In addition, the eye exam is eligible for the double-blind treatment phase, if it was performed until the end of the Week 52 protocol-specified visit window. For all other efficacy endpoints and safety information only assessments before the first dose of the open-label treatment phase or if assessments were done on the same day of the first open-label phase treatment are eligible for analysis of double-blind treatment phase data.

Table 5 Evaluation Intervals for Safety and Efficacy Analyses of the Double-Blind Phase

Evaluation (scheduled day)	Protocol-Specified Interval	Intervals for Analysis		
		Safety assessments	ADAS-cog$_{13}$, ADCS-ADL$_{23}$, MRI	^{18}F-FDG-PET, MMSE, CDR
Baseline (1) [a]	–1 to 1	≤1	≤1	1
Week 4 (29)	26 to 32 [±3]	2 to 67	-	-
Week 13 (92)	78 to 106 [±14]	68 to 137	2 to 137	-
Week 26 (183)	169 to 197 [±14]	138 to 228	138 to 228	-
Week 39 (274)	260 to 288 [±14]	229 to 319	229 to 319	-
Week 52 (365)	351 to 379 [±14]	320 to 379	320 to 456	>1

[a] Day 1 – first in-clinic dose of study drug

5.6. Subject Disposition

Based on the screened set, a subject data listing will give an overview of the following screening and randomization information (one row for each subject):

- Protocol version under which the subject has signed the initial informed consent
- Date of initial informed consent
- Duration of the screening period
- If screening failure. If so, reasons for screening failure
- Date of randomization, strata used for randomization, a flag if the subject was miss-stratified, treatment assignment, and initial screening number (if re-screened)

A separate listing will just include the subjects with an extended screening period due to the COVID-19 pandemic allowed by the Investigator. The identified subjects will be provided to Cytel after the BDRM.

Subjects who are mis-stratified during the randomization are flagged in the aforementioned listing, but will be also listed separately with the following information: randomized treatment group, strata used for randomization, and correct strata values.

Based on the ITT population, a subject data listing will give an overview of the following disposition information (one row for each subject):

- Protocol version under which the subject has been randomized
- First and last dose dates of study drug intake
- Date of study exit
- A flag for the completion of the study, and a flag for the TOTOS (see Section 4.4)
- All reasons why the subject did not complete the study, and a flag for the primary reason
- For the TOTOS, the reason why the subject discontinued the study drug

Based on the ITT population, a subject by-visit listing, including all planned and unplanned visits, will be created with the following information: randomized treatment group, visit name, and visit date range (including study day). Visit windowing will not be performed for this listing, but visits with a clear wrong label, with a visit date range outside of the associated visit window, will be flagged.

Based on the ITT population, a subject data listing will provide an overview of the double-blind treatment phase populations (see Section 3.1.1) and will list the following events (sorted by subject, and date; one row for each event):

- Affiliation to the study populations (one column per study population)
- Date of initial informed consent
- Date of randomization
- Protocol re-consents, with the protocol version and signing dates (one row for each re-consent)
- Date and primary reason of study discontinuation
- Date of study drug discontinuation, if study drug discontinuation is permanent and if the date is different from the date of study discontinuation
- Discontinuation date of AChEI and/or memantine for purposes of the study (if available)
- Date(s) of COVID-19 infection
- Date(s) of COVID-19 vaccination
- Date of Week 52 visit

The number of screening failure reasons will be tabulated (by region, and total). For large study sites, separate tables might be provided.

Information on the number of subjects randomized, the number of subjects in each analysis population, the number of subjects completing the study as well as the double-blind treatment phase (subsets on and off treatment), the number of subjects discontinuing the study drug but continuing the study (TOTOS), the primary reason for discontinuation of study drug and study, and all reasons for discontinuation of study drug and study will be tabulated. This will be done by treatment group and overall, for the ITT, E-MITT, E-MITTv5, ITTv5, and PPv5 populations, separately. Furthermore, based on the ITT population, this will be tabulated by region.

If the reason for discontinuation of study drug is missing the primary reason for discontinuation of study will be used instead.

5.7. Demographic and Baseline Characteristics

Data will be provided in subject data listings, based on the ITT population.

Demographic and Baseline characteristics will be summarized for the ITT, E-MITT, E-MITTv5, ITTv5, and PPv5 populations. This will also be done for subgroups (based on the ITTv5 population) by use of AChEI and/or memantine prior to Baseline, for subjects characterized as mild AD or MCI-AD (MMSE: 20-27), for subjects characterized as moderate AD (MMSE: 16-19), by region, and for highly recruiting sites (more than 10% of randomized subjects).

General baseline information to be summarized include age at informed consent, sex, ethnicity (Not Hispanic or Latino, Hispanic or Latino) including only the US sites, race, and geographic region; height, weight, creatinine clearance, smoking history, childbearing status/contraception, age at leaving full-time education, and Fazekas score (periventricular white matter score, deep white matter score, and overall score = maximum of periventricular white matter score and deep white matter score). Regarding the race: If race was answered in the eCRF with “not reported” or with a similar comment in “other”, such as “NA”, “NA in France”, “not allowed by law”, “not applicable”, “not authorized”, or “not permitted by law”, race is set to unknown.

Disease specific Baseline characteristics include the verified AD diagnosis (probable AD dementia, MCI-AD [mild cognitive impairment due to AD], based on the Diagnostic Verification form), time from diagnosis of AD to informed consent (years) and time from presumptive AD diagnosis to informed consent (years), *ApoE* genotype (in the subset who provide consent), MMSE, CDR, and previous use of an AChEI and/or memantine. Additionally, a summary of the amyloid PET will be provided, whether it was previously done or within this study. The Diagnostic Verification form was not available for subjects who have been randomized under protocol version 2.1, since only subjects with mild AD were included (see Section 1.3), therefore these subjects will be allocated to the probable AD dementia subgroup. The AD diagnosis is defined as medical history of cognitive impairment and is identified by the following

medical history Preferred Terms (PT): Dementia Alzheimer's type, Cognitive disorder, Memory impairment, Transient global amnesia, Amnesia, Amnestic disorder, Dementia, Mixed dementia. The presumptive AD diagnosis is defined as the earliest of the following dates:

- Use of AD medication: ATC code N06DA (e.g., Donepezil, Galantamine, Rivastigmine), and ATC code N06DX (Memantine, and 'other anti-dementia drugs')
- Positive amyloid PET scan
- Verified AD diagnosis

Medical history (coding see Section 4.3) will be summarized in a table presenting the numbers and percentages of subjects with medical history terms in a given MedDRA System Organ Classification (SOC) for the ITT and ITTv5 population.

Analysis of recently used medications and concomitant medications is described in the following Section 5.8.

No formal statistical comparisons of treatment groups for any Baseline characteristics will be performed.

5.8. Prior and Concomitant Medications

Prior used medications (discontinued before the start of study drug) and concomitant medications (on medication at the first dose of study drug or after) will be coded using the 01 March 2017 version of the WHO drug dictionary and the Anatomical Therapeutic Classification (ATC) level 1 term, ATC level 3 term, and PT. If the end-date and/or start-date are missing, the medication will be allocated to the concomitant medication.

If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior to or concomitantly with treatment, it will be considered a concomitant medication.

The use of prior medications, and concomitant medications will be included in subject data listings for the ITT population. For subjects who previously used an AChEI and/or memantine, the start and stop date of medication, whether the medication was stopped prior to screening or between screening and randomization, and reason for stopping usage will be listed separately; this listing will include a flag for subjects randomized under the UK study protocol version 5.0 or higher, since for these subjects, AChEI and/or memantine should end before the start of screening. A subset listing will also be provided for subjects who were using an antipsychotic treatment (see Section 10.4), which includes the reasons for use as well.

The following summaries/tabulations will be prepared for the ITT and ITTv5 populations.

Tabulations with frequency and percentage, by treatment group and medication, will be prepared separately for all prior, for all concomitantly used drugs (used at the time of first study drug or after),

and for all concomitantly used drugs that the patient is on at the time of first study drug, where subjects reporting more than one medication are counted only once within each level summation.

Summary tables will be provided, showing the numbers of subjects with initiated treatments of: SSRI/SNRI (see Section 12.4), drugs of serotonergic potential (see latest version of the Serotonergic Drugs List – a Sponsor controlled document, which was distributed to Cytel prior to the database lock of the double-blind treatment phase), and any antipsychotic medications. For antipsychotics initiated on-treatment, the reasons for use will be also summarized.

For subjects who previously used an AChEI and/or memantine, the reasons for stopping such medications, duration of use, and duration of time since stopping prior to randomization will be tabulated.

5.9. Efficacy Evaluation

The primary objective of the final amended version of the study protocol (see Section 1.1) is to evaluate the efficacy of HMTM 16 mg/day compared with control over 52 weeks in patients with AD using the MMRM (including the nominal visits Week 13, Week 26, Week 39 and Week 52), including the randomization stratification variables (see Section 2.6) as fixed factors, the respective efficacy Baseline value as covariate, and the treatment indicator (plus its interaction term with the visit variable). The co-primary endpoints are the difference between HMTM 16 mg/day and control in ADAS-cog_{11} and ADCS-ADL_{23} at Week 52.

The next section will give the definitions of the estimands, which are then used in the following efficacy endpoint analysis sections. As a reminder to Section 5.2 the pre-defined analysis sequence is MITTv5 analysis followed by the estimands analysis based on ITTv5. Despite the definition of this sequence, the MITT based analysis is primary for the FDA while the ITT based analysis is considered primary for the EMA.

Regarding the MITT 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 (MRI whole brain volume, and ^{18}F-FDG-PET temporal lobe).

5.9.1. Estimands

Whenever analyzed, the estimands for the comparison of 8 mg/day versus control are defined analogously.

5.9.1.1. Primary Estimand (ITTv5)

The Primary Estimand is designed to answer the question on the treatment effect of HMTM dose of 16 mg/day as monotherapy versus control (containing a small amount of MTC, spiked) in the targeted

population of subjects with probable AD and MCI-AD at Week 52, regardless of trial product 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:

A. Treatment: 52 weeks HMTM dose of 16 mg/day or matching control (containing a small amount of MTC) as monotherapy, regardless of adherence.

B. Population: Subjects with probable AD and MCI-AD as described by the inclusion and exclusion criteria, randomized under protocol version 5.0 or higher.

C. Patient-level outcomes / variables: The co-primary outcomes are the change from Baseline of the ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ at Week 52.

D. Population-level summary: Population weighted least squares means difference.

E. Intercurrent Events: The following ICE have been identified which could prevent measurement of the primary outcome or change the interpretation of the measured primary outcome:

1. Subjects withdraw from study before the completion of 52 weeks treatment phase for non-treatment related reason

2. Subjects withdraw from study before the completion of 52 weeks treatment phase 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 AE, or due to study drug dose interruption longer / more frequent than specified in ICE #5 below) (TOTOs, see Section 4.4)

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 due to safety concerns and initiated by the PI (see Section 4.4)

6. Intercurrent illnesses, or initiation of medical food or medications not allowed by protocol (which will be identified during the BDRM)

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. Deaths before the completion of 52 weeks treatment phase

9. COVID-19 infection

10. Death due to COVID-19

Events 1 will be handled according to a hypothetical strategy as if patients 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 treatment policy approach reflecting Copy Incremental from Reference strategy (using data after occurrence of the ICE for the estimation, if available). 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, in other words, assuming that the clinical course post ICE for either treatment group follows control treatment 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 HMTM 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 5.9.2.1).

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 control group, and one by imputing missing data for each treatment group based on data seen in their own group (see Section 4.5.2).

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 HMTM 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 did not start AChEI and/or memantine and will be analyzed the same as ICE #2.

Events 4 will be handled according to a treatment policy strategy, using data after occurrence of the ICE. A sensitivity analysis will be carried out using the strategy as described for the ICE #2.

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 patient dies prior to Week 52, the missing assessments will be imputed by the population average in decline, calculated by visit, within the control arm.

Events 9, and 10 will be handled with a hypothetical strategy assuming COVID-19 disease would not have happen, not using data after occurrence of the ICE.

5.9.1.2. Primary Estimand (ITT)

The Primary Estimand (ITT) is designed to answer the question on the treatment effect of HMTM dose of 16 mg/day as monotherapy versus control (with and/or without MTC) in the targeted population of subjects with probable AD and MCI-AD at Week 52, regardless of trial product discontinuation and enrollment before or after protocol version 5.0.

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

A. Treatment:	Up to 52 weeks HMTM dose of 16 mg/day as monotherapy or matching control (with and/or without MTC).
B. Population:	Subjects with probable AD and MCI-AD as described by the inclusion and exclusion criteria.
C. Patient-level outcomes / variables:	The co-primary outcomes are the change from Baseline of the ADAS-cog_{11} and ADCS-ADL_{23} at Week 52.
D. Population-level summary:	Population weighted least squares means difference.

E. Intercurrent Events:	Identification and handling of ICE as described for the primary estimand (see Section 5.9.1.1), excluding the sensitivity analyses.

5.9.1.3. Secondary Estimand – While on Treatment Strategy (ITTv5)

The Secondary Estimand is designed to answer the question on the treatment effect of HMTM dose of 16 mg/day as monotherapy versus control (containing a small amount of MTC, spiked) in the targeted population of subjects with probable AD and MCI-AD up to 52 weeks while on treatment, 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:

A. Treatment:	Up to 52 weeks of HMTM dose of 16 mg/day or matching control (containing a small amount of MTC) as monotherapy.
B. Population:	Subjects with probable AD and MCI-AD as described by the inclusion and exclusion criteria, randomized under protocol version 5.0 or higher.
C. Patient-level outcomes / variables:	The co-primary outcomes are the change from Baseline of the ADAS-cog_{11} and ADCS-ADL_{23} at the end of treatment of up to 52 weeks (see Section 4.5.1)
D. Population-level summary:	Population weighted least squares means difference.
E. Intercurrent Events:	The following ICE have been identified which could prevent measurement of the primary outcome or change the interpretation of the measured primary outcome: 1. 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 due to safety concerns and initiated by the PI (see Section 4.4) 2. Intercurrent illnesses and initiation of medical food or medications not allowed by protocol, identified during the BDRM 3. Study treatment non-compliance, defined as <80% or >120% taking into consideration any dose interruptions (if this cannot be estimated, it does not automatically result in a non-compliance) 4. Deaths before the completion of 52 weeks treatment phase

Events 1, 2, and 3 that occur while on treatment will be handled according to a treatment policy strategy, using data after occurrence of the ICE.

Events 4 will be handled as treatment failure. If the patient dies prior to Week 52, the missing assessment at the end of treatment will be imputed by the population average in decline at the end of treatment within the control arm.

5.9.1.4. MRI Estimand (ITTv5)

The MRI Estimand is designed to answer the question on the treatment effect of HMTM dose of 16 mg/day as monotherapy versus control (containing a small amount of MTC) in the targeted population of subjects with probable AD and MCI-AD at Week 52, regardless of trial product discontinuation, based on the MRI whole brain volume.

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

A. Treatment:	52 weeks HMTM dose of 16 mg/day or matching control (containing a small amount of MTC) as monotherapy, regardless of adherence.
B. Population:	Subjects with probable AD and MCI-AD as described by the inclusion and exclusion criteria, randomized under protocol version 5.0 or higher.
C. Patient-level outcome / variable:	Annualized rate, defined as the absolute change from Baseline, of whole brain atrophy as measured by MRI and quantified using the Boundary Shift Integral (BSI) at Week 52.
D. Population-level summary:	Population weighted least squares means difference.
E. Intercurrent Events:	Identification and handling of ICE as described for the primary estimand (see Section 5.9.1.1), including the sensitivity analyses.

The MRI Estimand (ITT) is defined as the MRI Estimand, extending the population to the ITT population as done for the Primary estimand (ITT) (see Section 5.9.1.2).

5.9.1.5. PET Estimand (ITTv5)

The PET Estimand is designed to answer the question on the treatment effect of HMTM dose of 16 mg/day as monotherapy versus control (containing a small amount of MTC) in the targeted population of subjects with *very mild* AD (CDR of 0.5) at Week 52, regardless of trial product discontinuation, based

on the ^{18}F-FDG-PET temporal lobe in SUVR. If data is available from subjects with other than a CDR of 0.5, these will not be included in the analysis.

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

A. Treatment: 52 weeks HMTM dose of 16 mg/day or matching control (containing a small amount of MTC) as monotherapy, regardless of adherence.

B. Population: Subjects with very mild AD (CDR of 0.5) and as further described by the inclusion and exclusion criteria, randomized under protocol version 5.0 or higher.

C. Patient-level outcome / variable: Change from Baseline of the ^{18}F-FDG-PET temporal lobe in SUVR at Week 52.

D. Population-level summary: Population weighted least squares means difference.

E. Intercurrent Events: Identification of ICE is as described for the primary estimand (see Section 5.9.1.1).

Events 1 will be handled according to a hypothetical strategy as if patients 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 assuming 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 HMTM treatment group who withdraw for potentially treatment-related reasons up to Week 52.

Events 3 will be handled according to the original randomized treatment group assuming they did not start AChEI and/or memantine and will be analyzed the same as ICE #2.

Events 4 will be handled according to a treatment policy strategy, using data after occurrence of the ICE. A sensitivity analysis will be carried out using the strategy as described for the ICE #2.

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 patient dies prior to Week 52, the missing assessment at Week 52 will be imputed by the population average in decline within the control arm.

Events 9, and 10 will be handled with a hypothetical strategy assuming COVID-19 disease would not have happen, not using data after occurrence of the ICE.

The PET Estimand (ITT) is defined as the PET Estimand, extending the population to the ITT population as done for the Primary estimand (ITT) (see Section 5.9.1.2).

5.9.2. Primary Efficacy Endpoint Analysis

5.9.2.1. MITT Population Analysis

Data will be analyzed based on the E-MITTv5 population (see Section 3.1.1) using a restricted maximum likelihood-based (REML) MMRM, including a nominal visit variable, the treatment indicator and the interaction term between treatment and visit, the randomization stratification variables (see Section 2.6) as fixed factors, and the respective efficacy Baseline value as covariate; with an unstructured covariance matrix and the Kenward and Roger method of calculating the denominator degrees of freedom for the tests of fixed effects.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') visit severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL scorediff = treatment|visit severity region prioruse scorebl / SOLUTION CL DDFM=KENWARDROGER;

REPEATED visit / SUB=subject TYPE=UN;

*LSMEANS treatment*visit visit / CL;*

**BY _IMPUTATION_;*

*LSMESTIMATE treatment*visit "intervention effect at Week 52" 0 0 0 1 0 0 0 -1 / CL;*

**Summary statistics for treatment difference based on LSM*

*LSMESTIMATE treatment*visit "intervention effect at Week 13" 1 0 0 0 -1 0 0 0 / CL;*

*LSMESTIMATE treatment*visit "intervention effect at Week 26" 0 1 0 0 0 -1 0 0 / CL;*

*LSMESTIMATE treatment*visit "intervention effect at Week 39" 0 0 1 0 0 0 -1 0 / CL;*

RUN;

If the mixed model does not converge, the unstructured covariance matrix is replaced by firstly, an auto-regressive covariance structure then by a compound symmetry covariance structure. If the model still does not converge, the randomization stratification variables will be removed, in the following order: region, prior AChEI and/or memantine use, MMSE.

Sensitivity analysis to the statistical model

Model-based sensitivity analysis are:

- Including the interaction term Baseline*visit (*scorebl*visit*) in model statement
- Maximum likelihood (ML) (rather than REML) based repeated measures model (*method=ml*) with polynomial (linear, quadratic, and cubic) time effects and time treated as a continuous variable (number of nominal weeks as well as actual study week defined by study day divided by 7). The estimated annualized change in mean values and standard errors from Baseline to Week 52 will be presented for each treatment group. For sample SAS code see Section 5.9.3.1.

Supplementary and other sensitivity analyses

Supplementary analyses are (starting population: E-MITTv5):

- Including subjects randomized before study protocol version 5.0 (E-MITT population)
- Restricted to the PP population
- Restricted to the completers (subjects who did not stop the study or the study medication early, during the double-blind treatment phase)
- Include assessments after initiation of an AChEI and/or memantine, if more than 5% of the randomized subjects initiated AChEI and/or memantine during the double-blind treatment phase
- Restricted to all visits not potentially confounded by intercurrent illnesses, COVID-19, and concomitant medications (which includes assessments after initiation of an AChEI and/or memantine) as identified during the BDRM
- Stratified by subgroups. If the subgroup consists of less than 10% of the randomized subjects, only summary statistics will be presented.
    - AChEI/memantine use (prior use, never used) [binary]
    - Verified AD diagnosis (probable AD, MCI-AD) [binary]
    - MMSE (16-19, 20-25, and 26-27), in case of mis-stratification the actual value is used

- MMSE (16-21, 22-27)
- CDR (0.5, 1 or 2) [binary], in case of mis-stratification the actual value is used
- Age group (<75 years, ≥75 years) [binary]
- Sex (male, female) [binary]
- Race (White, non-White) [binary], Race = White (if checked as only race), otherwise Race = non-White (even if multiple races, including White, were checked)
- Geographic region (North America, Europe) [binary]

- Including the *ApoE* genotype as fixed factor (Presence of the ε4 Allele, Absence of the ε4 Allele) [binary]
- Both HMTM treatment groups pooled versus control

Sensitivity analyses are:

- If more than 5% of the randomized subjects have been mis-stratified, then the primary analyses will be repeated using the actual status at randomization
- Multiple imputation analysis (see Section 4.5.2)

For the two co-primary endpoints and their change from Baseline to Week 52, the empirical distribution functions for HMTM 16 mg/day and control will be compared graphically and using a Kolmogorov-Smirnov test. If the Week 52 visit value is not available, the last available on-treatment value will be used.

Sample SAS code (will be fully validated at the analysis stage):

```
PROC NPAR1WAY DATA=dataset EDF PLOTS=EDFPLOT;
CLASS treatment;
VAR scorediff;
EXACT KS;
RUN;
```

For the following efficacy endpoint combinations, the correlation of their changes from Baseline to Week 52 will be analyzed (pooling the data from all three treatment groups):

- ADAS-cog$_{11}$ vs. MRI whole brain volume
- ADCS-ADL$_{23}$ vs. MRI whole brain volume

If for the respective pairwise comparison, the two Week 52 visit values are not available, the last available on-treatment visit with both respective values being available will be used. A scatter plot will compare the values for the two endpoints and will also present the p-value based on the Pearson correlation.

Sample SAS code (will be fully validated at the analysis stage):

PROC CORR DATA=dataset;

VAR endpoint1 endpoint2;

RUN;

Additional sensitivity / supplementary analyses due to COVID-19 for the two co-primary endpoints

Considerations made by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) (see Appendix, 8.1) guide possible changes to the statistical analysis due to COVID-19.

The following sensitivity and supplementary analysis will be performed for the two co-primary endpoints and based on the E-MITTv5 population (see Section 3.1.1) to investigate the impact of COVID-19:

- 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 by remote (excluding Baseline and Week 52, which must be performed in-clinic). If a visit was done in-clinic or by remote is documented in the eCRF *Covid-19 Impact Assessment*.
- ADAS-Cog_{11}: Include only the subset of items (for all visits), which can be administered by remote by telephone or video call (see Section 4.5.1).
- ADCS-ADL_{23}: Exclude items which are affected by COVID-19 restrictions (see Section 4.5.1).
- A composite scale designed as a COVID-19 impact free joint score ("COVID-19 Composite Scale") will be analyzed. The included items, selected from ADAS-Cog_{11} and ADCS-ADL_{23}, are indicated in section 12.2 and result in a score ranging from 0 to 113. Since a higher score for ADAS-cog_{13} indicates more impairment (less impairment for ADCS-ADL_{23}), the values of ADAS-cog_{13} will be transformed (maximal score minus actual score) before summarizing over both assessments.
- Subgroup of subjects with / without COVID-19 infection.
- Subgroup of subjects with / without COVID-19 vaccination.

If a subgroup consists of less than 10% of the randomized subjects, only summary statistics will be presented.

5.9.2.2. Estimand Analysis

The primary and secondary estimands (see Section 5.9.1.1, and 5.9.1.3) will be analyzed with the ITTv5 population (see Section 3.1.1) using the MMRM as described in the previous section for the MITT population.

With the estimand described in Section 5.9.1.2 the analysis of the primary estimand will be repeated for the ITT population, but without its sensitivity analyses.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') visit severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL scorediff = treatment|visit severity region prioruse scorebl / SOLUTION CL DDFM= KENWARDROGER;

REPEATED visit / SUB=subject TYPE=UN;

*LSMEANS treatment*visit visit / CL;*

**BY _IMPUTATION_;*

*LSMESTIMATE treatment*visit "intervention effect" nw13 nw26 nw39 nw52 -nw13 -nw26 -nw39 -nw52 / DIVISOR=Nhmtm CL;*

*LSMESTIMATE treatment*visit "intervention effect (sensitivity)" 0 0 0 nw52 0 0 0 -nw52 / DIVISOR=Nhmtm CL;*

RUN;

nw0, nw13, *nw26*, and *nw39* are the number of subjects within the respective HMTM treatment group who withdrew for potentially treatment-related reasons (ICE #2 in Section 5.9.1.1), have a non-missing efficacy parameter at Baseline, Week 13 (26, 39), and do not have any on-treatment assessments at any scheduled visit subsequent to Baseline, Week 13 (26, 39). With *Nhmtm* the sample size in the HMTM treatment group, *nw52* is calculated as *nw52 = Nhmtm – nw0 – nw13 – nw26 – nw39*. The numbers will need to be calculated before applying the analyses model (for example saved in macro variables). With respect to sensitivity analyses, *nwx* and *nw* will need to be re-calculated, when handling further ICEs as ICE #2.

The secondary estimand is analyzed using an ANCOVA, including the randomization stratification variables (see Section 2.6) as fixed factors, the respective efficacy Baseline value and the total duration of exposure (see Section 5.12.1) as covariates, and the treatment indicator; with the Kenward and Roger method used for calculating the denominator degrees of freedom for the tests of fixed effects.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL scorediff = treatment severity region prioruse scorebl (duration) / SOLUTION CL DDFM= KENWARDROGER;

LSMEANS treatment / CL;

LSMESTIMATE treatment "intervention effect at the end of treatment" 1 -1 / CL;

RUN;

5.9.3. Secondary Efficacy Endpoint Analysis

All secondary analyses have the underlying null hypothesis that there is no difference in change from Baseline in the quantity of interest between the HMTM 16 mg/day group, or the HMTM 8 mg/day group, and the control group.

The sequence of the secondary efficacy analysis is as follows:

- MRI whole brain: HMTM 16 mg/day versus control
- ^{18}F-FDG-PET temporal lobe (normalized to pons): HMTM 16 mg/day versus control
- ^{18}F-FDG-PET temporal lobe (normalized to pons): HMTM 8 mg/day versus control
- ADAS-cog$_{11}$ and ADCS-ADL$_{23}$: HMTM 8 mg/day versus control
- MRI temporoparietal lobe: HMTM 16 mg/day versus control, and HMTM 8 mg/day versus control

5.9.3.1. MRI: Whole Brain Atrophy

The atrophy, defined as the absolute change from Baseline, is already calculated by the responsible imaging core laboratory (see Section 2.9.1.1). The atrophy will be analyzed using the corresponding MMRM. The estimated annualized rates and the treatment group difference are obtained from the LSM.

MITT population analysis

Data will be analyzed based on the MI-MITTv5 population (see Section 3.1.1) according to Section 5.9.2.1 (including the supplementary and sensitivity analysis).

In a further exploratory analysis, the Baseline values of the MRI parameters putamen, nucleus accumbens, and nucleus basalis will be included as covariates.

Sample SAS code with time being continuous (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL atrophy = treatment|time severity region prioruse scorebl / SOLUTION CL DDFM=KENWARDROGER;

REPEATED / SUB=subject TYPE=UN;

LSMEANS treatment / CL;

*ESTIMATE "HMTM at Week 52" intercept 1 treatment 1 0 time 52 treatment*time 52 0 / CL;*

*ESTIMATE "Control at Week 52" intercept 1 treatment 0 1 time 52 treatment*time 0 52 / CL;*

*ESTIMATE "intervention effect at Week 52" treatment 1 -1 treatment*time 52 -52 / CL;*

**Polynomial time effects;*

**Quadratic;*

*ESTIMATE "HMTM at Week 52 (2)" intercept 1 treatment 1 0 time 52 treatment*time 52 0 time*time 2704 treatment*time*time 2704 0 / CL;*

*ESTIMATE "Control at Week 52 (2)" intercept 1 treatment 0 1 time 52 treatment*time 0 52 time*time 2704 treatment*time*time 0 2704 / CL;*

*ESTIMATE "intervention effect at Week 52 (2)" treatment 1 -1 treatment*time 52 -52 treatment*time*time 2704 -2704 / CL;*

**Cubic;*

*ESTIMATE "HMTM at Week 52 (3)" intercept 1 treatment 1 0 time 52 treatment*time 52 0 time*time 2704 treatment*time*time 2704 0 treatment*time*time*time 140608 0 / CL;*

*ESTIMATE "Control at Week 52 (3)" intercept 1 treatment 0 1 time 52 treatment*time 0 52 time*time 2704 treatment*time*time 0 2704 treatment*time*time*time 0 140608 / CL;*

*ESTIMATE "intervention effect at Week 52 (3)" treatment 1 -1 treatment*time 52 -52 treatment*time*time 2704 -2704 treatment*time*time*time 140608 -140608 / CL;*

RUN;

Estimand analysis

The MRI estimand (see Section 5.9.1.4) will be estimated analogously to the primary estimand (see Sections 5.9.1.1 and 5.9.2.2).

5.9.3.2. ^{18}F-FDG-PET: Temporal Lobe

If data is available from subjects with other than a CDR of 0.5, these will not be included in the analysis.

MITT population analysis

Data will be analyzed based on the PI-MITTv5 population (see Section 3.1.1), using an ANCOVA, including the randomization stratification variables (see Section 2.6) as fixed factors, the respective efficacy Baseline value as covariate, and the treatment indicator; with the Kenward and Roger method used for calculating the denominator degrees of freedom for the tests of fixed effects.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL scorediff = treatment severity region prioruse scorebl / SOLUTION CL DDFM=KENWARDROGER;

LSMEANS treatment / CL;

LSMESTIMATE treatment "intervention effect" 1 -1 / CL;

RUN;

Supplementary and sensitivity analysis will be performed as described in Section 5.9.2.1, except the model-based sensitivity analysis involving the time.

Estimand analysis

The PET estimand (see Section 5.9.1.5) will be estimated using the ANCOVA as described previously for the MITT population.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL scorediff = treatment severity region prioruse scorebl / SOLUTION CL DDFM=KENWARDROGER;

LSMEANS treatment / CL;

LSMESTIMATE treatment "intervention effect" nw52 -nw52 / DIVISOR=Nhmtm CL;

RUN;

With *nw* the total number of subjects who withdrew for potentially treatment-related reasons during the study until Week 52 in the respective HMTM group and *Nhmtm* the total sample size in the HMTM group, then *nw52* = *Nhmtm* - *nw*. The numbers will need to be calculated before applying the analyses model (for example saved in macro variables).

5.9.3.3. MRI: Temporoparietal Lobe Atrophy

For this secondary variable no further sensitivity / supplementary analyses are pre-specified. If necessary, post-hoc analysis will be performed to get a more in-depth understanding of the data.

MITT population analysis

Data will be analyzed based on the MI-MITTv5 population, using the MMRM as described in the sections 5.9.2.1 and 5.9.3.1.

In an exploratory analysis the Baseline values of the MRI parameters putamen, nucleus accumbens, and nucleus basalis will be included as covariates.

Estimand analysis

Data will be analyzed according to Section 5.9.2.1 using the estimand as described in Section 5.9.1.4 adapted to the temporoparietal lobe, based on the ITTv5 population.

5.9.3.4. HMTM 8 mg/day versus control

As a general remark, for the 8 mg/day versus control comparison, the order of analysis is ^{18}F-FDG-PET temporal lobe, MRI temporoparietal lobe, ADAS-cog$_{11}$, ADCS-ADL$_{23}$.

MITT population analysis

The analysis of ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ will be performed as outlined in Section 5.9.2, restricted to the primary analysis models and analysis populations ITTv5 and E-MITTv5, respectively. Further post-hoc analysis may follow.

In a sensitivity analysis for E-MITTv5, all three treatment groups are included in the PROC Mixed call using appropriate contrast statements for pairwise treatment comparisons against control.

The analysis of the ^{18}F-FDG-PET temporal Lobe will be done as described in Section 5.9.3.2 without the sensitivity / supplementary analysis.

The analysis of the MRI temporoparietal lobe atrophy will be done as described in Section 5.9.3.3 without the MITT explorative analysis.

Estimand analysis

The analysis of ADAS-cog$_{11}$ and ADCS-ADL$_{23}$ will be performed as outlined in Section 5.9.2, restricted to the primary estimand, without further sensitivity analysis. Further post-hoc analysis may follow.

The analysis of the ^{18}F-FDG-PET temporal lobe will be done as described in Section 5.9.3.2 without the sensitivity / supplementary analysis.

The analysis of the MRI temporoparietal lobe atrophy will be done as described in Section 5.9.3.3 without the MITT explorative analysis.

5.9.4. Responder Analysis (Sensitivity)

This analysis is based on the ITTv5 population and is done separately for each of the five primary / secondary efficacy variables (ADAS-cog$_{11}$, ADCS-ADL$_{23}$, MRI whole brain, MRI temporoparietal lobe, and ^{18}F-FDG-PET temporal lobe) and the exploratory efficacy variable Composite Scale, and furthermore separately for each HMTM group comparison versus control.

A responder will be defined as a subject whose change from Baseline to Week 52 is less or equal to a threshold *T* (if a larger value means greater impairment, otherwise: *more* or equal), which will be calculated based on the least squares means from the primary analysis model (in Section 5.9.2.1, including all three treatment groups together) and the respective MITTv5 population (E-MITTv5, MI-MITTv5, PI-MITTv5).

T is defined as follows, with LSM_C and LSM_T the LSM change from Baseline at Week 52 in the control arm and (HMTM) treated arm, respectively: $T = (LSM_C + LSM_T)/2$.

Subjects who do not have a final assessment at Week 52 will be classified as non-responders. Subjects with no Baseline assessment will not be included in the analysis and counted as missing.

According to the study protocol, the proportion of responders will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the randomization strata variables separately (severity, prior use of standard AD treatment, and region). In addition, the CMH test will be performed adjusting for the prior use of standard AD treatment stopped before Screening. Odds ratios and 95% confidence intervals will be presented.

Sample SAS code (will be fully validated at the analysis stage):

```
PROC LOGISTIC DATA=dataset;
CLASS treatment(REF='Control');
MODEL response=treatment;
STRATA (rand)stratum;
EXACT treatment;
RUN;
```

As a sensitivity analysis a logistic regression will be applied to include the randomization strata variables simultaneously (without prior use of standard AD treatment stopped before Screening):

PROC LOGISTIC DATA=dataset;

CLASS treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

MODEL response=treatment severity region prioruse;

RUN;

For statistically significant treatment effects (p-value < 0.05) on the aforementioned five efficacy variables, the association between responders across these variables 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.

Sample SAS code (will be fully validated at the analysis stage):

PROC FREQ DATA=dataset;

*TABLES response1*response2 / CHISQ;*

RUN;

5.9.5. Time-to-event/Decline Analysis (Sensitivity)

This analysis, based on the ITTv5 population, will include off-treatment measurements (TOTOS) and will be done separately for the primary and secondary efficacy variables ADAS-cog$_{11}$, ADCS-ADL$_{23}$, and MRI whole brain volume. It will only compare subjects on HMTM 16 mg/day and control.

Time-to-event/decline will be calculated as date of onset of decline – date of first dose + 1 and will use only data from the double-blind treatment phase and upscaled values for the two co-primary endpoints.

Time of onset of decline is the first of two consecutive measurements with worsening, whereas worsening is defined as an impairment, with respect to the Baseline value of at least a change in units as outlined here:

- ADAS-cog$_{11}$, ADCS-ADL$_{23}$: 1
- MRI whole brain volume: 6,500 (mm^3 = µL)

If the threshold of the MRI whole brain volume does not appear to be reasonable once the unblinded randomization codes are used, these can be modified slightly (similarly if a model may not converge).

If the available Week 52 value (or the value of the last assessment in general, in case of early termination) is worsened without a prior worsening, an onset of decline will be triggered at Week 52 (or the respective last visit) for that subject. 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.

Any missing efficacy/imaging value for a scheduled visit will be treated as a worsening from baseline, for that visit, but a single missing value at the last planned visit without a missing value or without a worsening in the previous visit will not count as a decline. If the time of onset is missing due to a missed scheduled visit the scheduled date of the missing visit will be used.

The Cox proportional hazards model with effects for treatment group and the randomization stratification variables will be used to compare HMTM 16 mg/day versus control by way of Hazard Ratio, 95% confidence interval, and p-value. A graph and a table of the Kaplan-Meier estimates will be provided.

Sample SAS code (will be fully validated at the analysis stage):

PROC PHREG DATA=dataset PLOTS(OVERLAY)=SURVIVAL;

CLASS subject treatment(REF='Control') severity(REF='moderate') region(REF='Europe') prioruse(REF='None');

*MODEL time*status(0) = treatment severity region prioruse;*

ID subject;

RUN;

One version will be based on the visit windows (nominal data), and another will use actual dates (continuous data).

5.10. Exploratory Analyses

If not indicated otherwise the analyses will be performed based on the respective MITTv5 population comparing HMTM 16 mg/day with control as described in Section 5.9.2.1, without any further sensitivity and supplementary analysis.

Descriptive analysis calculated by treatment group and visit based on the observed data will be given.

These analyses are broadly classified into two groups, analyses of clinical endpoints and imaging endpoints. Of particular interest are to test the hypotheses that HMTM 16mg/day leads to a reduction in MRI total lesion volume over time, that HMTM 16 mg/day increases the ^{18}F-FDG-PET SUVR in cerebellum measured with respect to pons, and that HMTM 16 mg/day shows a significant reduction in decline on the composite endpoint in the mild (CDR 0.5) population.

5.10.1. **ADAS-cog$_{13}$**

The ADAS-cog$_{13}$ is assessed at Baseline pre-dose, 13, 26, 39 and 52 weeks (or early termination) during the double-blind treatment phase and will be analyzed using the MMRM as described in Section 5.9.2.1.

This analysis will be repeated for the subgroup on subjects with MCI-AD, and mild AD (MMSE 20-27).

5.10.2. **Composite Scale**

The Composite Scale is assessed at Baseline pre-dose, 13, 26, 39 and 52 weeks (or early termination) during the double-blind treatment phase and will be analyzed using the MMRM as described in Section 5.9.2.1, but also investigating the treatment effect at Week 39.

Additionally, this analysis will be repeated in subjects with CDR of 0.5 at Screening, and CDR of 1-2 at Screening.

5.10.3. **MMSE**

The MMSE is assessed at Screening and Week 52 (or early termination) during the double-blind treatment phase and will be analyzed using the ANCOVA as described in Section 5.9.3.2 for the ITTv5 population.

5.10.4. **CDR-SOB**

The CDR-SOB is assessed at Screening and Week 52 (or early termination) during the double-blind treatment phase and will be analyzed using the ANCOVA as described in Section 5.9.3.2 for the ITTv5 population.

5.10.5. **MRI Parameters**

The atrophy of further brain MRI parameters (putamen, nucleus accumbens, and nucleus basalis) will be analyzed using the MMRM as described in Section 5.9.3.1.

Furthermore, the Baseline values of putamen, nucleus accumbens, and nucleus basalis will be included as covariates in the analysis of secondary endpoints whole brain, and temporoparietal lobe (see Sections 5.9.3.1 and 5.9.3.3).

In a sensitivity analysis of the two co-primary endpoints ADAS-cog$_{11}$ and ADCS-ADL$_{23}$, the Baseline values of MRI whole brain volume and MRI T1 imaging TLV and their interactions with treatment (the additive terms are included as well) will be added to the analysis model (see Section 5.9.2.1).

5.10.6. **^{18}F-FDG-PET Parameters**

The ^{18}F-FDG-PET SUVRs in subjects with mild AD (CDR of 0.5 at Screening):

- temporal lobe normalized to cerebellum,
- cerebellum normalized to pons,

- parietal lobe normalized to pons and normalized to cerebellum, and
- frontal lobe normalized to pons and normalized to cerebellum

will be analyzed using the ANCOVA as described in Section 5.9.3.2.

Other SUVR regions anterior, and posterior cingulate gyrus will be examined descriptively by summarizing the actual value and change from Baseline.

5.10.7. MRI Hypointensities and Hyperintensities

The TLV (hypointensities) based on MRI T1 imaging and the MRI hyperintensities total volume based on MRI FLAIR will be analyzed using the MMRM as described in Section 5.9.3.1.These parameters and the other MRI FLAIR sub-parameters deep volume, infratentorial volume, and periventricular volume will be listed together with the other MRI parameters.

5.10.8. *ApoE* Genotype

A subject data listing will be provided for *ApoE* genotype data, including only the subjects who consented to this determination. In this listing, the genotype classification (presence/absence of the ε4 allele) will be given, but not the detailed genotype.

The influence of the genotype (presence/absence of ε4 allele) will be evaluated for the two co-primary endpoints and selected secondary endpoints (MRI whole brain volume, and ^{18}F-FDG-PET temporal lobe) by adding the genotype classification as a fixed factor into the MMRM and ANCOVA model (see Section 5.9.2.1).

5.11. Statistical Parametric Mapping Analyses (SPM)

This section describes the planned SPM analyses, performed by an external vendor. Changes to these analyses, will be discussed and presented in the CSR or SPM analysis report. Further analyses might be performed dependent on the outcome of these exploratory analyses.

SPM12 is used to process volumetric MRI (vMRI), Arterial Spin Labeling (ASL) MRI and ^{18}F-FDG-PET images for the pre-specified voxel-wise analysis, and to define and estimate General Linear Models (GLM) yielding Statistical Parametric Maps (SPM) of each main effect. Pre-Processing includes format conversion, realignment, summing and co-registration to native MR space, tissue class segmentation, DARTEL registration and population template creation, normalization to standard template space and, smoothing of images.

Processed vMRI, ASL regional cerebral blood flow (rCBF) and ^{18}F-FDG-PET images will be used to fit a GLM for statistical inference at every voxel in the brain. A design matrix for each main effect analysis specifies a statistical model to explain variance in the image space. Statistical models are implemented as two-sample t-tests for group analysis, and linear regression for continuous variables, with control

and nuisance variables in each case. For each main effect analysis, a design matrix is created to estimate beta weights explaining how each model vector independently influences variance in the processed images, plus some error. A contrast vector specifies the relative contribution of these model vectors, using standard least squares, and is associated with a t-statistic reflecting the combined weights divided by the standard error at each voxel. Multiple comparison's correction employing the familywise error rate (FWE) is used to control for the large number of t-tests being performed. The FWE threshold is set to p<.05.

Specifically, a whole-brain GLM analysis will be performed to derive voxel-wise statistical maps for each of the following main effects:

1. Delta Drug vs Delta control, vMRI
2. Delta Drug vs Delta control, 18F-FDG-PET
3. Delta Drug vs Delta control, ASL MRI

5.11.1. **VBM volumetric MRI analysis**

The voxel based morphometry (VBM) analysis will be performed using the approach described by John Ashburner (www.fil.ion.ucl.ac.uk/~john/misc/VBMclass15.pdf), briefly described here:

Preprocessing

SPM→Spatial→Segment: To generate the roughly (via a rigid-body) aligned grey and white matter images of the subjects.

SPM→Tools→Dartel Tools→Run Dartel: (create Template): Determine the nonlinear deformations for warping all the grey and white matter images so that they match each other.

SPM→Tools→Dartel Tools→Normalise to MNI Space: Actually, generate the smoothed "modulated" warped grey and white matter images.

Statistical comparison

Within the SPM package we will construct a GLM for each voxel to compare the change in grey matter volume in the in the treated group with the change in grey matter volume in the control group. The comparison will be done correcting for the covariate total intracranial volume (TICV) and the randomization stratification variables. The effect of age and sex will also be tested.

Within the SPM package we will construct a GLM for each voxel to compare the change in white matter volume in the in the treated group with the change in white matter volume in the control group. The comparison will be done correcting for the same covariates mentioned above.

5.11.2. **FDG PET/CT analysis**

Preprocessing

As per the acquisition protocol the 6 by 5 minute reconstructed, attenuation corrected PET images will be realigned and summed to produce a single FDG image for each time point.

The single summed image will then be normalized into MNI space using the SPM provided template.

The normalized summed image will then be scaled using a ponds region of interest so that like for like comparisons can be made.

This step will be repeated using the cerebellum as the normalizing region of interest.

Statistical comparison

Within the SPM package we will construct a GLM for each voxel to compare the change in normalized pons scaled FDG uptake treated group with the change in FDG uptake in the control group. The comparison will be done correcting for randomization stratification variables as covariates, the effect of age and sex will be tested as well.

Within the SPM package we will construct a GLM for each voxel to compare the change in normalized cerebellum scaled FDG uptake treated group with the change in FDG uptake in the control group. The comparison will be done correcting for same covariates as mentioned above.

5.11.3. **ASL MR rCBF analysis**

Preprocessing

The ASL rCBF images will be normalized into Montreal Neurological Institute (MNI) space using the SPM provided template.

Statistical comparison

Within the SPM package we will construct a GLM for each voxel to compare the change in normalized ALS rCBF images treated group with the change ASL rCBF in the control group. The comparison will be done correcting for same covariates as for the PET analysis.

5.12. **Safety Analyses**

Safety analyses will be conducted using the Safety population. Key analyses will be repeated based on the Safetyv5 population. The analyses of the double-blind treatment phase are limited to the events up to the first dose of the open-label treatment phase. The eye exam is assigned to the double-blind treatment phase, if it was performed until the end of the Week 52 protocol-specified visit window.

5.12.1. **Extent of Drug Exposure and Compliance**

For subjects randomized under protocol version 5.0 or above, it was planned that a subject receives four tablets (2 tablets twice) orally per day for 52 weeks:

- 16 mg/day: 4 mg four times per day

- 8 mg/day: 4 mg twice and control twice per day
- Control: Control four times per day (with one MTC 4 mg tablet interspersed on two occasions within each week on a deterministic but variable schedule allowing one to five days between two doses)

For subjects randomized in version 2.1, it was planned that a subject receives two tablets orally per day for 6 months. If such a subject reconsented to version 3.0 or higher, they subsequently received four tablets orally per day.

First dose dates, dose interruptions, and last dose dates are documented in the eCRFs.

Drug accountability: the record of all study drug dispensed to and returned by subjects (including kit ID and a comment field) is recorded in the RTSM system. The drug accountability information is shared as an SAS file. Things to note are:

- Total Dispensed is auto populated by the system and is dependent on the kit type. Protocol versions v1-v3 have 210 tablets and protocol versions v4+ have 420 tablets.
- Total Used Qty, Total Unused Qty, Total Lost Qty & Total Damaged Qty along with the Accountability Comments are entered by the site. Any queries with the data in these columns should be directed to the person in column Accounted By or Verified By.
- There will be at least two rows per kit when accountability has been verified. Column Action Taken will be populated with an “I” or “U” where “I” is the initial entry and “U” is an updated/verification entry.
- The report only lists kits that have had drug accountability performed in Trident. If the site has not performed drug accountability in Trident, then the kit will not appear in the report.
- Baseline, Week 13, Week 26, and Week 39 visits are performed during double-blind treatment phase where one kit is dispensed at each visit. Week 52 (OL) and Week 78 (OL) are performed during the open-label treatment phase where two kits are dispensed.

The drug accountability sheet therefore has several rows for one dispensed visit/kit. It monitors the initial creation and every update done to it. To analyze the data, the most recent information will be used, which is the last entry, by using the sorting of the raw data file, of each kit.

The following information will be summarized descriptively by treatment group and overall, whereas subjects randomized to placebo/control will be analyzed separately by subjects receiving only true placebo and subjects receiving at least one dose of MTC:

- Total duration of exposure (in weeks): (last dose date – first dose date + 1)/7
- Total duration of treatment (in weeks), which excludes days in which dose was interrupted
- Mean daily dose: Total of administered dose during the duration of exposure, relative to the total duration of exposure

- Total subject-years of exposure: sum of total exposure in years

$$\frac{1}{365.25}\sum_{subjects}\frac{\#tablets\ taken\ during\ db\ phase}{\#tablets\ planned\ during\ db\ phase} * total\ duration\ of\ exposure\ (days)$$

- Compliance: # Tablets taken / # tablets planned until Week 52 (or until early study drug termination). Including frequency and percentage of subjects with <80% and >120% compliance. A compliance flag will be re-calculated together with the actual compliance figure.
- Frequency and percentage of subjects with dose interruptions
- Frequency and percentage of subjects in the duration of exposure categories (with categories based on the scheduled day for each planned visit, see Table 5: 1 day, 2 to 29 days, 30 to 92 days, etc.), based on total duration of exposure, including interruption days

This summarization will be done for the Safety population, but also repeated restricted to the subjects randomized before protocol version 5.0, and restricted to the subjects randomized under or after protocol version 5.0 (Safetyv5).

Subject data listings will encompass dosing, drug accountability, and compliance. Any doses that are other than that randomized will be flagged and the protocol version under which the subject had been randomized will be given.

5.12.2. **Adverse Events**

Adverse events (AEs) will be coded using the MedDRA version 20.1 and are displayed in tables and listings using SOC and PT.

Treatment emergent AEs (TEAE) are defined as AEs with:

- Onset after first dose of study drug or
- Worsen in intensity after first dose of study drug or
- Worsen in treatment relationship after first dose of study drug

Based on the Safety population, a time-to-event analysis (event: any TEAE) will be performed using the model as described in Section 5.9.5). The time-to-first TEAE will be calculated as date of onset – date of first dose + 1, and subjects with no TEAE will be censored at the time of study discontinuation.

AEs are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given AE (SOC or PT, most related occurrence, or most intense occurrence) regardless the number of episodes.

The total number of subjects and the numbers stratified by MedDRA SOC and PT, along with the corresponding percentage, with the following AE will be derived and summarized by treatment group and overall:

- Any TEAE (separate columns for true placebo and MTC)
- Any TEAE with an onset of Day 1 (separate columns for true placebo and MTC), complemented by a subject data listing
- Any TEAE (categorized by severity, and separate columns for true placebo and MTC), repeated for the Safetyv5 population.
- Any TEAE (categorized by severity) which occurred within two weeks after any COVID-19 vaccination (separate columns for true placebo and MTC)
- Any TEAEs assessed by the Investigator as related to treatment (i.e., related or possibly related) (separate columns for true placebo and MTC)
- Any TEAEs severe in intensity and assessed by the Investigator as related to treatment (as defined above) (separate columns for true placebo and MTC)
- Any TEAE that resulted in interruption or discontinuation of study drug (presented separately and combined) (separate columns for true placebo and MTC)
- Any SAE (separate columns for true placebo and MTC)
- Any serious adverse reaction (SAR), which are the SAEs judged to be possibly related or related to the study drug by the Investigator (separate columns for true placebo and MTC)
- Malignancies other than non-melanoma skin cancers (separate columns for true placebo and MTC)
- COVID-19 infection, a Pearson's chi-square test is used to compare the frequencies pairwise versus the control group
- *TauRx AE Groupings*: Subsets of TEAEs (defined by PT, the latest version of this allocation list, which is to be used in the analysis, was provided to Cytel prior to the database lock of the double-blind treatment phase), summarized per grouping and sub-grouping (separate columns for true placebo and MTC), repeated for the Safetyv5 population
    - Group: Targeted Gastrointestinal Events
        - Sub-group: Diarrhea
        - Sub-group: Gastrointestinal Irritation
        - Sub-group: Nausea/Vomiting
    - Group: Renal and Urinary Disorders (Including Infections)
        - Sub-group: Urinary Tract Infection
        - Sub-group: Urinary Frequency/Urgency

- Group: Anemia and Related Terms
  - Subgroup: Anemia (excluding vitamin deficiencies)
- Group: Falls and Related Terms
  - Sub-group: Falls
- Group: Hypersensitivity
  - Sub-group: Rash
- Group: Renal Function Impairment
- Group: Hepatic Function Impairment
- Group: Behavioral and Psychological Symptoms of Dementia
  - Sub-group: Affective/Anxiety Symptoms
  - Sub-group: Behavioral Symptoms
  - Sub-group Psychotic Symptoms
  - Sub-group: Sleep Disorders
- Group: Cardiac Ischemia

- TauRx AE Groupings will be repeated for the following subgroups, showing only the main *TauRx AE Groupings*:
  - AChEI/memantine use (prior use, never used) [binary], repeated for
    - Discontinuation of AChEI and/or memantine before entering the study
    - Discontinuation of AChEI and/or memantine for purposes of study participation
  - Age group (<75 years, ≥75 years) [binary]
  - Sex (male, female) [binary]
  - Race (White, non-White) [binary], Race = White (if only race checked), otherwise Race = non-White (even if multiple races, including White, were checked)
  - Renal Function at Baseline: Creatinine Clearance (≤ 50 mL/min, > 50 mL/min) [binary]
  - Use or no use of concomitant medications with serotonergic potential (see latest version of the Serotonergic Drugs List, Section 5.8) at any time during the study [binary]
  - Use or no use of SSRI/SNRI [binary]
  - Use or no use of MAOI [binary]

- The protocol-specified AEs of special interest (AESI), which are hemolytic anemia and lens discoloration (separate columns for true placebo and MTC). A list of all identified events will be provided to the Statistical Programming team.
- On-study TEAEs of subjects who withdrew from AChEI/memantine for purposes of the study (separate columns for true placebo and MTC)

No formal hypothesis-testing analysis of AEs incidence rates will be performed.

All AEs occurring on study will be listed in a subject data listing. Pre-treatment AEs (onset after informed consent and prior to the first dose of study drug) and post-treatment TEAEs (subset of TEAEs with an onset or worsen in intensity or treatment attribution more than 14 days after last dose of study drug) will be flagged. In addition, separate summaries of AEs by MedDRA SOC and PT will be provided for:

- Pre-treatment AEs
- Pre-treatment AEs of subjects who withdrew from AChEI/memantine for purposes of the study
- Post-treatment TEAEs (separate columns for true placebo and MTC)

Furthermore, subject data listings will be provided for the following: AEs leading to dose interruptions, SAEs (separate for fatal and non-fatal), SARs, AEs leading to withdrawal, and malignancies other than non-melanoma skin cancers.

A subject data listing will be provided, which presents additional SAE information.

5.12.3. **Laboratory Data**

Central laboratory data are transferred electronically by Labcorp (previously known as Covance). The Data Transfer Specification document provides a detailed description of the content and format of the laboratory datasets.

Clinical laboratory values will be reported in separate tables and listings for conventional and SI units, justified by the involvement of FDA and EMA.

The Baseline value is defined as the last non-missing value prior to first dose of study drug. Laboratory tests obtained on the date of the first dose will be assigned to pre-treatment; the relative times of blood sampling and dosing will be checked programmatically to confirm this assumption, if this is not true, the respective Screening value will be used.

The Baseline value, the actual value and change from Baseline to each on study evaluation and to the last available on-treatment value will be summarized for each clinical laboratory parameter, including hematology, and blood chemistry; restricted to subjects with at least one post-Baseline value. For continuous laboratory parameters n, Mean, Median, SD and (Min, Max) will be presented; and counts and percentages for categorical parameters. In the event of repeated values, the “worst” value per

study day will be used. For the hematology parameters hemoglobin and hematocrit, this descriptive analysis will be prepared separately for males and females.

Visit windows are used when results are presented by target visit (see Table 5). For each parameter, if a subject has multiple values within a visit window, the "worst" value will be used for that visit window summary (see Appendix 12.3).

Shift tables will be provided showing the change from Baseline relative to the reference range. Missing categories will be included in the shift tables.

Box-and-whisker plots and line graphs (showing the mean and standard error) of the observed data will be presented for selected parameters including hemoglobin (separately for males and females), reticulocytes, neutrophils, platelet counts, and liver function tests (ALT, AST, GGT, total bilirubin). Conventional and SI units will both be presented within each figure (as two y-axes), along with reference lines for the normal ranges. Other parameters may be identified during data review.

The treatmentwise correlation (HMTM 16 mg/day, HMTM 8 mg/day, and control) between the G6PD value at Screening and the change in hemoglobin from Baseline up to Week 52 visit will be analyzed. Separate scatter plots will present the values of G6PD and hemoglobin, along with the treatmentwise p-values based on the parametric Pearson correlation. If the Week 52 visit value is not available, the last available on-treatment value will be used. In addition, the change in hemoglobin from Baseline up to Week 52 visit will be analyzed using an ANCOVA, including the randomization stratification variables (see Section 2.6) as fixed factors, the hemoglobin Baseline value and the total duration of exposure (see Section 5.12.1) as covariates, and the treatment indicator; with the Kenward and Roger method used for calculating the denominator degrees of freedom for the tests of fixed effects. This will be performed in two G6PD subgroups: one subgroup includes all subjects with a G6PD Screening value between 60 and 80 percent relative to the lower bound of the laboratory's reference range, and one subgroup includes all subjects with a G6PD Screening value higher than 80 percent relative to the lower bound of the laboratory's reference range.

All laboratory data (hematology, and blood chemistry) will be provided in subject data listings, including flags for values outside the reference range, as well as for values being potentially clinically significant (PCS, see Table 6), and for value obtained at a local laboratory. When there are thresholds provided for low and high values, they will be handled separately. A listing will also be provided that details the normal ranges from the central laboratory for all parameters in this study.

Table 6 Laboratory – Potentially clinically significant values

Parameter	Criteria – SI Units	Criteria – Conventional Units
Hemoglobin	Female: ≤ 95 g/L Male: ≤ 115 g/L Decrease of ≥ 20%	Female: ≤ 9.5 g/dL Male: ≤ 11.5 g/dL Decrease of ≥ 20%
Hematocrit	Female: ≤ 0.32; Male: ≤ 0.37	Female: ≤ 32%; Male: ≤ 37%
WBC count	≤ 2.8×10^9/L ≥ 16×10^9/L	≤ 2800/µL ≥ 16000/µL
Neutrophils	≤ 1.0×10^9/L	≤ 1000/µL
Eosinophils	≥ 0.7×10^9/L	≥ 700/µL
Platelet count	≤ 75×10^9/L ≥ 700×10^9/L	≤ 75×10^3/µL ≥ 700×10^3/µL
Sodium	< 130 mmol/L > 150 mmol/L	< 130 mEq/L > 150 mEq/L
Potassium	< 3.0 mmol/L > 5.5 mmol/L	< 3.0 mEq/L > 5.5 mEq/L
Calcium (EDTA)	< 1.75 mmol/L > 3.00 mmol/L	< 7.00 mg/dL > 12.00 mg/dL
Glucose [a]	< 2.775 mmol/L > 13.878 mmol/L	< 50 mg/dL > 250 mg/dL
Albumin-BCG	< 25 g/L	< 2.5 g/dL
Total Bilirubin	≥ 34.2 µmol/L	≥ 2 mg/dL
ALT	≥ 3 × ULN	≥ 3 × ULN
AST	≥ 3 × ULN	≥ 3 × ULN
Alkaline Phosphatase	≥ 3 × ULN	≥ 3 × ULN
Urea Nitrogen	> 17.85 mmol/L	> 50 mg/dL

Parameter	Criteria – SI Units	Criteria – Conventional Units
Creatinine	≥ 177 µmol/L	≥ 2 mg/dL
GGT	≥ 3 × ULN	≥ 3 × ULN
LDH	≥ 3 × ULN	≥ 3 × ULN
Phosphorus	< 0.646 mmol/L > 1.777 mmol/L	< 2.0 mg/dL > 5.5 mg/dL

[a] Independent from fasting status.

Tabular summaries will include two categories defined as follows:

- Subjects with any post-Baseline PCS – the unique number of people who meet the criterion (regardless of whether or not they met it at Baseline)
- Subjects with any post-Baseline PCS Worsening
    - Subjects who do not meet PCS criteria at Baseline but do post-Baseline or
    - Subjects who already met the PCS criterion at Baseline and in whom the post-Baseline value is worse than it was at Baseline.

Separate subject data listings for each hematology and blood chemistry parameter will include only subjects with treatment-emergent PCS values. For these subjects, all results for a parameter meeting the PCS criterion will be provided. For a set of selected parameters (see Table 7), related parameters will be added to the listing. The blood chemistry parameter eGFR is not documented in the CRF and will be calculated as follows using the MDRD equation: 175 x $Creatinine^{-1.154}$ x $Age^{-0.203}$ x (0.742 if female) x (1.212 if Black Or African American). The resulting unit is mL/min/1.73m^2.

Table 7 Laboratory – Related parameters

Laboratory	Selected treatment-emergent PCS parameter	Related parameters
Hematology	Hemoglobin or Hematocrit	RBC count Reticulocytes Hemoglobin Hematocrit MCH MCV
Hematology	WBC count or Neutrophils	WBC count Neutrophils Lymphocytes Monocytes
Blood Chemistry	Urea Nitrogen or Creatinine	Urea Nitrogen Creatinine Creatinine Clearance eGFR
Blood Chemistry	ALT or AST	ALT AST GGT Total Bilirubin Direct Bilirubin Indirect Bilirubin Alkaline Phosphatase LDH

5.12.4. **Vital Signs**

The Baseline value, the actual value and change from Baseline to each on study evaluation and to the last available on-treatment value will be summarized, with the Baseline value being defined as the last non-missing value prior to first dose of study drug.

A similar summary will be generated for blood pressure values obtained on Day 1 (pre-dose and post-dose) in the subset of subjects identified as concomitantly taking the following pharmacological subgroup of serotonergic drugs at Baseline: SSRIs, SNRIs, or MAOIs (see latest version of the Serotonergic Drugs List, Section 5.8, and Section 12.4).

PCS vital sign changes are defined in Table 8 and will need to be calculated and identified prior to further analysis. The number and percentage of subjects meeting these criteria (any post-Baseline PCS) will be summarized according to the definition described in Section 5.12.3. Increasing and decreasing changes will be categorized separately.

Vital sign measurements will be presented in a subject data listing.

Table 8 Vital signs – Potentially clinically significant values

Parameter	Criteria
Systolic Blood Pressure	Increase of ≥ 20 mmHg from Baseline and ≥ 180 mmHg Decrease of ≥ 20 mmHg from Baseline and ≤ 90 mmHg
Diastolic Blood Pressure	Increase of ≥ 15 mmHg from Baseline and ≥ 105 mmHg Decrease of ≥ 15 mmHg from Baseline and ≤ 50 mmHg
Pulse	Increase of ≥ 15 beats/min from Baseline and ≥ 120 beats/min Decrease of ≥ 15 beats/min from Baseline and ≤ 50 beats/min
Weight	Decrease of ≥ 7% from Baseline Decrease of ≥ 10% from Baseline
	Increase of ≥ 7% from Baseline Increase of ≥ 10% from Baseline

5.12.5. Physical and Neurological Examinations

At Screening a complete physical (evaluation of the skin, head, eyes, ears/nose/throat, neck, thyroid, lungs, heart, lymph nodes, abdomen, and extremities) and neurological examination (evaluation of appearance and behavior, including observation for tremor and abnormal movements, and an evaluation of speech, cranial nerves (2-12), motor (muscle strength), muscle tone, sensory abnormalities, coordination, gait, and tendon reflexes) was performed. These results will be summarized by body system (by treatment group and overall).

Results from the targeted examinations performed at subsequent visits (including examinations after the first dose of study drug up to 14 days after the last dose date) will be summarized by presenting the number and percentage of subjects within each category by visit and by body system/parameter evaluated. For the physical examination, each body system is assessed as Normal or Abnormal. For the neurological examination, each body system is assessed as Normal, Abnormal or Absent.

All physical and neurological examination findings will be presented in subject data listings.

5.12.6. **Ophthalmological Examination**

Slit lamp ophthalmological examination of subjects with lens implants will be performed at Screening and at the Week 52 visit (or upon early termination), to assess whether the lens has been discolored during the trial. In addition, the slit lamp examination could also be performed if a subject had 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.

The following information will be used to identify subjects with lens implant:

- eCRF Medical History: *Does the subject have intraocular lens implants?* = Yes
- eCRF Medical History: Coded PT term = Cataract or Cataract operation
- eCRF Procedures / Therapies: *Was this procedure an intraocular lens implant?* = Yes

Results from the examination will be summarized by treatment phase (pre-treatment, double-blind treatment phase, and open-label treatment phase), presenting the number of subjects with lens implant, the number of subjects with lens implant and at least one examination during each treatment phase, and the number and percentage of subjects within lens discoloration by treatment phase, and treatment group.

A subject data listing will display the date of the ophthalmological examination, whether the lens was discolored, and any additional details.

6. STATISTICAL ANALYSIS OF OPEN-LABEL TREATMENT PHASE

6.1. Introduction

The rationale of a delayed-start design is that, 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 (null hypothesis). 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 controlled and delayed-start phases), all subjects and study personnel on-site are blinded to each subject's randomization to the early-start or late-start treatment group (HMTM treatment history).

Only subjects completing the 52-week double-blind treatment phase on- or off-treatment are eligible to enter the open-label treatment phase. This includes subjects, that have been randomized under a protocol version before version 5 and includes subjects who re-consented on a protocol version 5+ after the randomization and who completed the 52-week double-blind treatment phase. Subjects who have been off-treatment at Week 52 (TOTOS) stay off-treatment and do not receive any open-label treatment phase study drug.

6.2. Open-Label Treatment Phase Definitions

Based on the HMTM treatment history during the double-blind treatment phase "late" starters are defined as subjects originally randomized to control, and "early" starters are defined as subjects originally randomized to HMTM 16 mg/day or HMTM 8 mg/day. The last available assessment – for the scales: the last available (upscaled) value – prior to or on the same day of the start of the open-label treatment (Visit 7, Week 52) will serve as the Baseline assessment of the open-label treatment phase (Baseline-OL). A delayed performed Week 52 MRI assessment will be eligible for the Baseline-OL assessment if it has been done within 14 days after starting the open-label treatment phase.

The treatment group of subjects originally randomized to control will be labeled as "MTC 8 mg/week".

6.3. Summary Statistics

Summary tables and most of the efficacy tables will be presented by the original randomized treatment group from the double-blind treatment phase and will have the following labels:

- "MTC 8 mg/week -> HMTM 16 mg",
- "HMTM 8 mg -> HMTM 16 mg",

- "HMTM 16 mg -> HMTM 16 mg", and
- "HMTM Pooled -> HMTM 16 mg".

The "MTC 8 mg/week -> HMTM 16 mg" group presents the "late starters" and the "HMTM Pooled -> HMTM 16 mg" group presents the "early starters" (i.e., HMTM 8 mg and HMTM 16 mg). An explanatory footnote will be added to explain this. A total column, combining the early and late starters, will be presented as needed.

Summary statistics are described in more details in the post hoc efficacy Section 6.12.

Subject data listings conducted during the double-blind treatment phase will be re-run including the open-label treatment phase data, if open-label treatment phase data is available. If appropriate, a flag for open-label treatment phase data will be added and the open-label treatment phase study day will be presented as well (for subjects who have entered the open-label treatment phase). The treatment group labels for subjects participating in the open-label treatment phase as well will be changed to: "MTC 8 mg/week -> HMTM 16 mg", "HMTM 8 mg -> HMTM 16 mg", and "HMTM 16 mg -> HMTM 16 mg"; whereas the treatment group labels for subjects not participating in the open-label treatment phase stay unchanged: "Placebo Only", "MTC 8 mg/week", "HMTM 8 mg", and "HMTM 16 mg".

The summaries of assessments affected by COVID-19 (see Section 4.8), which are presented by study visit for the ITT population, will be extended by the open-label treatment phase study visits.

6.4. Sample Size Justification

With about 400 subjects randomized to control or HMTM 16 mg/day under protocol version 5.0 and above, which is the primary treatment group comparison in the double-blind treatment phase, an estimated 160 to 170 subjects per arm will enter the open-label, delayed-start phase assuming the dropout rates from Section 5.3. 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.

6.5. Protocol Deviations

The protocol deviations file, which was finalized for the double-blind treatment phase analysis prior to the unblinding of the double-blind treatment phase will be updated prior to the database lock of the open-label treatment phase.

This file will include a description of the protocol deviation, will provide the information regarding previous classification (minor/major), and will provide the classification done by the Sponsor into important/non-important.

The level of detail and information will provide full traceability.

Based on the ITTv5-OL and ITT-OL populations, summaries by categorization (important/non-important) and type (or code) will be provided. This will be done pooled and separately for COVID-19- and non-COVID-19-related protocol deviations. Also, one version will count all protocol deviations and one version will count only the overall unique deviations (when one deviation is resulting in subsequent ones).

6.6. Visit Windows

Since data might be documented under a wrong label (as a wrong visit) within the EDC system, all data will be (re-)assigned to a visit according to the column *Intervals for analysis* in Table 9.

Furthermore, if a subject has multiple values for a parameter within a visit window, the "worst" value will be used for that visit window summary (see Appendix 12.3), for efficacy endpoints the closest to the scheduled visit will be used (if two have the same distance from the scheduled visit the later one will be used).

For the analysis of the open-label treatment phase, only data after the first dose of the open-label treatment phase until the end of the study will be included, except Baseline-OL values, which are based on data assessed prior to the first dose of the open-label treatment phase. A delayed performed Week 52 MRI assessment will be eligible as the Baseline-OL assessment if it has been done within 14 days after starting the open-label treatment phase. In addition, eye exams will be assigned to the double-blind treatment phase, if it was performed until the end of the Week 52 protocol-specified visit window.

Table 9 Evaluation Intervals of the Open-Label Treatment Phase

Evaluation (scheduled day)	Protocol-Specified Interval	Intervals for Analysis		
		Safety assessments	ADAS-cog$_{13}$, ADCS-ADL$_{23}$, MRI	MMSE, CDR
Week 52 (365) [a]	351 to 379 [±14]	320 to 379	320 to 456	320 to 548
Open-Label Week 56 (394)	380 to 408 [±14]	380 to 470	-	-
Open-Label Week 78 (548)	534 to 562 [±14]	471 to 638	457 to 638	-
Open-Label Week 104 (730)	716 to 744 [±14]	≥639	≥639	>548

[a] Baseline visit for open-label treatment phase

6.7. Subject Disposition

The subject by-visit listing will be updated with the open-label treatment phase visits.

Based on the ITT population, the subject data listing from the double-blind treatment phase will be updated and extended with the disposition information from the open-label treatment phase:

- Protocol version under which the subject has been randomized
- First and last dose dates of study drug intake (by treatment phase)
- Last date (by treatment phase)
- A flag for the completion, and a flag for the TOTOS (see Section 4.4) (by treatment phase)
- All reasons why the subject did not complete the study/treatment phase, and a flag for the primary reason
- For the TOTOS, the reason why the subject discontinued the study drug

Based on the ITT-OL population, a subject data listing will provide an overview of the open-label treatment phase populations (see Section 3.1.2) and will list the following events (sorted by subject, and date; one row for each event):

- Affiliation to the study open-label treatment phase populations (one column per study population)
- Date of Week 52 visit
- Protocol re-consents during the open-label treatment phase, with the protocol version and signing dates (one row for each re-consent)
- Date and primary reason of study discontinuation during the open-label treatment phase
- Date of study drug discontinuation during the open-label treatment phase, if study drug discontinuation is permanent and if the date is different from the date of study discontinuation
- Any date of COVID-19 infection (during double-blind or open-label treatment phase)
- Any date of COVID-19 vaccination (during double-blind or open-label treatment phase)
- Date of Week 104 visit

The corresponding listing from the double-blind treatment phase will also be updated with the following information:

- Protocol re-consents during the open-label treatment phase, with the protocol version and signing dates (one row for each re-consent)
- Date and primary reason of study discontinuation during the open-label treatment phase

- Date of study drug discontinuation during the open-label treatment phase, if study drug discontinuation is permanent and if the date is different from the date of study discontinuation
- Any date of COVID-19 infection (during double-blind or open-label treatment phase)
- Any date of COVID-19 vaccination (during double-blind or open-label treatment phase)
- Date of Week 104 visit

Information on the number of subjects in each analysis population of the open-label treatment phase, the number of subjects completing the open-label treatment phase / the study (subsets on and off treatment), the number of subjects discontinuing the study drug but continuing the study, the primary reason for discontinuation of study drug and study, and all reasons for discontinuation of study drug and study will be tabulated. This will be done by HMTM treatment history and overall, for the ITTv5-OL, ITT-OL, and PPv5-OL populations. Furthermore, based on the ITTv5-OL population, this will be tabulated by region.

6.8. Demographic and Baseline Characteristics

The Demographic and Baseline table of the double-blind treatment phase will be repeated for the ITTv5-OL, ITT-OL, and PPv5-OL populations and will be extended by the Baseline-OL values of weight, creatinine clearance, MMSE, and CDR.

The subject data listing of the double-blind treatment phase will be extended by the Baseline-OL values.

No formal statistical comparisons of treatment groups for any Baseline characteristics will be performed.

6.9. Prior and Concomitant Medications

Any medication that has been discontinued before the intake of the first dose of the open-label treatment phase study drug will be defined as prior medication. Any medication that was taken at the day of the first dose of the open-label treatment phase study drug or after will be defined as concomitant medication. Prior used medications and concomitant medications will be coded using the 01 March 2017 version of the WHO drug dictionary and the ATC level 1 term, ATC level 3 term, and PT will be presented in the analysis.

Data conventions are as described in Section 5.8.

The subject data listing of prior medications, and concomitant medications of the double-blind treatment phase will be updated, and the records of the open-label treatment phase medications will be added. An additional flag will be added to indicate the concomitant medications of the open-label treatment phase. A subset of this subject data listing will also be provided for subjects who were using

an antipsychotic treatment (during the double-blind or open-label treatment phase, see Section 12.4), including the reasons for use.

The following summaries/tabulations will be prepared for the ITTv5-OL and ITT-OL populations.

Tabulations with frequency and percentage, by treatment history and for the pooled treatment histories, will be prepared separately for all prior, for all concomitantly used drugs, and for all concomitantly used drugs that the patient is on at the time of the first dose of the open-label treatment phase study drug. Subjects reporting more than one medication are counted only once within each level summation.

Summary tables will be provided, showing the numbers of subjects with initiated treatments of SSRI/SNRI (see Section 12.4), drugs of serotonergic potential (see latest version of the Serotonergic Drugs List, Section 5.8), and any antipsychotic medications. For antipsychotics initiated on-treatment, the reasons for use will be also summarized.

6.10. Secondary Efficacy Endpoint Analysis

The goal of the open-label phase is to demonstrate disease modification by comparing the ADAS-cog_{11} change from Baseline-OL at Week 104 between early and later starters using a non-inferiority margin. According to the study protocol the non-inferiority margin will be set to 2 units, based on the estimated treatment effect of 5.2 ± 1.3 (mean ± standard error) units from a pooled analysis of the studies TRx-237-005 / TRx-237-015.

This non-inferiority margin, and the thresholds mentioned in Section 6.11, have been selected based on the results of the two previous phase 3 studies TRx-237-005, and TRx-237-015. It was planned to change the non-inferiority margin to 50% of the observed 52 treatment effect, should the decline and treatment effect for this study, seen after topline and full analysis of the double-blind treatment phase, deviate strongly from the expectations based on the TRx-237-005/TRx-237-015 results. With the knowledge of the double-blind treatment phase results, the non-inferiority margin will be as selected, based on the two previous phase 3 studies TRx-237-005, and TRx-237-015.

Efficacy analyses will be conducted using the PPv5-OL population (see Section 3.1.2) with no imputation of missing values. Upscaling for the scales will be performed. The ITTv5-OL population will be analyzed as a supplementary analysis and will include only those subjects with at least one post-Baseline-OL value.

The key secondary endpoint is the Baseline-OL adjusted decline in ADAS-cog_{11} from Baseline-OL at Week 104. Repeated measures on this endpoint scheduled at Week 78, and Week 104 will be treated using a mixed effects model. Suppose μ_{early} and μ_{late} are the corresponding means of decline at Week 104 for the early and late starters, then the null and alternative hypothesis can be written as:

H_0: $\mu_{early} - \mu_{late} \geq 2$; versus

H_1: $\mu_{early} - \mu_{late} < 2$.

The analyses will be performed using the restricted maximum likelihood-based MMRM, including the randomization stratification variables (see Section 2.6) as fixed factors, the ADAS-cog_{11} Baseline-OL value as covariate, and the interaction term between early/ late starters (HMTM treatment history) indicator and visit; with an unstructured covariance matrix and the Kenward and Roger method of calculating the denominator degrees of freedom for the tests of fixed effects. According to the hypotheses, this is a lower-tailed test which will be performed at the alpha=0.025 level of significance.

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

CLASS subject treatmenthist(REF='Late') visit severity region prioruse;

MODEL scorediff = treatmenthist|visit severity region prioruse scorew52 / SOLUTION CL DDFM=kenwardroger;

REPEATED visit / SUB=subject TYPE=UN;

*LSMEANS treatmenthist*visit visit / CL;*

*LSMESTIMATE treatmenthist*visit "intervention effect at Week 104" 0 1 0 -1 / CL testvalue=2 LOWER ALPHA=.025;*

**Summary statistics for treatment difference based on LSM*

*LSMESTIMATE treatment*visit "intervention effect at Week 78" 1 0 -1 0 / CL testvalue=2 LOWER ALPHA=.025;*

RUN;

6.10.1. Sensitivity Analysis

The subgroups of subjects originally randomized to HMTM 16 mg/day and 8 mg/day will be analyzed separately, as described in Section 6.10.

6.11. Exploratory Efficacy Analysis

ADCS-ADL_{23}, and the MRI parameters (whole brain and temporoparietal lobe) will be analyzed analogously to the ADAS-cog_{11}, see Section 6.10, to directionally support a disease modifying argument. Subgroup analyses might be done in a post-hoc analysis.

6.11.1. **ADCS-ADL$_{23}$**

Compared to ADAS-cog$_{11}$, with a similar range of values and estimated treatment effect of 5.0 ± 1.6 (mean ± standard error) units from a pooled analysis of the studies TRx-237-005 / TRx-237-015, the non-inferiority margin will be set to -2.

The null and alternative hypothesis can be written as:

H_0: $\mu_{early} - \mu_{late} \leq -2$; versus

H_1: $\mu_{early} - \mu_{late} > -2$.

Regarding the SAS code, the *UPPER* option will be used in the *LSMESTIMATE* statement.

6.11.2. **MRI**

For the MRI parameters the non-inferiority margin will be set to -13,000 (mm^3 = µL) for whole brain volume and -800 (mm^3 = µL) for the temporoparietal lobe volume.

6.12. Post Hoc Efficacy Analysis

The following efficacy analysis have been added after partial unblinding of study team members. The partial unblinding was done to be able to perform the analysis of the double-blind treatment phase.

To complete the efficacy analysis (see Sections 6.10 and 6.11), based on the ITTv5-OL population (see Section 3.1.2), summary statistics of the absolute values and their change from Baseline-OL of the scales (ADAS-cog$_{11}$, ADAS-cog$_{13}$, ADCS-ADL$_{23}$, Composite Scale, and COVID-19 Composite Scale), MRI parameters (whole brain, temporoparietal lobe, putamen, nucleus accumbens, nucleus basalis, hyperintensities total volume, and hypointensities total lesion volume) will be tabulated by visit (including Baseline-OL, Week 78, and Week 104) and HMTM treatment group as described above. MMSE and CDR-SOB will be tabulated by visit (including Baseline-OL and Week 104) and HMTM treatment group. Upscaling rules will be applied (see Section 4.5.1) and analyses are performed on these upscaled values. The summary statistics of ADAS-cog$_{11}$, ADCS-ADL$_{23}$, and the MRI parameters whole brain volume and temporoparietal lobe volume will be presented based on the PPv5-OL population as well.

Also, summary statistics and treatment differences (with 95% confidence intervals) based on the least squares means (LSM) from the corresponding MMRM models (see Sections 6.10 and 6.11) will be presented for the study visits Baseline-OL, Week 78, and Week 104.

Based on the ITTv5-OL population, for ADAS-cog$_{13}$, ADAS-cog$_{11}$, ADCS-ADL$_{23}$, and the two MRI parameters whole brain volume and temporoparietal lobe volume, line graphs (showing the LSM and standard error) will be generated, presenting the MTC 8 mg/week group and the HMTM 16 mg group (along with their corresponding tables, presenting the LSM and treatment contrast for each visit). The LSM are based on a restricted maximum likelihood-based MMRM including a nominal visit variable, the

treatment indicator and the interaction term between treatment and visit, the randomization stratification variables (see Section 2.6) as fixed factors, and the respective efficacy Baseline/Baseline-OL value as covariate; with an unstructured covariance matrix and the Kenward and Roger method of calculating the denominator degrees of freedom for the tests of fixed effects. One version of the line graph will include/present the visits from Baseline to Week 104, including Baseline as the covariate in the model, and a second version will include/present the visits from Baseline-OL to Week 104, including Baseline-OL as the covariate in the model. This will be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD.

Based on the ITTv5-OL population, the following pairwise correlations will be analyzed by means of scatter plots with symbolized treatment groups, which include both the parametric Pearson correlation coefficient and the non-parametric Spearman's rank correlation coefficient and their corresponding p-values for each treatment group, along with the regression lines:

- (Changes from Baseline): MRI whole brain volume at Week 52 vs. ADAS-cog_{11} at Week 104
- (Changes from Baseline): MRI whole brain volume at Week 52 vs. ADCS-ADL_{23} at Week 104
- (Changes from Baseline): MRI whole brain volume at Week 52 vs. CDR-SOB at Week 104
- (Changes from Baseline): MRI whole brain volume at Week 52 vs. MMSE at Week 104

Based on the ITTv5 population, for ADAS-cog_{13}, ADAS-cog_{11}, ADCS-ADL_{23}, and the two MRI parameters whole brain volume and temporoparietal lobe volume, the observed change from Baseline at Weeks 26, 52, 78, and 104 will be analyzed with a paired t-test, separately for the subjects originally randomized to HMTM 16 mg/day and subjects originally randomized to MTC 8 mg/week. Two-sample t-test comparisons between the treatment groups for the respective endpoints and each of the Weeks 26, 52, 78, and 104 will be presented as well. This will be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD.

Based on the ITTv5 population, for the ADAS-cog_{11}, the change from Baseline at Week 52 will be analyzed with the paired t-test, separately for the subjects originally randomized to HMTM 16 mg/day and subjects originally randomized to MTC 8 mg/week. The change from Baseline-OL to Week 104 based on the ITTv5-OL population will be analyzed the same way. This will be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD.

Sample SAS code (will be fully validated at the analysis stage):

```
PROC TTEST DATA=dataset ALPHA=.05;
BY treatment;
VAR scorediff;
RUN;
```

6.13. Safety Analysis

Safety analyses will be conducted using the Safety-OL population (see Section 3.1.2), presenting the data from the open-label treatment phase, whereas the last non-missing value prior to the first dose of the open-label treatment phase study drug will serve as the Baseline-OL value.

Entries of the open-label treatment phase will be added to the subject data listings, which have been prepared for the double-blind treatment phase. An additional flag will be added to indicate the entries of the open-label treatment phase. Updated data and additional entries of the double-blind treatment phase, other than new information on AEs, will need to be investigated.

To assess the safety and tolerability of the HMTM treatment given for up to 104 weeks, exposure, compliance, AEs, and laboratory data will be analyzed including data from the double-blind and open-label treatment phases. For subjects originally randomized to control, data gathered during the double-blind treatment phase will be excluded from this analysis, unless it is needed for the determination of a Baseline. These analyses will be performed based on the Safety-HMTM population (see Section 3.1.3).

6.13.1. Extent of Drug Exposure and Compliance

The planned number of tablets taken by the subject each day for 52 weeks is four (2 tablets twice per day), with each tablet containing 4 mg of HMTM.

Based on the Safety-OL population, the following information will be summarized descriptively by treatment history and pooled treatment histories for the open-label treatment phase:

- Total duration of exposure (in weeks): (last dose date – first dose date + 1)/7
- Total duration of treatment (in weeks), which excludes days in which dose was interrupted
- Mean daily dose: Total of administered dose during the duration of exposure, relative to the total duration of exposure
- Total subject-years of exposure: sum of total exposure in years

$$\frac{1}{365.25}\sum_{subjects}\frac{\#tablets\ taken}{\#tablets\ planned} * total\ duration\ of\ exposure\ (days)$$

- Compliance: # Tablets taken / # tablets planned during the open-label treatment phase (or until early study drug termination), respectively. Including frequency and percentage of subjects with <80% and >120% compliance. The compliance values will be re-calculated and are not taken from the eCRF.
- Frequency and percentage of subjects with dose interruptions

- Frequency and percentage of subjects in the duration of exposure categories, based on total duration of exposure, including interruption days. The exposure categories can be taken from Section 5.12.1 (as done for the double-blind treatment phase analysis).

This summary will be also prepared including the combined treatment information from the double-blind and open-label treatment phases based on the Safety population, and for the HMTM treatment information from the double-blind and open-label treatment phases based on the Safety-HMTM population (see Section 3.1.3), which means that control treatment information during the double-blind treatment phase will be excluded from the analysis of the HMTM treatment information. The following exposure categories (in days) will be added for this analysis: 366-457, 458-548, 549-639, 640-730, and >730. For the summary of the combined treatment information, the treatment groups will distinguish between subjects who received no open-label treatment and subjects who did receive at least one dose of open-label treatment (e.g., MTC 8 mg/week, MTC 8 mg/week -> HMTM 16 mg).

For additional more general information regarding exposure and compliance, please see Section 5.12.1.

6.13.2. **Adverse Events**

Adverse events (AEs) will be coded using the MedDRA version 20.1 and are displayed in tables and listings using SOC and Preferred Term (PT).

TEAEs during the open-label treatment phase are defined as AEs with:

- Onset after first dose of study drug of the open-label treatment phase or
- Worsen in intensity after first dose of study drug of the open-label treatment phase or
- Worsen in treatment relationship after first dose of study drug of the open-label treatment phase.

The total number of subjects and the numbers stratified by MedDRA SOC and PT, along with the corresponding percentage, will be derived and summarized by the original randomized treatment group from the double-blind treatment phase (MTC 8 mg/week, HMTM 8 mg/day, HMTM 16 mg/day), the pooled HMTM group (HMTM 8 mg/day + HMTM 16 mg/day), and overall, for the following events:

- Any TEAE
- Any TEAE with an onset on the first day of the open-label treatment phase after the first dose of the open-label treatment phase, complemented by a subject data listing
- Any TEAE (categorized by severity)
- Any TEAEs assessed by the Investigator as related to treatment (i.e., related or possibly related)
- Any TEAEs severe in intensity and assessed by the Investigator as related to treatment (as defined above)

- Any TEAE that resulted in interruption or discontinuation of study drug (presented separately and combined)
- Any serious adverse event (SAE)
- Any serious adverse reaction (SAR), which are the SAEs judged to be possibly related or related to the study drug by the Investigator
- Malignancies other than non-melanoma skin cancers
- *TauRx AE Groupings*: Subsets of TEAEs (defined by PT), summarized per grouping and sub-grouping (see Section 5.12.2).
- The protocol-specified AEs of special interest (AESI), which are hemolytic anemia and lens discoloration. A list of all identified events will be provided to the Statistical Programming team.

In addition, separate summaries of AEs by MedDRA SOC and PT will be provided for:

- Post-treatment TEAEs (after the open-label treatment phase)

For TOTOS subjects from the double-blind treatment phase, which continued off-treatment during the open-label treatment phase, a sub-population of the ITT-OL population – which are not included in the Safety-OL population, the following table and listing will be prepared:

- Any TEAE
- Subject data listing, which presents additional SAE information

HMTM Treatment Phase

For the Safety-HMTM population (see Section 3.1.3), AEs of/ during the HMTM treatment will be analyzed. This means, that for subjects originally randomized to control, events of/ during the double-blind treatment phase (before the first dose of HMTM treatment during the open-label treatment phase) are excluded from this analysis.

The total number of subjects and the numbers stratified by MedDRA SOC and PT, along with the corresponding percentage, will be derived and summarized by the original randomized treatment group from the double-blind treatment phase (MTC 8 mg/week, HMTM 8 mg/day, HMTM 16 mg/day), the pooled HMTM group (HMTM 8 mg/day + HMTM 16 mg/day), and overall, for the following events:

- Any TEAE
- Any TEAE (categorized by severity)
- Any TEAEs assessed by the Investigator as related to treatment (i.e., related or possibly related)

- Any TEAEs severe in intensity and assessed by the Investigator as related to treatment (as defined above)
- Any TEAE that resulted in interruption or discontinuation of study drug (presented separately and combined)
- Any serious adverse event (SAE)
- Any serious adverse reaction (SAR), which are the SAEs judged to be possibly related or related to the study drug by the Investigator
- Malignancies other than non-melanoma skin cancers

For additional more general information regarding AEs, please see Section 5.12.2.

6.13.3. **Laboratory Data**

Based on the (double-blind treatment phase) Safety population, the Baseline value, the actual value and change from Baseline for the Week 13, Week 26, Week 39, Week 52, Week 78, and Week 104 visits will be summarized by treatment group for the clinical laboratory parameters hemoglobin (separately for males and females), neutrophils, ALT, and AST; restricted to subjects with at least one post-Baseline value. Line graphs (showing the mean and standard error) of the observed data from Baseline to Week 104 will be presented for those parameters as well. The treatment groups will distinguish between subjects who received no open-label treatment and subjects who did receive at least one dose of open-label treatment (e.g., MTC 8 mg/week, MTC 8 mg/week -> HMTM 16 mg).

The Baseline-OL value is defined as the last non-missing value prior to the first dose of the open-label treatment phase study drug. Laboratory tests obtained on the date of the first dose will be assigned to pre-treatment; the relative times of blood sampling and dosing will be checked programmatically to confirm this assumption; if this is not true, a prior value will be used.

The Baseline-OL value, the actual value and change from Baseline-OL for the Week 56, Week 78, Week 104 visits, and for the last available on-treatment value will be summarized by treatment history for each clinical laboratory parameter, including hematology, and blood chemistry; restricted to subjects with at least one post-Baseline-OL value. For the hematology parameters hemoglobin and hematocrit, this descriptive analysis will be prepared separately for males and females.

Visit windows are used when results are presented by target visit (see Table 5 and Table 9). For each parameter, if a subject has multiple values within a visit window, the “worst” value will be used for that visit window summary (see Appendix 12.3).

Shift tables will be provided showing the change from Baseline-OL relative to the reference range. Missing categories will be included in the shift tables.

Box-and-whisker plots and line graphs (showing the mean and standard error) of the observed data from Baseline-OL to Week 104 (excluding visit Week 56) will be presented for the selected parameters

as described in Section 5.12.3. In addition to the original randomized treatment groups from the double-blind treatment phase, the figures will present the HMTM Pooled group results as well. The treatment group labels will be as described in Section 6.3.

Analogously to the double-blind treatment phase analysis, a summary will present two categories of PCS values:

- Subjects with any post-Baseline-OL PCS – the unique number of people who meet the criterion (regardless of whether or not they met it at Baseline-OL)
- Subjects with any post-Baseline-OL PCS Worsening
    - Subjects who do not meet PCS criteria at Baseline-OL but do post-Baseline-OL or
    - Subjects who already met the PCS criterion at Baseline-OL and in whom the post-Baseline-OL value is worse than it was at Baseline-OL.

When the PCS values are summarized, assessments after the first dose of the open-label treatment phase, that have been assigned to Week 52 by using the visit windowing (see Section 6.6), will be analyzed as Week 56 values.

The separate subject data listings with treatment-emergent PCS values will be created analogously to the double-blind treatment phase analysis, presenting the Baseline-OL and post-Baseline-OL PCS values.

HMTM Treatment Phase

Since the scheduled study visits in the open-label treatment phase are planned every 26 weeks and not every 13 weeks as in the double-blind treatment phase, the analysis of the HMTM treatment phase will be divided into 26-week intervals. Visit windowing will be performed for the laboratory data based on the (double-blind treatment phase) study day for the early starters and based on the open-label treatment phase study day for the late starters. The following visit windows will be used: ≤1 (pre-dose) (Baseline-HMTM), 1 (post-dose) to 273 (Week 26, [day 183]), 274 to 456 (Week 52, [365]), 457 to 638 (Week 78, [548]), and ≥639 (Week 104, [730]), with the Baseline-HMTM value being defined as the last non-missing value prior to the first dose of HMTM treatment. If a subject has multiple values for a parameter within a visit window the rule from Section 5.5 will be used. For the subjects originally randomized to control, the values of the visits at Week 78 and 104 will be analyzed as Week 26 and Week 52 due to the delayed start of the HMTM treatment.

The following analysis will be performed based on the Safety-HMTM population (see Section 3.1.3).

The actual value and change from Baseline-HMTM for the Week 26, Week 52, Week 78, and Week 104 visits, and the last available on-treatment value, will be summarized by treatment history and overall, for each clinical laboratory parameter, including hematology, and blood chemistry; restricted to

subjects with at least one post-Baseline-HMTM value. For the hematology parameters hemoglobin and hematocrit, this descriptive analysis will be prepared separately for males and females.

Line graphs (showing the mean and standard error) of the observed data from Baseline-HMTM to Week 104 will be presented for selected parameters as described in Section 5.12.3. The treatment groups will be presented as described earlier in this section for the separate open-label treatment phase.

For additional more general information regarding laboratory analysis, please see Section 5.12.3.

6.13.4. **Vital Signs**

The Baseline-OL value, the actual value and change from Baseline-OL for the Week 56, Week 78, Week 104 visits, and for the last available on-treatment value will be summarized by treatment history, with the Baseline-OL value being defined as the last non-missing value prior to first dose of the open-label treatment phase study drug.

A tabular summary of subjects with PCS vital sign changes from Baseline-OL will be prepared analogously to the double-blind treatment phase table (see Section 5.12.4). When the PCS values are summarized, assessments after the first dose of the open-label treatment phase, that have been assigned to Week 52 by using the visit windowing (see Section 6.6), will be analyzed as Week 56 values.

6.13.5. **Physical and Neurological Examinations**

The summaries from the double-blind treatment phase (see Section 5.12.5) will be repeated for the Safety-OL population and extended by the visits Week 56, Week 78, and Week 104.

6.13.6. **Ophthalmological Examination**

The summary from the double-blind treatment phase (see Section 5.12.6) will be repeated for the Safety-OL population.

The subject data listing prepared for the double-blind treatment phase (see Section 5.12.6) will be extended by the open-label treatment phase visit(s). An additional flag will be added to indicate the entries of the open-label treatment phase.

7. PLASMA BIOMARKER ANALYSIS

The analysis described in this section is based on version 2.2 from 16-MAR-2023 of the TRx-237-039 Secondary Research Plan "Plasma Biomarker Analysis", in which a detailed background, scientific rationale, and sample size justification is given.

The following analysis are all exploratory of nature. The analyses stand on their own and corresponding nominal p-values will be reported and no correction for multiple comparisons will be conducted.

A subject data listing of the biomarkers will be provided.

The tau fragment analysis, which was introduced with the version 2.1 of the Secondary Research Plan, is based on a subset of pre-dose Baseline back-up PK plasma samples is not part of this SAP. This analysis will be performed by the University of Aberdeen (Scottish Biologics Facility).

7.1. Biomarker

The initial analysis focuses on the following primary exploratory biomarkers, which will be analyzed in the framework of primary and secondary biomarker endpoints:

- Tau phosphorylated at residue 181 (P-tau181)
- Neurofilament light (NfL)

The null hypotheses for each of these biomarkers are, that there is no difference from Baseline to Week 52 visit within the HMTM group and that HMTM does not have an impact on change of the respective endpoint from Week 52 to Baseline compared to control. For correlations between biomarkers and between other clinical study endpoints (see Section 7.3.3), the null hypothesis is that there is no correlation between those.

The following potential biomarkers are 'other' exploratory biomarker research and will be analyzed analogously to the primary exploratory biomarkers upon request, with T-tau being planned to be analyzed with version 2.2 of the Secondary Research Plan:

- Tau phosphorylated at residue 231 (P-tau231)
- Core-proline tau
- Total tau (T-tau)
- Glial fibrillary acidic protein (GFAP)

There is no prior evidence to show that these biomarkers will show a pharmacodynamic response to treatment with HMTM nor any other approved or investigational drugs for AD. Given this, no hypotheses are provided, but the above null-hypothesis apply here as well.

For the avoidance of doubt, even in the cases where a clear hypothesis exists which direction the change should take, all tests will be conducted at the two-sided, 0.05 level of significance.

7.1.1. Biomarker Samples

The investigated (potential) biomarkers are pre-analyzed in different companies and institutions: P-tau 181 and P-tau231 (Medpace Inc.), NfL (Drug Development Solutions Ltd.), Core-proline tau (University of Aberdeen Good Laboratory Practice Test Facility), T-tau (University College London Consultants Ltd.), and GFAP (*to be decided*). Due to different processing schedules, the pre-processed data will be provided to Cytel in batches and therefor the statistical analysis will be performed in batches.

Plasma samples have been taken at Baseline, Week 4, Week 52, and Week 104 visits, on three occasions: pre-dose, approximately 1 to 2 hours post-dose, and approximately 4 hours post-dose.

The biomarker data analysis is based on back-up PK plasma samples taken pre-dose during the Baseline and Week 52 visits.

On a subject level: If the pre-dose sample is unavailable, the earliest available post-dose sample (first: 1-2 hours post-dose, second: 4 hours post-dose) will be used; and furthermore, if the back-up plasma sample is unavailable the residual primary PK plasma will be utilized instead, if available. If no proper sample is available, the value is set to missing. This means, the order of samples is as follows:

- Back-up sample: 1. Pre-dose, 2. 1-2 hours pose-dose, 3. 4 hours post-dose
- Residual primary sample: 4. Pre-dose, 5. 1-2 hours pose-dose, 6. 4 hours post-dose
- 7. “Missing”

The first sample which is available will be used for the analysis. This means, for the avoidance of doubt, the analysis will be performed based on all available samples, irrespective of the actual sample used. Thus, pre-dose versus post-dose samples as well as primary versus back-up samples will be used alike. The only relevant characteristic of the sample is, which is used in the analysis, if it is Baseline or Week 52 visit.

Possible reasons for unavailability of a plasma sample are:

- More than one previous freeze-thaw cycle.
- An approximate hemoglobin concentration of 250 mg/dL or more.
- Incorrect collection of a sample.

For completeness, a summary table will be provided, that shows the number of samples used for each biomarker presented by treatment group and total, that were Baseline pre-dose, Baseline 1-2 hours post-dose, Baseline 4 hours post-dose, Week 52 pre-dose, Week 52 1-2 hours post-dose, and Week 52 4 hours post-dose. If needed, this will be further separated by back-up sample and primary sample.

7.2. Analysis Population

Biomarker Population: subjects randomized under protocol version 5.0 or higher, which completed the double-blind treatment phase, excluding the TOTOS (see Section 4.4). Subjects randomized under a protocol version before version 5 with available biomarker data at Week 52 and completed double-blind treatment phase will be included as well.

7.3. Statistical Analysis of Biomarker Outcomes

The following analysis will be performed based on the Biomarker Population.

Week 52 samples taken after the first day of the open-label treatment phase will not be used in the analysis.

Since from protocol version 5 on, the control group had occasional spiking with 4mg MTC with an average frequency of twice per week, it is therefore of interest to test not only the doses of HMTM compared to control, but also to a subpopulation of control that showed lowest predicted concentrations of parent MT at Week 52. A threshold of <=0.1 ng/mL for predicted Week 52 steady-state (Cmax,ss) parent MT concentration will be used to define the lowest parent MT group. In the analysis output the control group will be presented as “MTC 8 mg/week”.

The actual received treatment and the actual (verified) values of the randomization stratification variables will be used in the analysis.

7.3.1. Summary Statistics

The Baseline and Week 52 visit value of each biomarker to be analyzed, of the scales (ADAS-cog_{13}, ADAS-cog_{11}, and ADCS-ADL_{23}) and MRI and ^{18}F-FDG-PET parameter as mentioned in Section 7.3.3, will be analyzed descriptively (n, mean, median, lower quartile (Q1), upper quartile (Q3), standard deviation, standard error, minimum and maximum values) and will be presented by treatment group, and for the lowest parent MT group as a separate group, and by Baseline MMSE score subgroups.

Baseline MMSE score subgroups are defined as 16-19, and 20-27. An additional split of the scores into 16-21, and 22-27 will be investigated. Also, a split into the verified AD diagnosis subgroups MCI-AD and probable AD will be provided as per the information provided in the Diagnostic Verification form.

The descriptive analysis of the scales and parameters will be repeated, since the analysis population is different to the double-blind treatment phase populations.

7.3.2. Primary Outcomes

For each of the primary exploratory biomarkers P-tau181 and NfL, an ANCOVA will be used to analyze the change from Baseline at Week 52 visit within each treatment group (HMTM 16 mg/day, HMTM 8 mg/day, and control). In this ANCOVA, the change from Baseline at Week 52 will be compared pairwise

for these three treatment groups. The ANCOVA model will include the randomization stratification variables (see Section 2.6) as fixed factors, the respective efficacy Baseline value as covariate, and the treatment indicator; with the Kenward and Roger method used for calculating the denominator degrees of freedom for the tests of fixed effects. One table will present the LSM for the change from Baseline and the pairwise treatment contrasts at Week 52, and one table will present the p-values of the type 3 tests of the fixed effects along with the estimates of the factors and covariates which are included in the model.

In a sensitivity analysis, subject's age and sex, as well as *ApoE*4 carrier status and plasma sample age will be added as further covariates in the primary model. The plasma sample age (of the Week 52 sample) is the difference between the day when the sample was analyzed and the day when the sample was taken + 1. For NfL: a mid-point sample analysis date will be applied, to calculate the plasma sample age. In a second and third sensitivity analysis, Baseline values of MRI whole brain volume and ^{18}F-FDG-PET temporal lobe glucose uptake normalized to pons will be included separately as covariates as well. Factors with a p-value of 0.2 or smaller will be investigated further upon request.

In addition, this primary model will be repeated with the control group being restricted to the subpopulation with lowest parent MT.

This primary model will be repeated (not including the sensitivity analyses and not including the analysis with respect to the lowest parent MT control group) for the subgroups of the stratification variables region, prior use of AChEI and/or memantine, and Baseline MMSE severity (16-19, and 20-27). For the Baseline MMSE severity, the additional split into the subgroups of scores 16-21, and 22-27 will be done as well. This analysis will also be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD.

It is of interest to analyze the correlation between change in NfL and ADAS-cog$_{11}$ accounting for baseline values of NfL and potentially treatment allocation; to address this: the ADAS-cog$_{11}$ change from Baseline at Week 52 will be added as a covariate to a simplified ANCOVA model, additionally only accounting for baseline NfL. In an additional model the ADAS-cog$_{11}$ change from Baseline at Week 104 will be added as a covariate instead. These analyses will be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD, and further repeated replacing ADAS-cog$_{11}$ by ADCS-ADL$_{23}$ and MRI whole brain volume (separately). More advanced versions of this simple model relying on interaction terms or additional covariates might be explored. Analyses targeting a more direct evaluation of the correlation might be explored still accounting for potential covariates. This might be repeated for other potential biomarkers.

It is also of interest to analyze the correlation between baseline values of NfL and ADAS-cog$_{11}$ accounting for the randomization stratification variables (see Section 2.6) in an ANCOVA model with NfL Baseline being the independent variable and ADAS-cog$_{11}$ Baseline the dependent variable. This analysis will be repeated for the verified AD diagnosis subgroups MCI-AD and probable AD, and further repeated replacing ADAS-cog$_{11}$ by ADCS-ADL$_{23}$ and MRI whole brain volume (separately).

Sample SAS code (will be fully validated at the analysis stage):

PROC MIXED DATA=dataset METHOD=REML COVTEST;

*CLASS subject treatment(REF='Control') severity(REF='16-19') region(REF='Europe') prioruse(REF='None'); /*additional MMSE split: severity(REF='16-21'); by diagnostic criterion: diagnostic(REF='probable AD')*/*

*MODEL diff = treatment severity region prioruse scorebl / SOLUTION CL DDFM= KENWARDROGER; /*diff: change from Baseline*/*

LSMEANS treatment / CL;

*LSMESTIMATE treatment "HMTM 16 vs. Control" 1 0 -1 / CL; /*Pairwise treatment comparison*/*

LSMESTIMATE treatment "HMTM 8 vs. Control" 0 1 -1 / CL;

LSMESTIMATE treatment "HMTM 16 vs. HMTM 8" 1 -1 0 / CL;

ODS OUTPUT LSMeans SolutionF Tests3;

RUN;

7.3.3. Secondary Outcomes

In the following, the changes from Baseline at Week 52 visit will be analyzed for the primary exploratory biomarkers P-tau181 and NfL through pairwise correlations.

These will be analyzed and presented through scatter plots with symbolized treatment group. For each treatment group, both the parametric Pearson correlation coefficient and the non-parametric Spearman's rank correlation coefficient and their corresponding p-values will be presented in this plot, along with the regression lines.

This analysis will be repeated for the Baseline MMSE score subgroups (16-19, 20-27, 16-21, 22-27), and the verified AD diagnosis subgroups MCI-AD and probable AD.

Furthermore, for each primary exploratory biomarker P-tau181 and NfL the change from Baseline at Week 52 visit will be compared pairwise with the change from Baseline at Week 52 for the following scales and parameters:

- ADAS-cog$_{11}$ (after upscaling was applied)
- ADAS-cog$_{13}$ (after upscaling was applied)
- ADCS-ADL$_{23}$ (after upscaling was applied)
- MRI whole brain volume

- MRI lateral ventricular volume
- MRI temporoparietal lobe volume
- ^{18}F-FDG-PET temporal lobe glucose uptake (includes only subjects with a Baseline CDR of 0.5), normalized to pons and normalized to cerebellum

For each primary exploratory biomarker, the correlation between the change from Baseline at Week 52 visit with the predicted steady state plasma level of parent MT at Week 52 will be analyzed as well for the two HMTM treatment groups.

Sample SAS code (will be fully validated at the analysis stage):

PROC CORR DATA=dataset pearson spearman;

VAR endpoint1 endpoint2;

RUN;

7.3.4. Additional Potential Biomarkers

Additional potential biomarkers are P-tau231, Core-proline tau, T-tau, and GFAP. For each of those biomarkers, if a decision will be made to investigate the respective potential biomarker further, the analyses described in the three previous sections (7.3.1 to 7.3.3) will be repeated. In addition to the pairwise comparison between P-tau181 and NfL, all other pairwise biomarker comparisons will need to be added.

7.3.5. Additional Analysis

The pairwise correlation of Baseline values between the primary exploratory biomarker (P-tau181 and NfL), and the above-mentioned scales and parameters (see Section 7.3.3) will be analyzed irrespective of the treatment group (not per treatment group).

For each of the primary exploratory biomarker (P-tau181 and NfL), an ANCOVA will be used to analyze the natural logarithm of percentage change from Baseline at Week 52. The ANCOVA model will be the same as for the primary outcome (see Section 7.3.2) and the two sensitivity analyses will be performed as well, one including subject's age and sex, as well as *ApoE*4 carrier status and plasma sample age, and the second including MRI whole brain volume and ^{18}F-FDG-PET temporal lobe glucose uptake. Additional analysis will be performed upon request.

7.4. Future Sample Analysis

If evidence of a beneficial treatment effect of HMTM is apparent for any of the biomarkers, further analysis at all other timepoints (Week 4 and Week 104) for that biomarker will be performed. In such an event, this analysis will be confirmed by amendment to the biomarker research plan, to the test-site-specific plans, and to this SAP, as appropriate.

If beneficial treatment effect of HMTM is apparent for any of the biomarkers, further sample analysis would be required to show pre-dose and post-dose samples are equivalent for that biomarker.

8. PHARMACOKINETIC EVALUATIONS

A subject data listing with the plasma concentrations (including available modelled parent MT Cmax,ss values) and whole blood concentration data and associated dosing data will be prepared. Calculated values and summary tables will be listed elsewhere.

Statistical Analysis of Pharmacokinetic data will be performed by Certara USA, Inc., and thus its analysis is not within the scope of this SAP but is described elsewhere.

9. ADNI AND META ANALYSIS

Study data will be compared with ADNI (Alzheimer's Disease Neuroimaging Initiative) data and meta-analysis. This analysis is not within the scope of this SAP but is described elsewhere.

10. CHANGES TO PLANNED ANALYSES

The exploratory efficacy ^{18}F-FDG-PET parameters inferior temporal gyrus and angular gyrus will not be analyzed, since these are included in the lateral temporal cortex and parietal cortex region of interests, respectively.

The exploratory Bayesian analysis, accounting for and using historic data more generally such as placebo decline or treatment effects as priors to inform the analyses of this study, will not be performed.

After the data snapshot (28-APR-2022), the SAP v2.0 signature and the partial study team members unblinding to perform the analysis of the double-blind treatment phase, the version 2.0 of the SAP has been updated to a version 3.0 with added analyses.

11. REFERENCES

ICH E9 (R1) addendum on estimands and Sensitivity Analysis in Clinical Trials to the guideline on statistical principles for clinical trials EMA/CHMP/ICH/436221/2017.

Liu, Y., & De, A. (2015). Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. International journal of statistics in medical research, 4(3), 287–295. https://doi.org/10.6000/1929-6029.2015.04.03.7

Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, 26 June 2020, EMA/158330/2020 Rev. 1

Ratitch, B., & O'Kelly, M. Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. PharmaSUG 2011 - Paper SP04

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry, June 2020, FDA-2020-D-1136

12. APPENDIX

12.1. Considerations regarding COVID-19

This section gives a brief overview of recommendations mentioned therein and their impact to this study regarding its implementation and their applicability. The wording from the guidelines was mostly copied and re-phrased, without changing its essential meaning.

12.1.1. FDA: Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

In this guideline a change of study conduct, requiring a protocol amendment, is proposed to meet the trial objectives, while prioritizing the safety of (all) study participants: This was addressed with the protocol version 6.0 with changes as described in Section 2.5, allowing a less stringent conduct (e.g., remote assessment, use of local laboratories).

Modifications should not be proposed based on data that may introduce bias into the interpretation of trial findings, such as knowledge about magnitude of the treatment effect or information presented by treatment arm: The changes in study conduct suggest no bias, since they should affect all treatment groups likewise.

Information at the participant level should be documented, describing the context and/or reasons for post-Baseline events as they relate to COVID-19, such as discontinuation of treatment, withdrawal of the trial, use of alternative or rescue treatments, missed endpoint ascertainment, and the use of alternative endpoint ascertainment methods: This was addressed with eCRF *Covid-19 Impact Assessment* and the less stringent conduct (remote assessments, local laboratory). Also, corresponding sensitivity analyses were added (see Section 5.9.2.1).

Considerations with respect to the loss of statistical power due to smaller number of randomized subjects are not needed, since the enrollment of patients or study conduct were not stopped early. To overcome the potential loss of information (more generally) from the impact of COVID-19, the number of randomized subjects was increased with study protocol version 6.0.

In an event driven trial the follow-up could be extended: Not applicable.

Sensitivity analyses should be performed examining differences in Baseline characteristics and post-Baseline events (including endpoints and AEs) between the originally enrolled participants and the additional participants to understand the impact of the change in recruitment, including changes to recruitment locations and time of recruitment: Considering that most of the subjects under protocol version 5.0 or higher were randomized during COVID-19 and the quite long follow-up time of 12 months, this is not necessary. Furthermore, enrolment was not extended due to COVID-19 per se.

Closure of a site for a certain period of time could lead to missing endpoint ascertainments, which may not necessarily be related to the treatment assignment or participant characteristics and outcomes. In this case, removing all participants from closed sites who were scheduled for an endpoint ascertainment from the analysis should not bias the findings. It is important to remove all the participants from the closed sites who were scheduled for the ascertainment, regardless of whether they had previously withdrawn. For this approach, the exclusion of participants should not use post-Baseline participant information but instead use only information at randomization (e.g., site location and randomization date). If a significant number of participants are affected, this strategy may result in a significant loss of information: Remote assessment was enabled to minimize missing endpoint ascertainments.

Similarly, closure of a site for a certain period of time could greatly impact trial-specified treatment for subjects such that it is unlikely that any treatment effect can be observed, then it may be reasonable to exclude participants who were impacted during that period of time. The decision to exclude subjects should not use post-Baseline subject information (e.g., on-treatment time), but instead use Baseline information (e.g., site location and randomization date).

Using alternative ascertainment methods, such as replacing in-person endpoint ascertainment based on performance outcomes or interview-based clinician-reported outcomes with remote ascertainment: Remote assessment and use of local laboratories were established.

Extending the protocol-defined window of time for performing the endpoint ascertainment or using an earlier or later planned ascertainment: The study visit windows were extended.

For a composite endpoint, including additional and clinically relevant components or removing components that cannot be ascertained: For subitems which could not be assessed by remote, those are reported missing and upscaling will be used. Furthermore, only the subset of items for ADAS-Cog and MMSE, which could be administered remotely (see Section 4.5), will be analyzed in a sensitivity analysis.

For a binary endpoint that is based on a continuous or ordinal measurement, using the continuous or ordinal measurement as the endpoint: Not applicable.

Evaluation of the impact of any change in endpoint definition or ascertainment, either through a change in methods or a change in timing, should be carefully evaluated in sensitivity analyses. In particular, any differences in the ascertainment between trial arms or among participants with different Baseline characteristics should be explored: The latter is not applicable, since there are no different approaches between trial arms or based on subjects with different Baseline characteristics. Stratified analysis by way of endpoint ascertainment (in-clinic or remote) will be performed in a sensitivity analysis.

12.1.2. **EMA: Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials**

In this document, similar to the FDA guideline, the impact analysis should have been performed using unblinded data or being supervised by an independent DMC. Also, the need of a protocol amendment to address changes due to COVID-19. Additional guidance is given regarding the conduct of the study.

Capture systematic deviations resulting from the measures and individual decisions related to the COVID-19 pandemic. Such information will prove valuable in the assessment of the potential impact of these decisions on the trial outcome and should help distinguish between data 'affected' and 'unaffected' by the COVID-19 pandemic. In order to assist efficiently with the identification of deviations related to the COVID-19 pandemic that are of major importance for interpretation of trial results, Sponsors should ensure that their existing systems are able to record pandemic-related protocol deviations and capture related reasons: This was addressed with eCRF *Covid-19 Impact Assessment*.

Data collection should preferably not stop and should continue as long as possible. However, potential risks for study participants when undergoing study-specific procedures take priority in decisions taken. Measures taken in relation to the COVID-19 pandemic may interfere with study treatments, study assessment schedule and individual participants' observation time. It can be expected that study participants within a certain trial will be unequally affected by such general (i.e. external to the trial) COVID-19 pandemic measures: some study participants may already have completed all study relevant activities and recorded measurements before pandemic-related issues started impacting the trial; for other participants, the main individual study phase might fall during a time when it can be affected by the COVID-19 pandemic. Where preparation for the pandemic situation is still possible, investigators should consider which information is essential for the interpretation of the trial and whether an alternative method of data collection might be warranted: The study visit window was extended, remote assessment and use of local laboratories were made possible.

In a pandemic situation, capability and willingness to follow the trial protocol is expected to vary between and within trial participants. All aforementioned issues are assumed to be of particular relevance in multi-center and multi-regional clinical trials. Any attempt to address those issues at the time of study reporting will require information external to the trial concerning COVID-19 pandemic measures per region and per study site. Such information pertains for example to dates and duration of (partial) lockdowns and travel restrictions, as well as any further measures which would affect recruiting study sites. On the individual participant level, any available information concerning COVID-19 testing or infection status should be recorded in trial documentation whenever possible: COVID-19 infections are documented as AE. Subgroup analysis of region is already planned.

Proposals to deal with any identified potential sources of bias comprising identification of newly emerging intercurrent events or missing values, or other unforeseeable required changes to trial elements: Several sensitivity analyses are implemented to deal will missing value and impacted measurements.

The need/possibility to adjust the trial sample size: See subsection above.

Additional measures when completing the trial after the pandemic, e.g., validation of outcomes that were measured differently: Stratified analysis by way of endpoint ascertainment (in-clinic, remote).

12.2. Scales

12.2.1. ADAS-cog Scoring

Domain	#	Subitem	Maximum Subscore
Memory	1	Word Recall [a, c]	10
	2	Word Recognition [c]	12
	3	Remembering Test Instructions [c]	5
	4	Delayed Word Recall [b, c]	10
Attention	5	Number Cancellation [b]	5
Praxis	6	Constructional Praxis [a, c]	5
	7	Ideational Praxis	5
Orientation	8	Orientation [a, c]	8
Language	9	Naming Objects and Fingers [c]	5
	10	(Following) Commands	5
	11	Spoken Language Ability [a]	5
	12	Word-Finding Difficulty	5
	13	Comprehension [a]	5

[a] Items included in the Composite Scale

[b] Items included in ADAS-cog$_{13}$, but not in ADAS-cog$_{11}$

[c] Items included in COVID-19 Composite Scale. The sum of these subitems is 55.

12.2.2. **ADCS-ADL$_{23}$ Scoring**

#	Item	Maximum score	#	Item	Maximum score
1	Eating	3	12	Beverage	3
2	Walking	3	13	Cooking and preparation of meals [a]	4
3	Bowel and bladder function at the toilet	3	14	Dispose of garbage or litter	3
4	Bathing	3	15	Travel [b]	4
5	Grooming	3	16	Shopping [b]	4
6a	Dressing Performance	3	17	Keeping appointments [a, b]	3
6b	Physically Dressing Performance	4	18	Left alone [b]	3
7	Use of telephone [a]	5	19	Talk about current events [b]	3
8	Television	3	20	Reading	2
9	Conversation	3	21	Writing	3
10	Cleaning dishes [a]	3	22	Pastime, hobby or game [b]	3
11	Finds personal belongings	3	23	Household appliance	4

[a] Items included in the Composite Scale

[b] Items affected by COVID-19. All other items, whose sum is 58, are included in the COVID-19 Composite Scale.

12.2.3. **MMSE**

#	Item (alternative item naming)	Maximum Score
1	Temporal orientation (Orientation – Time)	5
2	Spatial orientation (Orientation – Place)	5
3	Immediate memory (Memory – Registration)	3
4	Attention and concentration	5
5	Delayed recall (Memory – Recall)	3
6	Naming (Language – Naming)	2
7	Verbal repetition (Language – Repetition)	1
8	Verbal comprehension (Praxis ideational)	3
9	Writing (Language – Writing Spontaneous)	1
10	Reading a sentence (Language reading Comprehension)	1
11	Constructional praxis (Praxis – Drawing)	1

12.2.4. **CDR-SOB**

#	Item	Maximum Score
1	Memory	3
2	Orientation	3
3	Judgment and Problem Solving	3
4	Community Affairs	3
5	Home and Hobbies	3
6	Personal Care	3

12.3. Rules for Determining "Worst" Value

12.3.1. Clinical Laboratory Parameters

Rule	Parameters
Highest value	Hematology: eosinophils, basophils, monocytes, reticulocytes Blood chemistry: ALT, AST, ALK-P, bicarbonate, creatinine, direct/indirect/total bilirubin, BUN, LDH, TSH, GGT, urea nitrogen
Lowest value	Hematology: neutrophils, RBC count, HCT, hemoglobin, platelets Blood chemistry: albumin, creatinine clearance, total protein, Triiodothyronine, Thyroxine, folate, and B12
Farthest from normal range midpoint	Hematology: WBC count, lymphocytes, MCV, MCH, MCHC Blood chemistry: glucose (random), sodium, potassium, phosphorus, calcium, chloride

12.3.2. Scales, Vital Signs, and Weight Measurement

Parameter	Rule
ADAS-cog$_{13}$	Highest score
ADCS-ADL$_{23}$	Lowest score
Systolic blood pressure	Value farthest from 125 mmHg
Diastolic blood pressure	Value farthest from 75 mmHg
Pulse	Value farthest from 75 beats per minute
Weight	Greatest weight loss from Baseline

12.4. ATC Codes or Preferred Terms for Medications

Category of Medications	ATC Codes or Preferred Terms
Antipsychotics	Flagged in the eCRF
MAOIs	N06AF, N06AG (ATC level 4 codes)
SNRIs	Preferred Terms that contain any of the following terms: desvenlafaxine, duloxetine, levomilnacipran, milnacipran, reboxetine, venlafaxine, and vilazodone.
SSRIs	N06AB (ATC level 4 codes)

13. STATISTICAL OUTPUTS TO BE GENERATED

Will be provided in a separate document.

14. CLINICAL STUDY REPORT APPENDICES

Will be provided in a separate document.