Official Protocol Title:	A Phase 2a/2b Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of MK-1942 as Adjunctive Therapy in Participants with Mild to Moderate Alzheimer's Disease Dementia
NCT number:	NCT05602727
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Title Page

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Protocol Title: A Phase 2a/2b Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of MK-1942 as Adjunctive Therapy in Participants with Mild to Moderate Alzheimer's Disease Dementia

Protocol Number: 008-00

Compound Number: MK-1942

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	139557
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Approval Date: 07 July 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	07-JUL-2022	Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a/2b Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of MK-1942 as Adjunctive Therapy in Participants with Mild to Moderate Alzheimer's Disease Dementia

Short Title: Phase 2a/2b Study of MK-1942 in Participants with Alzheimer's Disease dementia

Acronym: not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with mild to moderate Alzheimer's Disease dementia:

Objectives	Endpoints
Primary	
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADAS-Cog11 score compared with placebo at Week 12. Hypothesis: At least one MK-1942 dose is superior to placebo with respect to change from baseline in the ADAS-Cog11 score at Week 12.	• Change from baseline in the ADAS-Cog11 score at Week 12
• To evaluate the safety and tolerability of MK-1942 as adjunctive therapy.	• AEs • Discontinuation of study intervention due to AEs

Objectives	Endpoints
Secondary	
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADCS-CGIC Overall score compared with placebo at Week 12. Hypothesis: At least one MK-1942 dose is superior to placebo with respect to ADCS-CGIC Overall score at Week 12.	• ADCS-CGIC Overall score at Week 12
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADCS-ADL Total score as compared with placebo at Week 12. • Hypothesis: At least one MK-1942 dose is superior to placebo with respect to the change from baseline ADCS-ADL Total score at Week 12.	• Change from baseline in the ADCS-ADL Total score at Week 12

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of AD dementia
Population	Participants with mild to moderate AD dementia
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo-controlled
Study Blinding	Double-blind with in-house blinding

Blinding Roles	Investigator Sponsor Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 41 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 408 participants will be allocated/randomized such that approximately 324 evaluable participants complete the study as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Adminis-tration	Treatment Period	Use
MK-1942 5 mg	MK-1942	5 mg	bid	oral	Week 1-Week 12	Test Product
MK-1942 15 mg	MK-1942	8 mg	bid	oral	Week 1	Test Product
	MK-1942	15 mg	bid	oral	Week 2-Week 12	Test Product
Placebo	Placebo	0 mg	bid	oral	Week 1-Week 12	Placebo

bid=twice daily

Note 1: The dose of MK-1942 for participants in the MK-1942 15-mg dose group will be up-titrated as follows: 8 mg bid (Visit 2/Day 1 to Visit 3/Week 1) and 15 mg bid (Visit 3/Week 1 to Visit 4/Week 2). Placebo and MK-1942 5 mg treatment groups will undergo a mock titration to maintain the study blinding.

Total Number of Intervention Groups/ Arms	3
Duration of Participation	Each participant will participate in the study for approximately 26 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 12 weeks, each participant will receive assigned intervention for approximately 12 weeks. After the end of treatment, each participant will be followed for 14 days.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

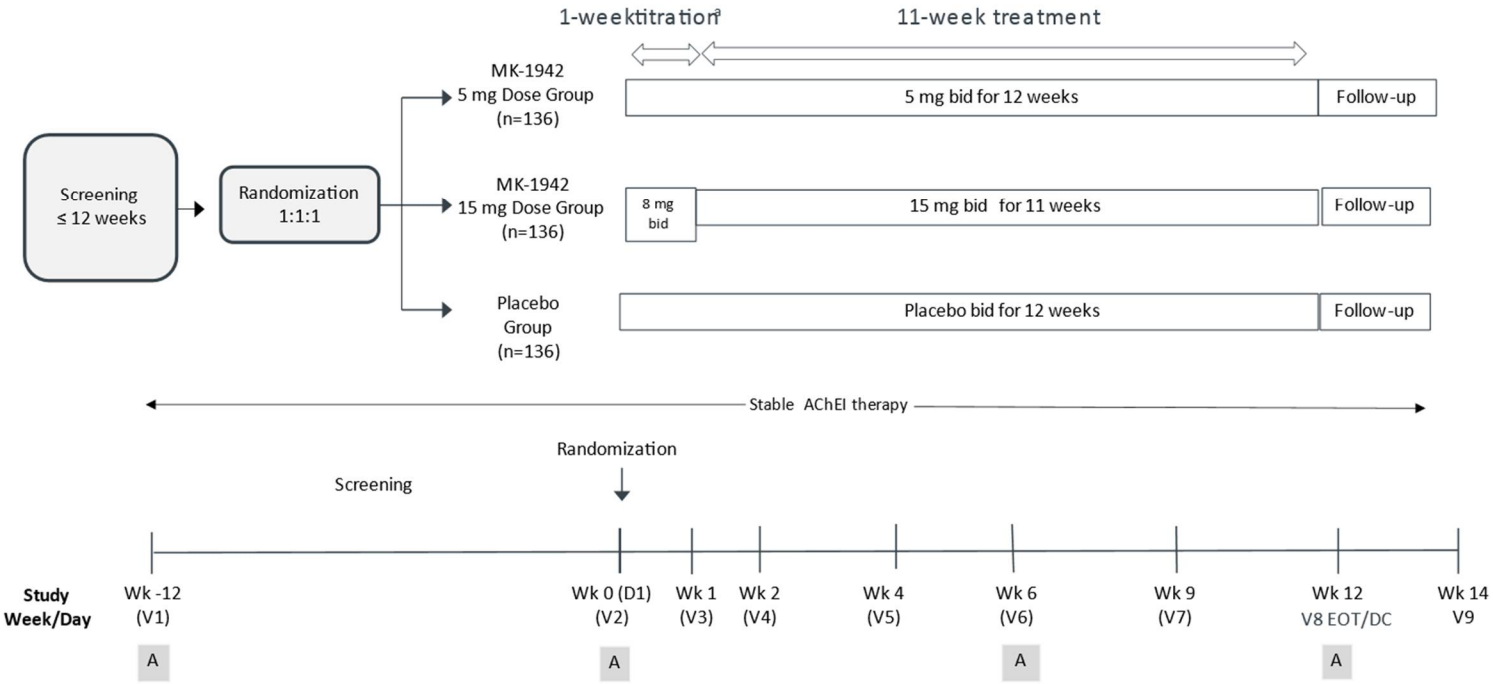
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



- AChEI=acetylcholinesterase inhibitor, A=ADAS-Cog11,DC=discontinuation, EOT= End of Treatment, TC=telephone call, Wk=Week, V=Visit.
- Safety follow-up will occur at least 14 days after the last dose of study intervention.
- The primary diagnosis of AD will be confirmed during the screening period.
- [a]Titration to occur from Week 0 to Week 1. Placebo and MK -1942 5 mg treatment groups will undergo a mock titration in order to maintain th e study blinding.

1.3 Schedule of Activities

Study Period:	Screen -ing	Double-Blind Treatment Period							Postdose Follow-up Period	Notes
Visit Number/Title:	1	2	3	4	5	6	7	8/EOT/ DC[a]	9/ 14 days postdose	
Scheduled Visit Week/Day:	Wk -12	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 4/ Day 29	Wk 6/ Day 43	Wk 9/ Day 64	Wk 12/ Day 85	Wk 14/ Day 99	Screening period may be <12 weeks and can be split across >1 visit if needed (see Section 8.11.1)
Visit Window (Days)		0	±2	±2	±3	±3	±5	±5	+3	
Administrative Procedures										
Informed Consent (Participant and Study Partner)	X									
Informed Consent for FBR	X									Participants remain eligible for the main study if they opt out of FBR
Inclusion/Exclusion Criteria	X	X								
Participant Identification Card	X	X								Randomization number will be added to the card at Visit 2
Medical History	X									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	
Diagnostic Verification Form Review	X									
Assignment of Screening Number	X									
IRT Visit Registration	X	X	X	X	X	X	X	X		
IRT Randomization		X								
Study Intervention Dispensing		X	X	X	X	X	X			Participants should fast for 1 hour before and 1 hour after dosing. See Section 5.3.1
Study Medication Guidance Dispensing and Review		X	X	X	X	X	X	X		
Witnessed Dose		X	X			X				To be taken after all assessments and procedures are complete, except Visit 6 where dose to be taken after first PK draw.
Study Intervention Accountability			X	X	X	X	X	X		

Study Period:	Screen -ing	Double-Blind Treatment Period							Postdose Follow-up Period	Notes
Visit Number/Title:	1	2	3	4	5	6	7	8/EOT/ DC[a]	9/ 14 days postdose	
Scheduled Visit Week/Day:	Wk -12	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 4/ Day 29	Wk 6/ Day 43	Wk 9/ Day 64	Wk 12/ Day 85	Wk 14/ Day 99	Screening period may be <12 weeks and can be split across >1 visit if needed (see Section 8.11.1)
Visit Window (Days)		0	±2	±2	±3	±3	±5	±5	+3	
Telephone Contacts After Visits		X	X							TCs will be made 2-4 days after Visits 2 and 3, if applicable (see Section 8.1.13).
Efficacy Procedures:										See Section 8.2 for recommended efficacy assessment order
MMSE	X	X				X		X		
ADAS-Cog13	X	X				X		X		To be administered to every participant; however, ADAS-Cog11 will be primary efficacy endpoint
CERAD Verbal Fluency Test	X	X				X		X		
COWAT	X	X				X		X		
Trail Making Test Parts A and B	X	X				X		X		
Coding	X	X				X		X		
ADCS-CGIC		X				X		X		Participant and Study Partner assessed (See Section 8.2.2)
Efficacy Procedures: study partner assessed										
ADCS-ADL		X				X		X		
NPI-Q		X				X		X		
EQ-5D-5L (caregiver self-assessment version)		X				X		X		
EQ-5D-5L (proxy version)		X				X		X		
Screening Procedures										
MHIS	X									
MRI	X									Digital MRI performed within 18 months before Screening Visit is acceptable if images are available and suitable for central review

Study Period:	Screen -ing	Double-Blind Treatment Period							Postdose Follow-up Period	Notes
Visit Number/Title:	1	2	3	4	5	6	7	8/EOT/ DC[a]	9/ 14 days postdose	
Scheduled Visit Week/Day:	Wk -12	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 4/ Day 29	Wk 6/ Day 43	Wk 9/ Day 64	Wk 12/ Day 85	Wk 14/ Day 99	Screening period may be <12 weeks and can be split across >1 visit if needed (see Section 8.11.1)
Visit Window (Days)		0	±2	±2	±3	±3	±5	±5	+3	
Safety Procedures										
Full physical examination	X							X		
Neurological Examination	X							X		
Height	X									
Weight	X	X				X		X		
Vital Signs (temperature, blood pressure, pulse rate, and respiratory rate)	X	X	X	X	X	X	X	X		
12-lead ECG (centrally read)	X	X		X				X		Measured in triplicate at each visit (see Section 8.3.4)
Serum Follicle-Stimulating Hormone (FSH) (if applicable)	X									FSH may be measured to confirm postmenopausal state. (See Appendix 5).
Chemistry and Hematology	X	X		X	X	X	X	X	X	Visit 9 laboratory assessments may be performed at a local laboratory, as needed. See Appendix 2.
Urinalysis	X	X				X		X		
INR		X								
TSH	X									with reflex FT4
AE/SAE review	X	X	X	X	X	X	X	X	X	Visit 9 AE monitoring may be performed by TC, as needed
C-SSRS Baseline/Screening version	X									
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	Visit 9 C-SSRS may be performed by TC, as needed.

Study Period:	Screen -ing	Double-Blind Treatment Period							Postdose Follow-up Period	Notes
Visit Number/Title:	1	2	3	4	5	6	7	8/EOT/ DC[a]	9/ 14 days postdose	
Scheduled Visit Week/Day:	Wk -12	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 4/ Day 29	Wk 6/ Day 43	Wk 9/ Day 64	Wk 12/ Day 85	Wk 14/ Day 99	Screening period may be <12 weeks and can be split across >1 visit if needed (see Section 8.11.1)
Visit Window (Days)		0	±2	±2	±3	±3	±5	±5	+3	
PK and Biomarkers										
MK-1942/Placebo Plasma PK sample		X				X		X		Two PK samples will be drawn at Visit 6. See Section 8.6 for details.
AChEI Plasma PK sample		X				X		X		See Section 8.6 for details Will be collected for all randomized participants.
Memantine Plasma PK sample		X				X		X		Will be collected for participants taking memantine (see Section 8.6).
Blood for Genetic Analysis		X								Sample will be collected predose in randomized participants only (see Section 8.8).
Plasma for Exploratory Research		X								
Genotyping for CYP2C19		X								
Blood Sample for APOE4		X								
Blood Sample for AD Biomarkers		X						X		

AChEI=acetylcholinesterase inhibitor, AD=Alzheimer's Disease Dementia; ADAS-Cog13=Alzheimer's Disease Assessment Scale- 11-item cognitive subscale; ADCS-CGIC=Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living; AE=adverse event; APOE=apolipoprotein E; hCG=human chorionic gonadotropin; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; COWAT=Controlled Oral Word Association Test; C-SSRS=Columbia Suicide Severity Rating Scale; DC=discontinuation from study intervention or discontinuation from study; EOT=End of Treatment; FBR=future biomedical research; FSH=follicle-stimulating hormone; ID=identification; INR=international normalized ratio; IRT=interactive response technology; MMSE=Mini-Mental State Examination; MRI=Magnetic Resonance Imaging; NPI-Q=Neuropsychiatric Inventory; PK=pharmacokinetic; SAE=serious adverse event; TC=telephone contact; TSH=thyroid-stimulating hormone

Note: For HBV, HCV, and HIV testing at screening, see Appendix 7 (Country-specific Requirements).
[a] If a participant discontinues study intervention prematurely (before Visit 8) and continues with study visits off study intervention, a visit will still be completed at the scheduled Visit 8. If the participant who discontinues study intervention discontinues the study before Visit 8, a study DC visit will be conducted at that time with the same procedures as the EOT visit. See Section 8.11.4 for details.

2 INTRODUCTION

2.1 Study Rationale

AD is the leading cause of dementia in elderly people and affects an estimated 35 million individuals worldwide. AD is characterized by the progressive loss of neurons in the cerebral cortex, hippocampus, and selective subcortical regions. This leads to the dysregulation of various neurotransmitter systems, including cholinergic and glutamatergic pathways, which play important roles in memory and higher cognitive function. Current therapies, including the standard of care AChEIs, offer symptomatic relief from cognitive difficulties. However, they provide only modest efficacy and are accompanied by dose-limiting tolerability issues, including nausea, emesis, diarrhea, muscle cramps, and general malaise. As such, there remains a significant unmet medical need for treatments offering better efficacy in treating cognitive deficiencies, as well as for those offering enhanced tolerability.

CCI [redacted]

The purpose of this Phase 2a/2b study is to evaluate the therapeutic effect of MK-1942 in participants with mild to moderate AD dementia on stable AChEI therapy and to characterize the safety and tolerability of MK-1942 in this population.

Details on the scientific rationale and the dose regimens of MK-1942 in this study are in Sections 4.2 and 4.3, respectively.

2.2 Background

Refer to the IB for detailed background information on MK-1942.

2.2.1 Pharmaceutical and Therapeutic Background

CCI [redacted]. When administered to rhesus monkeys in the scopolamine-impaired object retrieval assessment, MK-1942 improved cognitive performance at doses yielding ROs up CCI [redacted] although it is not clear whether higher exposures would yield incrementally greater effects. Data obtained in preclinical studies where a structurally unrelated CCI [redacted] CCI [redacted] was repeatedly administered suggests further improvements in cognition can be obtained as ROs exceeding approximately CCI [redacted]. These effects on cognition are consistent

with those observed with other, structurally diverse [CCI redacted], both across species (mice, rats, rhesus monkeys, and African Green monkeys) and cognitive domains (attention, working memory, episodic memory, and executive function).

An absorption, metabolism, excretion study conducted in bile duct-cannulated monkeys and rats resulted in >90% recovery of the [^{3}H]MK-1942 associated radioactivity. The majority of the radioactivity was excreted in nearly equivalent amounts in bile (33%) and urine (38%). These results indicate that MK-1942 was well absorbed at the doses studied and is consistent with the oral bioavailability observed in PK studies.

2.2.2 Nonclinical and Clinical Studies

The in vivo pharmacodynamic effect of MK-1942 was evaluated in rhesus monkeys utilizing the object retrieval task as a measure of executive function. In this nonclinical cognition model, MK-1942 reversed scopolamine-induced deficits at acute doses up to 0.2 mg/kg. Doses of 0.07, 0.2, and 0.4 mg/kg, corresponding [CCI redacted] respectively, were administered in this study. The results from this model indicate that MK-1942 exhibits procognitive effects in nonhuman primates at RO [CCI redacted] under these test conditions. These observations are consistent with the performance of [CCI redacted] in a number of nonclinical models, showing consistent pharmacodynamic effects across structural series, species, and cognitive domain assays at RO between [CCI redacted] targeted for producing an optimal pharmacodynamic response from human subjects.

The nonclinical safety profile of MK-1942 indicates that there are no adverse CNS and cardiovascular findings at C_{max} exposure margins approximately 64-fold above the top clinical target [CCI redacted]. No effects on cardiovascular parameters or vital signs were observed in rats or guinea pigs, and the changes observed in a cardiovascular and respiratory safety study in rhesus monkeys were reversible and/or not considered adverse. MK-1942 did not induce seizures or abnormal spike cluster activity in a 9-day electroencephalogram study in monkeys at plasma concentrations that were 61 × higher than the C_{max} associated with a RO level of approximately [CCI redacted] In repeat-dose toxicity studies up to 3 months in duration, MK-1942 was generally well tolerated in rats and nonhuman primates at exposures that were 108 to 164 × the $AUC_{0\text{-}24hr}$ corresponding to a RO of approximately [CCI redacted]. In a 3-month combination toxicity study in rats, coadministration of MK-1942 with donepezil did not result in increased toxicity. [CCI redacted] WOCBP are not eligible to participate in this study.

Six Phase 1 clinical studies of MK-1942 are complete. Further details can be found in the IB Section 5.P001 was a first-in-human, randomized, double-blind, placebo-controlled, single ascending dose study of the safety and PK of MK-1942 in healthy adult men. The study consisted of 2 alternating panels (A and B), each consisting of 8 participants administered single doses of either MK-1942 or placebo in a 3:1 ratio as an on-site formulation (oral suspension). All doses (0.1 mg to 12 mg) were administered in the fasted state except for participants in Panel A, Period 5, where 4-mg MK-1942 was administered immediately after

a standard, high-fat breakfast. P002 was an ascending multiple-dose study being conducted in healthy adult men. The objective of MK-1942-002 is to evaluate the safety and PK of multiple doses of MK-1942 projected to achieve plasma levels CCI [redacted] Because administration of single doses of MK-1942 >4 mg were associated with nonserious AEs of dizziness, gait abnormalities, and nausea in study MK-1942-001, this investigation evaluated the ability of titration dosing regimens to prevent or reduce the incidence and severity of treatment associated AEs (ie, dizziness, nausea) at doses capable of achieving CCI [redacted] MK-1942 at steady state. P003 was an open-label, adaptive-design positron emission tomography study evaluating the degree of RO of the CCI [redacted] site in the brain of healthy adult male participants after oral administration of single doses of MK-1942.

P004 was an ascending, multiple-dose study conducted in healthy adult men (Panel B) and healthy elderly men and WONCBP (Panels A and C), consistent with the age and gender demographics of patients with AD. Because administration of MK-1942 in a titration dosing regimen appeared to reduce the incidence and severity of episodes of dizziness and headache in MK-1942-002, this investigation administered MK-1942 by titrating up to 50 mg bid over 4 weeks.

P005 was a Phase 1, double-blind, placebo-controlled, DDI study of the safety, tolerability, and PK of MK-1942 and donepezil conducted in patients with AD receiving donepezil as part of their treatment for cognitive impairment associated with AD. This study is clinically complete although the CSR is not final.

P007 was a Phase 1, double-blind, placebo-controlled, single- and multiple-dose clinical study to evaluate the safety, tolerability, and PK of MK-1942 in healthy Japanese adult participants. This study is clinically complete although the CSR is not final.

In the completed Phase 1 studies, MK-1942 was readily absorbed after oral administration, but this absorption was impaired in the presence of food. While generally well tolerated, single (4 mg to 12 mg) and repeated doses (5 mg to 50 mg) of MK-1942 were associated with episodes of dizziness, headache, and nausea of mild to moderate intensity that resolved without intervention. These AEs were alleviated by titration dosing regimens. No clinically significant abnormalities were observed in safety measures, including those of vital signs, laboratory chemistry, hematology, urinalysis, physical examinations, or ECGs with one exception. Nonserious adverse events of increased liver transaminases have been CCI [redacted]

Given that the AEs observed were reversible and monitorable, there are currently no safety issues from the completed or ongoing clinical studies that preclude continued clinical investigation.

2.2.3 Ongoing Clinical Studies

One clinical study of MK-1942 is ongoing. Further details can be found in the IB Section 5.

P006 is a Phase 2a double-blind, placebo-controlled, multiple-dose clinical study to evaluate the efficacy and safety of MK-1942 added to stable antidepressant therapy in participants with treatment-resistant depression.

2.2.4 Information on Other Study-related Therapy

This section does not apply to the current study.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Phase 1 clinical studies to date have shown that treatment with MK-1942 is generally well tolerated. Participants may also experience headaches that are mild to moderate in intensity. Episodes of dizziness and headache may be accompanied by feelings of nausea with or without emesis. There are limited treatment options and tolerability issues with current treatments for participants with mild to moderate AD dementia, and given the available nonclinical and clinical data for MK-1942 summarized above and in the IB, the benefit-to-risk assessment for conducting the current study is considered favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In male and female participants with mild to moderate Alzheimer's Disease dementia:

Objectives	Endpoints
Primary	
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADAS-Cog11 score compared with placebo at Week 12. Hypothesis: At least one MK-1942 dose is superior to placebo with respect to change from baseline in the ADAS-Cog11 score at Week 12. • To evaluate the safety and tolerability of MK-1942 as adjunctive therapy.	• Change from baseline in the ADAS-Cog11 score at Week 12 • AEs • Discontinuation of study intervention due to AEs
Secondary	
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADCS-CGIC Overall score compared with placebo at Week 12. Hypothesis: At least one MK-1942 dose is superior to placebo with respect to ADCS-CGIC Overall score at Week 12. • To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the ADCS-ADL Total score as compared with placebo at Week 12. • Hypothesis: At least one MK-1942 dose is superior to placebo with respect to the change from baseline ADCS-ADL Total score at Week 12.	• ADCS-CGIC Overall Score at Week 12 • Change from baseline in the ADCS-ADL total score at Week 12

Objectives	Endpoints
Tertiary/Exploratory	
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the on the NPI-Q Total severity score as compared with placebo at Week 12.	• Change from baseline in the NPI-Q total severity score at Week 12
• To assess the efficacy of MK-1942 at 5 mg and 15 mg bid as adjunctive therapy on the following scores compared with placebo over time up to Week 12: • ADAS-Cog11 • ADAS-Cog13 • ADCS-CGIC Scores (General Condition, Cognition, Behavior, Function, Overall) • COWAT • Coding • Trail Making Test Parts A and B • CERAD Verbal Fluency Test • MMSE • EQ-5D-5L	• ADAS-Cog11 score over time up to Week 12 • ADAS-Cog13 score over time up to Week 12 • ADCS-CGIC scores (General Condition, Cognition, Behavior, Function, Overall) over time up to Week 12 • COWAT score over time up to Week 12 • Coding score over time up to Week 12 • Trail Making Test Parts A&B score over time up to Week 12 • CERAD Verbal Fluency Test score over time up to Week 12 • MMSE over time up to Week 12 • EQ-5D-5L score over time up to Week 12
• To assess the percentage of participants who have an improvement in the ADCS-CGIC Overall score at Week 12.	• Improvement in the ADCS-CGIC Overall score at Week 12 (with a score of 1, 2, or 3 indicating improvement)
• To assess the effect of MK-1942 on the composite scores of Memory, Executive function, and Attention over time up to Week 12.	• Composite score of Memory over time up to Week 12 • Composite score of Executive function over time up to Week 12 • Composite score of Attention over time up to Week 12

Objectives	Endpoints
• To assess the effect of MK-1942 on the ADAS-Cog11 score at the item-level over time up to Week 12.	• Item response theory derived ADAS-Cog11 score over time up to Week 12
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, PD activity, and/or the mechanism of action of MK-1942.	• Molecular (genomic, metabolic, and/or proteomic) determinants using blood
• To explore the relationship between the germline genetic variation and the response to the treatment(s), and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation
• To evaluate the plasma PK of MK-1942.	• MK-1942 plasma PK
• To explore the relationship between MK-1942 PK and treatment response on clinical measures of efficacy.	• MK-1942 plasma PK and clinical efficacy measures (eg, ADAS-Cog11)

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of MK-1942 as adjunctive therapy in participants with mild to moderate AD dementia. The study population will consist of male and female participants aged 55 to 90 years with mild to moderate AD dementia according to clinical criteria (NINCDS-ADRDA) [McKhann, G., et al 1984]. Participants will continue taking their stable background AD therapy during the study.

Approximately 408 participants will be randomized in a 1:1:1 ratio to treatment with either (1) MK-1942 5 mg bid, (2) MK-1942 15 mg bid, or (3) placebo bid, respectively (Section 1.2). MK-1942 or matching placebo will be administered as oral capsules, all of which are the same image. No more than ~ 60% of participants are to be enrolled in each of 2 MMSE strata (MMSE ≤16, ≥17).

Note that initial dosing and titration of study intervention to target dose is described in Section 6.6.

For each participant, this study will last approximately 26 weeks, with an initial screening period up to 12 weeks, followed by a treatment period of 12 weeks. The 12-week treatment period consists of an initial 1-week titration period to reach target dose for the 15-mg bid treatment group. A follow-up period consists of 14 days after the last dose of study intervention.

If the participant discontinues study intervention treatment before the intended last visit at Week 12, then an EOT visit should be completed as soon as possible after the last dose. For participants who continue study visits after the EOT visit, refer to Section 8.11.4.

A nonbinding futility IA may be performed when the first 50% of randomized participants have had the opportunity to treat for 12 weeks (ie, the IA will be based on a data cutoff that is 12 weeks after the randomization of the 204th participant). An eDMC will review the results of the one unblinded futility analysis in addition to reviewing unblinded safety data on a regular basis.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This Phase 2a/2b study will evaluate the therapeutic effect of MK-1942 in participants with mild to moderate AD dementia on stable AChEI therapy, and to characterize the safety and tolerability of MK-1942 in this population. The treatment duration will be 12 weeks. This duration is sufficient to show the effect of MK-1942 on cognition and function. The study will use a double-blind, parallel-group design in the assessment of MK-1942 versus placebo. This design is compatible with standard of care and recruitment of a typical AD dementia population given the wide use of AChEIs. Rationale for doses is described in Section 4.3.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints/QoL Endpoints

The ADAS-Cog [Rosen, W. G., et al 1984]has become the standard instrument for demonstrating cognitive efficacy in AD drug trials. The traditional 11-item version of the ADAS-Cog (ie, the ADAS-Cog11) will be the primary endpoint. The ADAS-Cog13 (which includes all components of the ADAS-Cog11 in addition to Delayed Word Recall and Number Cancellation) will be administered to all participants.

Symptomatic treatments for AD dementia must show efficacy in terms of cognition and global function. The ADCS-CGIC Overall Score is a measure of global performance [Becker, R. 1996]. Improvement on the ADCS-CGIC Overall Score at Week 12 will be a key secondary efficacy endpoint. The ADCS-ADL is a measure of daily function, assessing both instrumental and basic activities of daily living [Galasko, D., et al 1997]. Improvement on the ADCS-ADL Total score at Week 12 will be a secondary efficacy endpoint.

The NPI-Q is a behavior instrument widely used in clinical trials of antidementia agents [Cummings, J. L., et al 1994]. Improvement on the NPI-Q Total severity score at Week 12 will be an exploratory efficacy endpoint.

There are some cognitive domains which are not well assessed by the ADAS-Cog11, specifically, executive functioning and working memory. The mechanism of action of MK-1942 is believed to positively impact these cognitive subdomains. Therefore, additional assessment items are included in this protocol to further interrogate these domains: Trail Making Tests [Reitan, R. M. 1955] [Reitan, R. M. and Wolfson, D. 1985], Coding [Wechsler, D. 1981], CERAD Verbal Fluency Test [Morris, J. C., et al 1989], COWAT [Lezak, M. D. 1995], and composite scores of memory, executive function, and attention. MMSE is used extensively in clinical and research settings to detect and measure cognitive impairment [Folstein, M. F., et al 1975]. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time. All of the above will be exploratory endpoints.

Developed by the EuroQol Group, the EQ-5D [Herdman, M., et al 2011] is a simple, generic questionnaire, which is widely used in clinical trials around the world as a standardized measure of health-related quality of life. The EQ-5D-5L assesses health status in terms of 5 dimensions of health and is considered a “generic” questionnaire because these dimensions are not specific to any one patient group or health condition. This will be an exploratory endpoint.

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for AEs. Physical examinations, neurological examinations, vital signs, 12-lead ECGs, and laboratory safety tests will be performed to detect any clinically meaningful effects. C-SSRS will be administered to assess the presence and severity of possible suicidal ideation and behavior in all study participants (Section 4.2.3). Liver enzymes will be monitored every two to three weeks.

4.2.1.3 Pharmacokinetic Endpoints

Plasma PK sampling for MK-1942, AChEIs, and memantine will be conducted. PK assessments of MK-1942 may be used to support exposure-response analyses and to understand PK variability. AChEI (donepezil, rivastigmine, or galantamine) and memantine (if applicable) PK will also inform PK variability and treatment compliance. The analysis (quantitative or semiquantitative) and reporting of any additional, yet to be identified metabolites may be conducted using collected PK samples.

The final decision as to which plasma samples will be measured will be made by the Sponsor’s Department of Quantitative Pharmacology and Pharmacometrics and the Clinical Monitor.

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic endpoints are not applicable.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

In addition to studying variation across the human genome, CYP2C19/APOE4 will specifically be investigated and their impact on MK-1942 PK and drug response.

4.2.1.5.2 Exploratory Biomarker Analysis

The study will collect blood samples for exploratory analysis of biomarkers that may indicate the presence of AD pathology. These emerging biomarkers are being explored for utility as possible supportive markers to potentially corroborate the clinical diagnosis of AD dementia and indicate neurodegenerative pathology. The rationale for inclusion of exploratory analysis in this study is to ascertain the value of using the evaluated biomarker assays as potential screening tests for use in a mild/moderate AD dementia population. These exploratory analyses will be performed on a post hoc basis, including the possibility of using biomarker assays or panels that have not been specifically identified at the time of this protocol finalization, but are under development and are anticipated to be available by the completion of this study.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

Despite the seriousness of the indication, a placebo group is necessary to evaluate the efficacy and safety of the addition of MK-1942 treatment in participants with mild to moderate AD dementia. Without the use of placebo, false assumptions regarding the true efficacy of new drugs may be made. In the absence of a placebo control, it is nearly impossible to distinguish true drug effects from placebo effects in this study population. In addition, all participants will continue to take their stable background AD dementia treatment.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

Prospective assessment of suicidal ideation and behavior will be performed in this study using the C-SSRS. This assessment is being conducted in compliance with the 2012 FDA guidance requiring prospective assessment in clinical studies conducted under IND applications and studies that are intended for submission in a NDA to the Neurology or Psychiatry Divisions of the FDA or BLA, as well as assessment in studies that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The starting dose for MK-1942 in this study is 5 mg bid. The completed multiple ascending-dose study (P002) in healthy adults showed that a titration regimen with a starting dose of 5 mg bid is well tolerated. No participants in Study P002 discontinued study intervention due to an AE, and all reported AEs were either mild or moderate in intensity and resolved. The most common AEs were transient dizziness, headache, and nausea. The completed multiple ascending-dose study (P004) in healthy adults (non-elderly and elderly) had starting doses of either 5 mg bid or 8 mg bid, with extended dosing regimens that were generally well tolerated. The dose of 5 mg BID is expected to provide receptor occupancy (RO) of CCI [redacted]. Based on preclinical data, this dose is hypothesized to be the minimally effective dose.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose for MK-1942 in this study is 15 mg bid. Participants allocated to this dose will be up-titrated for the first week of the study (8 mg bid and 15 mg bid; see Section 6.6). The selection of this titration regimen is informed by the same well-tolerated dosing regimens tested in healthy elderly patients in a Phase 1 study (P004) where a gradual, stepwise up-titration approach was associated with good tolerability for AEs such as dizziness, headache, and gait disturbances. The dose of 15 mg bid is expected to provide CCI [redacted]

4.3.3 Rationale for Dose Interval and Study Design

This study provides opportunity to explore dose- and exposure-response relationships to enhance late-stage dose selection and may enable direct progression to a pivotal study. Combined, these doses will sample a large part of the PK/RO relationship with nonoverlapping PK. Clinical investigation from the MK-1942-002 and MK-1942-004 (Section 2.2.2) indicated that administration of MK-1942 bid was well tolerated with only mild and transient AEs, mostly consisting of dizziness, nausea, and headache. The majority of patients developed tolerance to these AEs within the first week of treatment. The terminal half-life of MK-1942 (approximately 10-15 hours) is consistent with bid dosing.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has mild to moderate AD dementia based on the NINCDS-ADRDA criteria [McKhann, G., et al 1984].

2. Has MMSE score between 12-22 (inclusive) at Screening.

Demographics

3. Is male or female, from 55 years to 90 years of age inclusive, at the time of providing documented informed consent.

Male Participants

4. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention):

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

5. A female participant is eligible to participate if:

   - She is a WONCBP, as defined in Appendix 5.

Informed Consent

6. The participant (or legally acceptable representative) has provided documented informed consent for the study in accordance with local requirements. The participant (or legally acceptable representative) may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

7. Is using AChEI therapy for management of AD dementia at Screening and during the study. These medications must be at stable approved dose levels ≥3 months before the first dose of study intervention and the regimens must remain constant throughout the study to the extent that is clinically appropriate (see Section 8.1.5.2 for allowed AChEI therapies and doses).

8. Has an MRI scan at Screening that is consistent with the diagnosis of AD. MRI scans will be analyzed by a central MRI reviewer. A digital MRI performed within 18 months before the Screening Visit is acceptable provided the images are available and suitable for central review.
   NOTE: If MRI is not available, it can be performed as part of study procedures. A CT scan instead of an MRI can be accepted with Sponsor consultation in certain cases (eg, participant has contraindication to MRI). See Section 8.11.1.2 for details.

9. Is able to speak, read, hear, and understand the language and information provided by the study staff; and possesses the ability to respond verbally to questions, follow instructions, and complete clinical assessments, including cognitive assessments, based on the investigator's judgment.

10. Is able and willing to adhere to dose and visit schedules in the investigator's judgment, and is willing to have selected interviews audio recorded.

11. Has a designated study partner who can fulfill the requirements of this study. The study partner will need to spend sufficient time with the participant to be familiar with their overall function and behavior and be able to provide adequate information about the participant needed for the study including, knowledge of functional and basic activities of daily life, work/educational history, cognitive performance, emotional/psychological state, and general health status. The investigator will assess the study partner's

capabilities to reliably assess the participant. See Section 8.11 for details of study partner responsibilities.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a known history of stroke or cerebrovascular disease that is clinically important in the investigator's opinion.

2. Has diagnosis of a clinically relevant central nervous system disease other than AD dementia (eg, vascular dementia, Parkinson disease, Huntington disease, frontotemporal dementia, multi-infarct dementia, dementia with Lewy bodies, normal pressure hydrocephalus, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, neurosyphilis, posterior cortical atrophy, logopenic primary progressive aphasia, other types of dementia, cognitive developmental delay, hypoxic cerebral damage, cognitive impairment due to other disorders, or head trauma with loss of consciousness that led to persistent cognitive deficits) or other condition that negatively impacts cognition or cognitive status chronically.

3. Has structural brain disease or other features such as acute ischemic disease, hemorrhages, large infarct, lacunes in critical areas, (eg, thalamus or hippocampus) space occupying lesions, extensive white matter disease, or other brain abnormalities (eg, normal pressure hydrocephalus) as assessed by blinded independent central review of MRI/CT scans.

4. Has a history of seizures or epilepsy within the 10 years preceding Screening.

5. Has any other major CNS trauma, or infections that affect brain function (eg, HIV, syphilis, and/or neurological sequelae of COVID-19, including impact on cognition).

6. Has evidence of a clinically relevant or unstable psychiatric disorder, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition), including schizophrenia or other psychotic disorder, bipolar disorder, major depression, or delirium. Major depression in remission is not exclusionary.

7. Has major medical illness or unstable medical condition within 3 months before Screening that, in the opinion of the investigator, may interfere with the participant's ability to comply with study procedures and abide by study restrictions, or with the ability to interpret safety or efficacy data, including any physical disability (eg, blindness, deafness, non-AD-related speech impairment, sensory or motor dysfunction) that would prevent completion of study procedures or assessments.

8. Has a severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or administration of study

intervention or may interfere with the interpretation of study results and, in the opinion of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

9. Has a history of malignancy occurring within the 5 years immediately before Screening, except for a participant who has been adequately treated for 1 or more of the following:

    a. Basal cell or squamous cell skin cancer

    b. In situ cervical cancer

    c. Localized prostate carcinoma

    d. Who has undergone potentially curative therapy with no evidence of recurrence for ≥3 years post-therapy, and who is deemed to be at low risk for recurrence by their treating physician

    Note: Participants with stable chronic lymphocytic leukemia may participate in the study.

10. Has one of the following:

    a. Vitamin B12 or folate deficiency confirmed by laboratory test results in the 3 months immediately before Screening, or

    b. Vitamin B12 or folate deficiency in addition to increased serum homocysteine or methylmalonic acid levels at Screening as determined by central laboratory normal values.

11. Has a risk factor for QTc prolongation as defined by:

    - A known history or current evidence of QTc interval >470 msec (men) or >480 msec (women), OR

    - A known history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome). Note that participants with stable history of congestive heart failure Stage A and B according to the ACC/AHA guidelines are eligible to participate in the trial.

    Note: ECGs will be performed in triplicate. At Screening, the average of the 3 QTcF intervals based on the central vendor overread will be used to assess eligibility. At Visit 2 (Day 1), the average of the 3 QTcF intervals based on the local ECG printout will be used to assess eligibility (additional details on ECG assessments are in Section 8.3.4).

12. Has a history of alcoholism or drug dependency/abuse within the 5 years preceding Screening.

13. Based on clinical interview and responses on the C-SSRS, is at imminent risk of self-harm or of harm to others, in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.

14. Has a known allergy or intolerance to the active or inert ingredients in MK-1942.

Prior/Concomitant Therapy

15. Has received any of the treatments listed in Table 1 more recently than the indicated period before Screening.

16. Anticipates receiving any of the treatments listed in Table 1 during the current study

Table 1 Prohibited Medications and Specified Washout Period

Prohibited Medications, Supplements, and Other Substances	Period Before Screening
Anti-amyloid agents (eg, tarenflurbil, tramiprosate)	3 months
Anti-amyloid antibodies (eg, bapineuzumab, aducanumab)	ever
CNS-penetrant anticholinergic medications Regularly used (>2 doses/week) CNS-penetrant anticholinergic medications of moderate potency or greater (eg, benztropine, cyclobenzaprine, cyproheptadine, dicyclomine, diphenhydramine, promethazine, diphenoxylate with atropine, hydroxyzine, hyoscyamine, prochlorperazine,). **Exception:** Daily use of anticholinergic medications for incontinence (eg, oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine), nasal spray for rhinorrhea (ipratropium) or inhalants for pulmonary disorders (eg, tiotropium) are acceptable if stable for ≥4 weeks before the first dose of study intervention.	4 weeks
Antidepressants Antidepressants that are monoamine oxidase inhibitors or antidepressants with moderate or greater anticholinergic potency or cognitive side effects, including tricyclics (eg, amoxapine, isocarboxazide, maprotiline, phenelzine, protriptyline, tranylcypromine, trimipramine).	4 weeks
Neuroleptics Neuroleptics with moderate or greater anticholinergic potency (eg, chlorpromazine, fluphenazine, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, clozapine)	4 weeks
Mood stabilizers and anticonvulsants (eg, lithium, valproic acid, levetiracetam, carbamazepine) **Exception**: use of pregabalin and gabapentin for neuropathic pain is acceptable and must be stable dose for 4 weeks before first dose of study intervention.	4 weeks
General anesthetics	3 months

Prohibited Medications, Supplements, and Other Substances	Period Before Screening
Sedatives/benzodiazepines Doses of lorazepam >3 mg/day or the equivalent dose of other benzodiazepines Doses of the following partial benzodiazepine agonists: zolpidem >10 mg/day, zaleplon >20 mg/day, zopiclone >15 mg/day **Exception:** For participants on an allowed dose of a benzodiazepine or partial benzodiazepine, the dose should be stable for ≥4 weeks before first dose of study intervention. For other medications in this category not specified here, please contact the Sponsor for guidance.	4 weeks
Analgesics/narcotics Regularly used (>2 doses/week) narcotic analgesics (eg, codeine, morphine, hydromorphone, oxycodone, propoxyphene (Darvon) and its variations, and combination products that contain a narcotic). **Exception:** short-term use (<4 weeks) more than 2 doses/week is acceptable for temporary conditions.	4 weeks
CYP2C19 inducers and substrates Strong CYP2C19 inducers: carbamazepine (strong inducer), artemisinin, norethisterone, rifampin CYP2C19 substrates: clopidogrel, propranolol, tolbutamide, warfarin, primidone, tapentadol, fluoxetine (doses >40 mg/day are prohibited), moclobemide, voriconazole Note: Participants must discontinue CYP2C19 substrates at Screening or earlier.	4 weeks
Agents with glutamatergic activity (ketamine, esketamine, N-acetylcysteine, lamotrigine, riluzole). **Exception: use of memantine is acceptable and must be stable approved dose for at least 3 months before first dose of study intervention.**	4 weeks
Anti-parkinsonian medications (eg, L-dopa, amantadine, bromocriptine, pergolide, selegiline, I-deprenyl/selegiline, rasagiline). **Exception:** carbidopa/levodopa and dopamine agonists are allowed for treating restless leg syndrome and must be stable dose for ≥4 weeks before first dose of study intervention.	3 months
Stimulant medications (eg, amphetamine, methylphenidate, atomoxetine, modafinil)	4 weeks
Supplements with possible psychotropic effects (eg, kava-kava, melatonin, S-Adenosyl methionine [SAMe], St. John's Wort, tryptophan, gingko, and valerian) **Exception:** use of melatonin is acceptable and must be stable dose for at least 4 weeks before first dose of study intervention.	4 weeks
COVID-19 experimental therapies Note: any licensed COVID 19 vaccine is allowed in the study and will be treated just as any other concomitant therapy**.**	4 weeks
NOTE: This is not a complete list of excluded medications. Contact the Sponsor if there is a question about a specific medication.	

Prior/Concurrent Clinical Study Experience

17. Is currently participating in or has previously participated in an interventional clinical study within the 3 months before Screening.

Diagnostic Assessments

18. Has MHIS >4 at Screening.

19. Has laboratory or clinical evidence of clinically significant hepatic conditions such as one or more of the following:

    ALT ≥1.5 × ULN at Screening* or

    AST ≥2 × ULN at Screening*

    *Note: Participants may be retested 1 time at least 1 day after initial Screening bloodwork.

20. Has liver disease, including but not limited to chronic viral hepatitis, nonviral hepatitis, cirrhosis, malignancies, autoimmune liver diseases (eg, autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis).

21. Has known renal disease or is experiencing renal insufficiency as defined by eGFR <30 mL/min/1.73 m^2 (MDRD) at Screening).

22. Has an abnormal TSH value at Visit 1 (Screening). Exception: A participant with an abnormal TSH value and a normal FT4 value may be eligible if clinically stable and without signs of hypo- or hyperthyroidism, in the investigator's judgment. Any thyroid treatment must be stable for ≥3 months before Visit 1 (Screening).

Other Exclusions

23. Resides in a nursing home or assisted care facility with need for direct continuous medical care and nursing supervision. Participant may reside in such facilities provided continuous direct medical care is not required and a qualified study partner is available for coparticipation and the participant is physically able to attend all required study visits.

24. Had major surgical procedure or donated or lost >1 unit of blood (approximately 500 mL) within the 4 weeks before Screening.

25. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, trial partner or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will refrain from consuming grapefruit juice, grapefruits, and grapefruit products from Screening through Visit 8 (EOT/DC Visit). Other types of fruit juice, fruits, and fruit products are permitted during the study. Sites should instruct participants to take study intervention with water.

The participant should fast for at least 1 hour before and 1 hour after dosing with study intervention.

Evening dosing: Participants should take their evening dose of study intervention close to bedtime, at least 1 hour after the evening meal, and should continue to fast for at least 1 hour after dosing.

Morning dosing (days with no clinic visit and Visit 4, Visit 5, Visit 7, Visit 8): Participants should take their morning dose of study intervention at least 1 hour after a light breakfast, and should continue to fast for at least 1 hour after dosing.

Morning dosing (Visit 3 and Visit 6): participants must NOT take a morning dose of study intervention from the blister cards dispensed at the previous visit. A light breakfast (eg, a slice of toast with low fat spread, a cup of skim or 1% milk, a cup of nonfat yogurt, a packet of oatmeal made with water, or a piece of fruit [except grapefruit]) can be eaten at least 1 hour before dosing at these visits to minimize hunger. Participants should NOT eat a meal until at least 1 hour after taking study intervention from the new blister cards dispensed in the clinic.

For details of timing of visits, see Section 8.11.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will abstain from alcohol for 24 hours before each visit.

5.3.3 Activity Restrictions

Participants will be informed about the risk of dizziness with MK-1942 treatment and instructed not to drive or operate heavy machinery until they determine that study intervention, taken as directed, does not affect their ability to engage in these activities.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2. Country-specific differences are noted in Appendix.7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
MK-1942 5 mg	Experimental	MK-1942	Drug	Capsule	5 mg	5 mg bid	Oral	Weeks 1-12	Test Product	IMP	Central
MK-1942 15 mg	Experimental	MK-1942	Drug	Capsule	8 mg	8 mg bid	Oral	Week 1	Test Product	IMP	Central
MK-1942 15 mg	Experimental	MK-1942	Drug	Capsule	15 mg	15mg bid	Oral	Weeks 2-12	Test Product	IMP	Central
Placebo	Placebo Comparator	Placebo	Drug	Capsule	0 mg	0 mg bid	Oral	Weeks 1-12	Placebo	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible.

Refer to Section 8.1.10 for details regarding administration of the study intervention.

6.1.1 Medical Devices

No medical devices are used in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio to MK-1942 5 mg bid, MK-1942 15 mg bid, or placebo bid, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

2. MMSE ≤16, ≥17

3. Region (US/Canada, LATAM, Japan/South Korea, Europe/Australia/NZ)

Note that no more than approximately 60% of participants are to be enrolled in each MMSE stratum.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-1942 and placebo will be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for >3 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Study partners will be directed to bring all dispensed blister cards to each visit. Compliance will be assessed by direct questioning, review of Study Medication Guidance, and counting returned capsules in blister cards during the site visits and documented in the source documents. Deviation(s) from the prescribed dosage regimen should be documented.

- Participants and study partners will also be reminded that the participant must continue their AD therapy.

- A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose interruptions will also be recorded in the CRF according to data entry guidelines.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

- Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded according to the data entry guidelines.

- Concomitant use of memantine is allowed as long as the participant is on an approved and stable dose ≥3 months before first dose of study intervention and throughout the study.

- Concomitant use of products including THC and CBD is allowed provided that it is not taken within 3 days before cognitive testing.

- Concomitant use of atypical antipsychotics is allowed as long as the participant is on a stable dose ≥6 weeks before first dose of study intervention.

- Concomitant use of long-term steroids (≥6 weeks) is allowed with doses of prednisone up to 10 mg/day or equivalent.

- Concomitant use of short-term steroids at higher doses (<6 weeks) is allowed.

    - Note that local injections into joints or bursae; topical, inhaled or nasal use is permitted.

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

For country-specific requirements, see Appendix 7.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration)

As described in Section 4.1 and shown in Section 1.2, the dose of MK-1942 for participants in the 15-mg dose group will be up-titrated as follows: 8 mg bid (Visit 2/Day 1) and 15 mg bid (Visit 3/Week 1 to Visit 8/Week 12). The 5-mg dose of MK-1942 does not require titration. Participants in the placebo group will not receive treatment with MK-1942.

If a participant experiences clinically relevant tolerability issues, one of the 2 daily doses (morning or evening) can be held at the discretion of the investigator for a brief period (1-2 days) as needed. Every effort should be made to return to bid dosing as soon as possible. The expectation is for the investigator to hold doses only when necessary, as achieving steady state is important for long-term tolerability and interpretation of the study results. The dose modification and reason for the dose modification is to be documented in source documents. If a dose is held for an AE, then it is to be recorded as such and not recorded as a compliance issue. Compliance is described in Section 6.4.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.15). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant's study partner is no longer willing or able to participate in the study and a suitable replacement study partner cannot be identified within a reasonable period.
- The participant is unable to tolerate study intervention after being up-titrated at Visit 3 (See Section 6.6).
- The participant has an ALT ≥3 × ULN
- The participant has an AST ≥3 × ULN with a total bilirubin ≥2 × ULN and ALP <2 × ULN
- The participant has an AST ≥3 × ULN with ALT value >100 IU/L

  Note 1: Such observed elevations in liver function tests should be confirmed by repeat testing within 48 hours of initial test results. If test results are unable to be confirmed within this timeframe, the study intervention should be withheld until test results are available. Study intervention should be discontinued if unable to repeat testing.

  Note 2: If the investigator identifies a clear cause for the liver enzyme elevations unrelated to study intervention, then study intervention may be continued with approval by the Sponsor.

- The participant meets either of the following criteria for QTcF interval at a visit (**Note**: ECGs will be performed in triplicate [Section 8.3.4]):
  - The average of the 3 QTcF intervals based on either the local ECG printout or subsequent central vendor overread is >500 msec.
  - The average of the 3 QTcF intervals based on either the local ECG printout or subsequent central vendor overread increased by >60 msec, relative to the central vendor overread average at Visit 2 (Day 1).

- The participant begins to use a prohibited medication/therapy/product or a prohibited dose of an allowed medication listed in Section 5.2 (Concomitant Medications, Table 1) that presents a safety concern in the investigator's judgment.

Note: Participants who are willing and able to safely (per the investigator) stop using the prohibited medication/therapy/product or reduce from a prohibited to an acceptable dose for an allowed medication through Visit 8 (Week 12) may continue study intervention at the investigator's discretion.

- The participant reports suicidal ideation with intent, with or without a plan or method through an AE or C-SSRS assessment (ie, a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior. If the reported suicidal ideation is passive, and participant expressly denies any intent to act, and who, after evaluation, is not judged to be at serious risk for self-harm during the study, the participant may continue on study intervention. Refer to Section 8.3.6.1 on Clinical Assessments for Suicidal Ideation and Behavior Monitoring (for requirements pertaining to the evaluation of such events), and Section 8.4.7 for Events of Clinical Interest.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.14. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The approximate amount of blood collected from each participant over the duration of the study will be 128 ml (Appendix 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. Documented consent from each participant's study partner (referred to as study partner consent) will also be obtained by the investigator or qualified designee. If there are changes to the participant's/study partner's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion. Study partner consent will similarly be documented by the study partner's dated signature on a consent form and the dated signature of the person conducting the consent discussion.

A copy of the signed and dated informed consent forms (participant and study partner consents) should be given to the participant (or their legally acceptable representative) and study partner before participation in the study.

The initial participant and study partner ICFs, any subsequent revised ICFs, and any written information provided to the participant/study partner must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative and the participant's study partner should be informed in a timely manner if new information becomes available that may be relevant to the participant's/study partner's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's or the study partner's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related

to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

Active medical conditions, detailed neurological history, and other relevant medical history within the last 5 years will be obtained by the investigator or qualified designee.

Clinically significant findings in physical examination, laboratory tests, ECGs, and other physical evaluations during Screening are to be noted in the medical history. Clinically significant changes from the screening evaluation during the study should be captured as AEs.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medications for AD dementia taken by the participant within 1 year before Screening. Other prior medications taken by the participant within 3 months before Screening will also be recorded. The investigator or qualified designee will also review for history of anti-amyloid antibodies, as these have lifetime exclusions (Table 1).

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Participants are to remain on their fixed/unchanged course of background AChEI therapy from Screening through Visit 9 as follows:

- Donepezil 5 or 10 mg/day (capsule or tablet)
- Donepezil 23 mg SR/day
- Rivastigmine 6 or 12 mg/day (capsule or tablet)
- Rivastigmine 9.5 mg or 13.3 mg/24 hours (patch)
- Galantamine 16 or 24 mg/day (capsule or tablet)

Note that other approved formulations are acceptable as long as dose ranges are consistent with those noted in this protocol.

Participants taking memantine should also continue stable therapy at approved dose until Visit 9.

Prohibited medications/therapies/products and prohibited doses for allowed medications listed in Table 1 should not be administered from the indicated period before Screening to Visit 9 (Postdose Follow-up Visit).

The list of prohibited medications/therapies/products in Table 1 is not comprehensive. Investigators should use their medical judgment when a participant presents with a treatment that meets a prohibited category, but is not on the list or contact the Sponsor for clarification.

8.1.6 Diagnostic Assessment and External Verification of Diagnosis

Note that the investigator should take a comprehensive history and summarize in the DxV for the vendor. A Rater Training Vendor will be used to confirm that each participant randomized to study intervention meets entry criteria for probable AD dementia. To support confirmation of eligibility, the site will submit information for each participant to the Rater Training Vendor rater during the pretreatment period (Section 8.11.1.1). The required materials are specified in a diagnostic verification form.

A participant is not eligible for randomization until confirmation of eligibility is provided by the Rater Training Vendor who will approve randomization in IRT.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.9 IRT Visit Registration, IRT Randomization, and Study Intervention Dispensing

The investigator (or designee) will register the participant in IRT at the visits specified in the SoA. Participants who satisfy all entry criteria will be assigned a randomization number via IRT at Visit 2 (Day 1). Participants who do not meet eligibility criteria will be entered into IRT as screen failures. IRT will also be used to identify the study intervention supplies that will be dispensed to participants at the visits specified in the SoA. Refer to the IRT user manual for details about the IRT system.

8.1.10 Study Intervention Administration

Blinded study intervention will be administered as oral capsules and packaged in blister cards. At Visit 2 (Day 1), participants and study partners will be educated by a trained member of the site staff on appropriate dosing and fasting instructions (see Section 5.3.1), package opening, and the requirement to return all blister cards at each visit. At Visit 2 (Day 1). Sites will provide participants/study partners with a copy of the Study Medication Guidance and train participants on how to use the guide. Sites will be expected to review this guide during each treatment visit (Visit 3 to Visit 8) and provide retraining, as needed. Documentation of participant/study partner training will be filed with the participant's source documents.

Details on appropriate handling, storage, and accountability of study intervention are provided in Section 6.2.2.

8.1.10.1 Timing of Dose Administration

The first dose of blinded study intervention will be witnessed (see Section 8.1.11) in the clinic at Visit 2 (Day 1) after all assessments and procedures as specified in the SoA are complete. The next dose of blinded study intervention will be taken at home with supervision from the study partner in the evening after Visit 2 (Day 1).

For Visit 4, Visit 5, Visit 7, and Visit 8 during the treatment period, administration of study intervention will continue to occur at home with supervision by the study partner at approximately the same time in the morning and approximately the same time in evening.

On days with scheduled clinic visits during the titration period (Visit 3) and Visit 6, participants must not take a morning dose of study intervention from the blister cards dispensed at the previous visit. Participants will take their morning dose of study intervention in the clinic from the newly dispensed blister cards.

Dosing guidelines relative to meals are provided in Section 5.3.1. If a participant accidentally misses a dose of study intervention in the morning or evening, the missed dose should be taken as soon as possible. If more than 6 hours have passed since the participant's normal morning or evening dosing time, then the missed dose should be skipped, and the next dose should be taken as normal. Participants should refer to the Study Medication Guidance for further information.

8.1.11 Witnessed Dose

Administration of study intervention will be witnessed by a trained member of the site staff at visits specified in the SoA. At Visit 6, the witnessed dose will occur after the first PK sample collection, but before assessments for the visit. For the other visits, each witnessed dose will be taken after assessments and procedures for the visit are complete. The time of dosing will be recorded for any witnessed dose and for the last 3 doses of study intervention before PK sample collection.

8.1.12 Study Intervention Accountability

Accounting for compliance and adherence with study intervention is described in Section 6.4.

8.1.13 Telephone Contacts (Site to Study Partner)

A telephone contact will be performed 2-4 days after Visits 2 and 3, by trained site personnel to monitor for AEs and compliance with study intervention and to encourage adherence with the fasting guidelines (Section 5.3.1). Additional telephone contacts/visits may be scheduled at the investigator's discretion.

The investigator is responsible for ensuring that all telephone contacts are performed by trained site personnel (eg, a staff member who is a health care professional qualified to elicit a discussion with the study partner that will lead to a clinically meaningful disclosure on the participant's well-being). Telephone contacts are to be documented in the source documents, and the investigator must review the entry within 2 business days. However, if the study partner reports any clinically concerning events for the participant (eg, SAEs, ECIs) during a telephone call, then the investigator must be promptly notified. The investigator will contact the participant to determine whether a clinic visit is warranted.

If the study partner cannot be reached by telephone at the regularly scheduled time or misses a visit, the site should make at least 3 attempts (in addition to the initial phone call) to contact

the study partner within 48 hours of the missed scheduled time. All phone contacts and attempts should be recorded in source documents.

8.1.14 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.4.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT/DC visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.14.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.15 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the

intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.16 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/QoL/Screening Assessments

Rating scale assessments at clinic visits will be performed by site raters who meet the qualification and training requirements per scale. Rater qualifications, training, and applicable certification processes are established in a separate document. Each assessment scale may require different raters, but it is strongly encouraged that the same rater evaluates the same participant for the duration of the study. As a best practice, back-up raters should be identified for each participant to improve continuity and reliability of the ratings.

To avoid the influence of participant fatigue on the diagnostic and primary outcome data, the recommended order of assessments is to perform the MMSE as the first clinical assessment at Screening to assess eligibility. At baseline (Visit 2) and later visits, the ADAS-Cog is to be conducted first, followed by shorter tests, such as CERAD Verbal Fluency Test, COWAT, Trail Making Tests, Coding, and MMSE. The ADCS-CGIC is recommended as the last clinical efficacy assessment so that all relevant information can be reviewed when completing the ADCS-CGIC.

Assessments will be performed at Screening for ADAS-Cog, CERAD Verbal Fluency Test, COWAT, Coding, and Trail Making Test to minimize practice effects before baseline (Visit 2) assessments are conducted at Visit 2.

The following assessments may be audio recorded by sites for submission and review by a central rater vendor: MMSE, ADCS-ADL, ADCS-CGIC, ADAS-Cog13, NPI-Q, CERAD Verbal Fluency Test, COWAT, Trail Making Tests, and/or Coding. Some or all of the recorded interviews will be reviewed and scored by an external expert. The external expert will provide feedback to the site raters on the quality of the site rater interviews and ratings to help develop and maintain good interrater reliability. Additionally, the external expert feedback may be used to refine the scores entered by the site for an individual rating, at the discretion of the site rater.

While concerns have been raised that recording assessments via audiotaping or videotaping could theoretically compromise participant privacy, this issue must be balanced with the need to conduct methodologically adequate and scientifically rigorous trials that are capable of testing key hypotheses. Given that the key endpoints in this study involve subjective clinical judgments, monitoring the adequacy of participant interviews and ratings is essential and part of strong research methodology. Prior studies suggest that the failure to adequately monitor such ratings can substantially increase the risk of failed trials [Khan, A., et al 2013]. Recorded interviews will be encrypted using state-of-the-art methods to ensure privacy. Additional steps will be taken to ensure anonymity of specific private health information. Recordings will be reviewed only by approved study personnel for quality control purposes and will be destroyed in accordance with current retention requirements. Additional details are provided in a vendor operations manual.

8.2.1 Participant Assessed

8.2.1.1 MMSE

The MMSE is a brief 30-point questionnaire electronically administered and used to assess cognitive impairment with lower scores indicating greater impairment [Folstein, M. F., et al 1975]. The MMSE assesses 11 categories of cognition including orientation to time, memory, attention, concentration, naming, repetition, comprehension, and the ability to create a sentence and to copy 2 intersecting polygons. These assessments will be used as an exploratory cognitive measure of clinical effect. The Screening MMSE will be used for purposes of determining participant enrollment.

8.2.1.2 Modified Hachinski Ischemia Scale

The MHIS, [Rosen, W. G., et al 1980] a tool to identify the possibility of a vascular etiology for the participant's dementia, will be completed based on history obtained from the participant and study partner, physical and neurological examinations, and/or medical records. The MHIS will be completed electronically.

8.2.1.3 ADAS-Cog

The ADAS-Cog11 [Rosen, W. G., et al 1984] is a structured scale that evaluates memory, orientation, attention, reasoning, language, and constructional praxis. Higher scores indicate greater impairment. These assessments will be used as the primary cognitive measure of clinical effect and will be electronically administered.

The ADAS-Cog11 includes Word Recall, Commands, Constructional Praxis, Naming Objects and Fingers, Ideational Praxis, Orientation, Word Recognition, Remembering Test Instructions, Spoken Language Ability, Word-Finding Difficulty, and Comprehension of Spoken Language.

The ADAS-Cog13 [Petersen, R. C., et al 2001], which includes the optional performance items of Delayed Word Recall and Number Cancellation as well as the traditional 11 items, will be administered to every participant; however, the ADAS-Cog11 will be used as the primary efficacy endpoint.

8.2.1.4 CERAD Verbal Fluency Test

The CERAD Verbal Fluency Test [Morris, J. C., et al 1989], a brief paper/pencil measure of semantic processing and executive functioning. This protocol will use animal naming only (test of semantic fluency).

8.2.1.5 Controlled Oral Word Association Test

The COWAT is a short, paper/pencil measure of phonemic fluency and executive functioning from the Multilingual Aphasia Examination [Schum, R., et al 1989].

8.2.1.6 Coding

The Coding subtest of the Wechsler Adult Intelligence Scale-IV is a brief paper/pencil task assessing attention, psychomotor speed and visuomotor coordination [Wechsler, D. 1981].

8.2.1.7 Trail Making Test

The Trail Making Test is a brief paper/pencil assessment of visual scanning (Part A) and visuomotor sequencing (Part B) [Reitan, R. M. 1955] [Reitan, R. M. and Wolfson, D. 1985].

8.2.2 ADCS-CGIC

The ADCS-CGIC [Becker, R. 1996] is a global scale assessing cognition and function based on structured interviews of both the participant and study partner. Two versions will be used (baseline and follow-up) and administered electronically. The clinician makes a judgment as to whether the participant is improved or worsened as compared with baseline.

8.2.3 Study Partner Assessed

8.2.3.1 ADCS-ADL

The ADCS-ADL [Galasko, D., et al 1997] assesses the competence of participants with AD dementia in basic and instrumental activities of daily living (ADLs). It will be administered electronically to the participant's study partner. All responses should relate to the 4 weeks before the time of rating. Each ADL item takes an ADL (eg, eating) and provide descriptions of level of competence with the rater selecting the most appropriate option (eg, ate without physical help and used a knife; used a fork or spoon, but not a knife; used fingers to eat; was usually or always fed by someone else).

8.2.3.2 Neuropsychiatric Inventory - Questionnaire (NPI-Q)

The NPI-Q is adapted from the NPI [Cummings, J. L., et al 1994] a validated informant-based interview that assesses NPS over the previous month. It assesses the same 12 behavioral symptoms as the NPI; however, the NPI-Q assesses only the severity of NPS and caregiver distress. These assessments will be used as a secondary behavioral measure of clinical effect and will be administered electronically.

This study uses the NPI version with 12 behavioral domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating.

The NPI-Q provides symptom severity and distress ratings for each symptom reported, and total severity and distress scores reflecting the sum of individual domain scores. The severity scale has scores ranging from 1 to 3 points and the scale for assessing caregiver distress has scores ranging from 0 to 5 points. The total NPI-Q severity score is the sum of the individual severity scores for each symptom and ranges from 0 to 36, with higher scores indicating more severe behavioral impairment. The total NPI-Q distress score is the sum of the individual distress scores for each symptom and ranges from 0 to 60, with higher scores indicating greater distress.

8.2.3.3 EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D-5L)

The EuroQol 5D-5L [Herdman, M., et al 2011] is a standardized instrument for use as a measure of health outcome. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from "no problem" to "extreme problem." Two different administrations of the EQ-5D-5L will be performed at time points according to the SoA. First, the caregiver will electronically provide a self-report of his or her own health status. Second, the participant's caregiver will electronically provide a proxy-rating of the participant's health status. In both situations, the EQ-5D-5L questionnaire will be completed by the participant's caregiver.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examination

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. The investigator (or qualified designee, consistent with local requirements) will perform the examinations of the following organ systems:

- Head, eyes, ears, nose, and throat
- Neck
- Respiratory system
- Cardiovascular system
- Abdomen
- Skin and extremities
- General appearance

8.3.2 Neurological Examination

The general neurological examination includes all of the following:

- Cranial nerve assessment
- Motor system
- Reflexes
- Coordination and gait
- Sensory system
- Abnormal movements

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any medical conditions found during the physical and neurological examinations will be recorded in the Sponsor database.

8.3.3 Vital Signs, Height, and Weight

- Vital signs will be measured in a semisupine position after 5 minutes' rest and include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.
- It is recommended that individual sites use the same method for measuring temperature (eg, oral, tympanic) in all participants throughout the study.

- For blood pressure readings, the correct size of the blood pressure cuff and correct positioning on the participant's arm is essential for accurate measurements. It is recommended that individual sites use the same method (manual or automated) for measuring blood pressure and pulse throughout the study.

- Height (cm/in) and body weight (kg/lbs) will be collected and recorded. Measurements should be recorded to the nearest centimeter/inch and kilogram/pound. Body weight data will be collected without shoes and with heavy clothing (such as coats) removed. The site should follow their local procedures to ensure the body weight scale is working properly.

8.3.4 Electrocardiograms

Twelve-lead ECGs will be performed when the participant is in the supine position after 5 to 10 minutes of rest using a central ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTcF intervals according to the instructions in a separate ECG instruction manual. Cardiologist overread will be provided by the central ECG vendor.

All scheduled ECGs will be performed in triplicate. ECG measurements should be obtained in close succession, ie, less than 2 minutes apart, with all 3 measurements completed in less than 4 minutes.

At Screening, the average of the 3 QTcF intervals based on the central vendor overread will be used to assess eligibility. At Visit 2 (Day 1), the average of the 3 QTcF intervals based on the local ECG printout will be used to assess eligibility (Section 5.2).

During the double-blind treatment period, participants will discontinue study intervention if the average of the 3 QTcF intervals at a visit is either >500 msec or increases by >60 msec relative to Visit 2 (Day 1). Details on discontinuation of study intervention due to QTcF results are in Section 7.1.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are

considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention or through completion of Visit 9, whichever is late, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Suicidal Ideation and Behavior Monitoring

8.3.6.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at specified time points, as indicated in the SoA, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness.

If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, before their assessment of the participant and to further inform their evaluation.

The C-SSRS is not explicit about whether the participant specifically has ideation at the time of Screening. If a participant reports a prior history of ideation/behavior, the assessor should also inquire and document if this is also present at the time of the Screening Visit.

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). After that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety. In addition, all AEs of suicidal ideation or behavior must be recorded as an ECI (See Section 8.4.7). Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation/randomization through 14 days after cessation of study intervention, or through the completion of Visit 9, whichever is later, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - hepatic-related events listed in Section 8.4.7 - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-hepatic-related events as listed in Section 8.4.7 (unless serious) - do not require regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Not applicable.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Elevated AST ≥3x ULN
2. Elevated ALT ≥2x ULN or twice the baseline value
3. Elevated total bilirubin ≥2x ULN with ALP <2x ULN
4. AEs of dizziness that are rated by the investigator as being moderate or severe in intensity
5. AEs related to gait disturbance (if not already captured in the narrative of AEs related to moderate or severe dizziness)
6. AEs of falls (if not already captured in the narrative of AEs related to moderate or severe dizziness)
7. AEs of suicidal ideation and/or behavior or any self-injurious behavior
8. QTcF interval meeting either of the criteria specified for study intervention discontinuation (Section 7.1)

Note that the above AEs are classified as ECIs only after the first dose of study intervention is administered. An AE of fall or gait disturbance must be reported as an ECI unless associated with moderate or severe dizziness and fully described in that ECI narrative. Sites should refer to the study ECI guidance document for details on assessment and follow-up including follow-up on elevated liver function tests that met ECI criteria as assessed at Visit 9.

8.5 Treatment of Overdose

In this study, an overdose is defined as more than 3 capsules on a calendar day.

No specific information is available on the treatment of overdose of MK-1942.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK sampling information is displayed in Table 4.

Table 4 PK Sampling Information

PK Sample #	PK sample name	PK Collection Day	PK Collection Time Window
1	MK-1942 PK sample/Placebo	Visit 2 (Day 1)	Any time before first dose
2	AChEI Plasma PK sample	Visit 2 (Day 1)	Any time before first dose
3	Memantine Plasma PK sample	Visit 2 (Day 1)	Any time before first dose
4	MK-1942 PK sample/Placebo	Visit 6 (Day 43)	Two PK samples to be drawn 1) predose and prescheduled assessments 2) postdose and post scheduled assessments (2-3 hours) Note: at this visit the participant will be given a witnessed dose of study medication after the first PK draw
5	AChEI Plasma PK sample	Visit 6 (Day 43)	After all scheduled assessments and at the time of postdose MK sample
6	Memantine Plasma PK sample	Visit 6 (Day 43)	After all scheduled assessments and at the time of postdose MK sample
7	MK-1942 PK sample/Placebo	Visit 8	After all cognitive assessments have been performed
8	AChEI Plasma PK sample	Visit 8	After all cognitive assessments have been performed
9	Memantine Plasma PK sample	Visit 8	After all cognitive assessments have been performed

PK=pharmacokinetic; V=visit
Note: sites to record the time of dose of MK-1942/Placebo for the last 3 doses before PK sample draw

PK collection is not required once the participant discontinues study intervention treatment. If a participant discontinues before Visit 8, then the last PK sample is collected at any time during the EOT visit. Blood samples collected may be stored and further analyses may be performed, if required.

8.6.1 Blood Collection for Plasma MK-1942

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Operations/Laboratory Manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Plasma for exploratory research

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C19/APOE4 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C19/APOE4. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Leftover plasma for exploratory research

8.10 Health Economics Medical Resource Utilization and Health Economics

Health Economics, Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.1.

Study Partner Specifics

The study partner:

- Is not diagnosed with dementia.
- Provides their own documented informed consent after the study has been explained to them.
- Accompanies the participant to all study visits and participates in study telephone contacts.
- Assesses side effects or corroborates any safety signals.
- Assumes responsibility for study intervention procedures (eg, witnessing and/or helping to administer study medication, assessing compliance, review/completion of Study Medication Guidance).
- Completes assessments specified in the protocol (eg, ADCS-ADL NPI-Q, EQ-5D-5L)

Every effort should be made to maintain the same study partner for the duration of the study. However, if the study partner is unable to continue with the study requirements, the study partner should discuss with the site whether a suitable replacement can be found. If a new study partner is identified, the new study partner will need to sign the study partner informed consent.

Scheduling Visits

It is preferable for visits to be scheduled at about the same time of day in the mornings for consistency, and for in-clinic visits, to minimize prolonged fasting durations (fasting guidance is provided in Section 5.3.1). Afternoon clinic visits are not preferred, but may be performed if morning visits are not feasible for participants. Participants with afternoon clinic visits should be scheduled at about the same time of day in the afternoon for consistency. See study operations manual for more information on afternoon clinic visits.

A visit should occur within the scheduling window shown in the SoA. Visits during the double-blind treatment period should be scheduled relative to Visit 2 (Day 1), regardless of the actual day the previous visit occurred on. If any visits deviate from the schedule, an attempt should be made to follow the original visit schedule for subsequent visits.

Visit Reminders

During the double-blind treatment period, it is recommended that site personnel contact participants/study partners on the day before each clinic visit to remind participants to (1) fast according to Section 5.3.1, (2) hold their morning doses of study intervention from the blister cards dispensed at the previous visit (up-titration visit [Visit 3] and Visit 6), (3) bring their

opened and unopened blister cards to the visit (not applicable at Visit 2 [Day 1]), and (4) bring their Study Medication Guidance (not applicable at Visit 2 [Day 1]).

8.11.1 Screening

Approximately 12 weeks before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

Screening could take up to 12 weeks to complete the full assessment of the participant's eligibility requirements (eg, MRI scan via central reader, MMSE review by Rater Training Vendor, prohibited medication washout). Assessments that are to be reviewed by the Rater Training Vendor, such as the MMSE, should be sent to the Rater Training Vendor as soon as possible (ie, same day that assessment was performed) so specific eligibility criteria can be determined, and the results can be sent back to the site in a timely manner. Once final eligibility is determined, the participant's Visit 2 should be scheduled to occur as soon as possible.

For country-specific requirements, see Appendix 7.

Split Screening Visit Option

To reduce participant burden, Screening may be split into more than 1 day. If this screening option is chosen, it is required that documented informed consent for the main study is obtained (Section 8.1.1.1) and a screening number is assigned (Section 8.1.7) on the first day of Screening.

Prohibited medications will be discontinued in accordance with Table 1. If a participant requires a washout for a prohibited medication, an abbreviated Screening may be performed (eg, obtain informed consent, review medical history, preliminary review of inclusion/exclusion criteria, review of prior and concomitant medications, assignment of a screening number). After the participant has completed the specified washout, the participant will return to complete the remaining Screening procedures. Once the participant has fully completed Screening and eligibility has been confirmed, the participant may proceed to Visit 2 per protocol.

Rescreening

In some circumstances, participants who are excluded may be rescreened once per investigator judgment. Consultation with the Sponsor or its designee should take place before any additional rescreening. All rescreening should be documented, and rescreening will be reviewed on an individual basis. Note: Repeat MMSE is acceptable, but may not be completed for at least 6 months for participants whose score is above the upper range for inclusion.

Additional details on rescreening procedures and other reasons for rescreening are described in the study operations manual.

Ordering of Procedures/Assessments:

Below is a recommended guide on the ordering of procedures/assessments (non-inclusive), when applicable, for Screening:

- Administrative Procedures
- Cognitive/clinical assessments
- Physical and neurological examinations
- Vital signs, ECGs, laboratory test results
- MRI

Additional information regarding procedures for clinical and cognitive assessments, including the preferred order of administration for cognitive and clinical assessments will be specified in Rater Training Vendor documentation and training.

8.11.1.1 Rater Training Vendor Review of Participant Eligibility

This study will include a review by outside expert(s) associated with the Rater Training Vendor of each participant before randomization. Participants cannot be randomized without the approval of the Rater Training Vendor. This review may include all available medically relevant data, a narrative summary of the participant's history, and audiotapes of key clinical and cognitive assessments performed at the Screening Visit. These assessments may include the MMSE and/or the ADAS-Cog13 assessments.

The DxV is a questionnaire to ensure that participants are enrolled on the basis of objectively ascertained and well-documented diagnosis of probable AD dementia. The DxV is to be completed by the site investigator, requiring their review of the key study entry criteria at the Screening Visit. The DxV also collects additional information that supports the NINCDS-ADRDA (1984) criteria [McKhann, G., et al 1984] such as the clinical history, neuropsychological testing, other supportive diagnostic information, and facilitates timely review of the site-based assessments by site-independent clinicians.

The Rater Training Vendor will inform the site if a participant is eligible before Visit 2 (Day 1). Participants who do not meet eligibility criteria will be screen-failed.

8.11.1.2 MRI

To evaluate the eligibility criteria, each participant must have either: an MRI scan performed during the Screening period or a previous MRI performed within 18 months before the Screening Visit that is available for review by the blinded independent central reviewing vendor. A head CT scan without contrast obtained at Screening or within 18 months before Screening may be accepted instead of MRI on a case-by-case basis, as approved by the Sponsor (eg, when MRI is contraindicated for the participant); if applicable, the CT scan

must also be available for blinded independent central review per Imaging Charter. If a new MRI needs to be performed for Screening, the scan should be scheduled to occur during the screening period after the participant has met all the inclusion and exclusion criteria that do not require an MRI.

8.11.2 Treatment Period

Each visit should be performed as specified in the SoA.

Participants who satisfy all entry criteria will be randomized (via IRT) to double-blind study intervention at Visit 2 (Day 1). Participants and study partners will be educated by a trained member of the site staff on appropriate dosing instructions (including missed doses, Section 8.1.10) and fasting guidance (Section 5.3.1). The first dose of study intervention will be witnessed by a member of the site staff in the clinic. Witnessed dosing will continue at the up-titration visit (Visit 3) and Visit 6.

A telephone contact will be performed 2-4 days after Visits 2 and 3, by trained site personnel (Section 8.1.13) to monitor for AEs and compliance with study intervention and to encourage adherence with the fasting guidelines (Section 5.3.1). Additional telephone contacts/visits may be scheduled at the investigator's discretion.

There may be instances where visit procedures are conducted over more than 1 day provided that they are completed within the allowed window (see SoA).

If there are extenuating circumstances where time does not enable an entire scheduled clinic visit, remote assessments for study partners only may be done, if allowed by local regulations, in accordance with Sponsor guidelines. In addition, the C-SSRS can be remotely completed with the participant. See Rater Training Vendor documentation and training for specific guidelines.

8.11.3 EOT/DC Visit

EOT/DC Visit procedures specified in the SoA will be performed at the end of the treatment period (Visit 8 [Week 12]). Additionally, participants who discontinue study intervention prematurely should have an EOT/DC Visit as soon as possible after the decision to discontinue study intervention is made and should also complete a 14-day postdose follow-up visit for laboratory assessments if possible. For participants who discontinue study intervention prematurely, prohibited medications/products/therapies (Table 1) can be started after the EOT/DC Visit.

8.11.4 Participants Discontinued From Study Intervention but Continuing to Be Monitored in the Study

Any participant who prematurely discontinues study intervention will be encouraged to continue their participation in the study off study intervention and be followed up for all remaining study visits (Section 7.1) as outlined in the SoA. The subsequent scheduled visit may be skipped if within 7 days of the DC visit. Note that PK samples will not be collected if

a participant discontinues study intervention. In addition, the postdose follow-up visit (Visit 9) does not need to be conducted for participants who discontinue study intervention and are continuing to be monitored in the study, as long as safety follow-up has been completed through 14 days after last dose.

If a participant discontinues study intervention prematurely (before Visit 8) and continues with study visits off study intervention, an EOT/DC visit will still be completed as indicated in the SoA. If the participant subsequently discontinues the study (before Visit 8), a study DC visit will be conducted at that time with the same procedures as the EOT visit.

8.11.5 Postdose Follow-up Visit

Visit procedures specified in the SoA will be performed at the Postdose Follow-up visit (Visit 9). Participants will be off study intervention; therefore, there are no fasting requirements associated with this visit. If needed, instead of a site visit, Visit 9 laboratory assessments may be performed at a local laboratory and Visit 9 nonlaboratory assessments may be performed by TC.

8.11.6 Poststudy

Participants will not be followed up after completion of the postdose follow-up visit.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but before any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data, patient-reported outcomes, and future biomedical research) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 2a/2b Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of MK-1942 as Adjunctive Therapy in Participants with Mild to Moderate Alzheimer's Disease Dementia
Treatment Assignment	The study will be conducted as a double-blind study under in-house blinding procedures. Treatment randomization will occur centrally using an IRT. Participants will be assigned randomly in a 1:1:1 ratio to one of the 2 MK-1942 doses or the placebo. The randomization will be stratified by AD dementia severity via baseline MMSE (≤16, ≥17) and geographic region (US/Canada, LATAM, Japan/South Korea, Europe/Australia/NZ).
Analysis Populations	Efficacy: FAS Safety: APaT PK: PP
Primary Endpoint(s)	The primary endpoint is the change from baseline in ADAS-Cog11 at Week 12.
Key Secondary Endpoints	The key secondary endpoint is the ADCS-CGIC Overall score at Week 12.
Statistical Methods for Key Efficacy	The primary hypothesis will be evaluated by comparing each MK-1942 dose to placebo with respect to mean change from baseline in ADAS-Cog11 score at Week 12 using a longitudinal ANCOVA model.
Statistical Methods for Key Safety Analyses	For overall safety endpoints, specific AEs and safety topics of special interest that meet predefined threshold rules, point estimates, and 95% CIs for the differences between treatment groups in the percentage of participants with events will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	Two types of interim analyses may be performed in this study. Results will be reviewed by an eDMC. These interim analyses are summarized below. Additional details are provided in Section 9.7. The first type of interim analysis will be for safety only and will be conducted approximately every 4 to 6 months, with the frequency subject to change per eDMC recommendation. In addition, a nonbinding futility IA may be performed when the first 50% of randomized participants have had the opportunity to treat for 12 weeks (ie, the IA will be based on a data cutoff that is 12 weeks after the randomization of the 204th participant). Results will be reviewed by an eDMC. Futility may be declared if the Bayesian predictive conditional probability for the primary hypothesis based on the CFB in ADAS-Cog11 at Week 12 is less than 15% for both between-treatment comparisons (MK-1942 5 mg vs placebo and MK-1942 15 mg vs placebo). Details are provided in Section 9.7.
Multiplicity	The Type-I error rate over the multiple treatment comparisons will be controlled using a Bonferroni procedure (across dose comparisons with placebo), in conjunction with sequential testing over the multiple endpoints (see Figure 2).

Sample Size and Power	The planned sample size is 408 participants, with 136 participants per arm. The study has ~90% power to show at least 1 MK-1942 dose is superior to the placebo as measured by the CFB in ADAS-Cog11 at Week 12 under the primary assumptions as provided in Section 9.9.1, at an overall two-sided 5% alpha-level.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Participants are considered to have finished the study when they complete the last study-related telephone call or visit, withdraw from the study, or are lost to follow-up.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.3.1 Estimands

In the language of ICH E9 (R1) [Food and Drug Administration 2021] there are 3 "intercurrent events" of interest: IE1) discontinuation of MK-1942 or placebo, IE2) discontinuation of stable background AD treatment (list to be provided in the sSAP), and IE3) use of any non-AD treatment that has the potential to adversely affect cognition (hereafter, "adverse non-AD treatment"; list to be provided in the sSAP).

Primary Objective

Primary Estimand (based on 'treatment policy strategy' in ICH E9(R1))

To address the primary objective, an estimand based on the TPS will be used. This "TPS estimand" is intended to contrast the effect of MK-1942 (at a specified dose level), relative to placebo, when initiated with stable background AD treatment, regardless of how long any of these treatments or any adverse non-AD treatment are used during an envisioned 12-week follow-up period.

The TPS estimand consists of the following attributes:

- Target population: participants between the ages of 55 and 90 years (inclusive) with mild to moderate AD dementia
- Endpoint: change from baseline in the ADAS-Cog11 Total score at Week 12
- Treatment regimen: MK-1942 (at a specified dose level) or placebo initiated with stable background AD treatment, with potential discontinuation of any of these treatments or use of any adverse non-AD treatment during an envisioned 12-week follow-up period
- Population-level summary: mean of the endpoint noted above, compared between treatment regimens

(Note: for estimating the TPS estimand, data collected after occurrence of IE1, IE2, or IE3 will be used in the main analysis; see details in Section 9.6.1.)

Supplemental Estimand (based on 'hypothetical strategy' in ICH E9[R1])

A supplemental estimand based on the HS will be used. This "HS estimand" is intended to contrast the effect of MK-1942 (at a specified dose level), relative to placebo, when initiated with stable background AD treatment under a ***hypothetical*** scenario in which there is no discontinuation of the stable background AD treatment and no use of any adverse non-AD treatment during an envisioned 12-week follow-up period.

The HS estimand has the same target population, endpoint, and population-level summary as the TPS estimand, but differs in the treatment regimen attribute.

The HS estimand consists of the following attributes:

- Target population: participants between the ages of 55 and 90 years (inclusive) with mild to moderate AD Dementia
- Endpoint: change from baseline in the ADAS-Cog11 Total score at Week 12
- Treatment regimen: MK-1942 (at a specified dose level) or placebo initiated with stable background AD treatment, without discontinuation of the latter and without use of any adverse non-AD treatment during an envisioned 12-week follow-up period
- Population-level summary: mean of the endpoint noted above, compared between treatment regimens

(Note: for estimating the HS estimand, data collected after occurrence of IE2 or IE3, or after occurrence of IE1 followed by at least one of IE2 or IE3, will be discarded in the main analysis; see details in Section 9.6.1.)

Secondary Objectives

Both TPS and HS estimands, as described for the primary efficacy endpoint, will be applied to the key secondary efficacy endpoint (ADCS-CGIC) and to the secondary endpoint (ADCS-ADL). For all other efficacy endpoints, where applicable, only the TPS estimand, as described for the primary efficacy endpoint, will be applied.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

In general, if a baseline value (defined as the most recent measurement before the first dose) exists for a particular efficacy measure, then the change from baseline in that value will be evaluated. The primary efficacy evaluation period of this study is the 12-week double-blind treatment period.

Primary Endpoint

The ADAS-Cog11 is an 11-item assessment for cognition. The primary endpoint of this study is the change from baseline in the ADAS-Cog11 Total score at Week 12.

Key Secondary Endpoint

The ADCS-CGIC focuses on clinicians' observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of the study. The ADCS-CGIC Overall score at Week 12 is the key secondary endpoint.

Secondary Endpoints

The ADCS-ADL is an informant-based measure of the patient's functional ability in activities of daily living. The change from baseline in total ADCS-ADL score at Week 12 is a secondary endpoint.

Tertiary/Exploratory Endpoints

The exploratory endpoints for this study will be detailed in the sSAP and include the following measurements at all planned postdose time points up to, and including, Week 12:

- The change from baseline in total NPI-Q severity score
- The ADAS-Cog11 Total score
- The ADAS-Cog13 Total score

- The ADCS-CGIC scores (General Condition, Cognition, Behavior, Function, Overall)
- The COWAT Total score
- The Coding Total score
- The Trail Making Test Parts A and B scores, respectively
- The CERAD Verbal Fluency Test score
- The MMSE Total score
- The EQ-5D-5L
- Improvement in the ADCS-CGIC Overall score, with a score of 1, 2, or 3 indicating improvement
- Composite score of Memory
- Composite score of Executive Function
- Composite score of Attention
- Item response theory derived ADAS-Cog11 score

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, ECGs, and vital signs.

Responses on the C-SSRS are classified according to 11 prespecified categories (Ideation: Passive, Active-nonspecific, Active-method, Active-method and intent, and Active-method, intent and plan; Behavior: Preparatory actions or behaviors, Aborted attempt, Interrupted attempt, Suicide attempt, and Completed suicide; Non-suicidal Self-Injurious Behavior). The most severe treatment-emergent event within each of 3 broad categories (suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior) reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it is either newly emerged or is more severe than the most severe event reported to have occurred in the study-defined pretreatment reference period.

9.4.3 Pharmacokinetic Endpoints

The PK endpoint is MK-1942 plasma concentrations.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population will be defined separately for each efficacy endpoint and consists of all randomized participants who:

- Receive at least 1 dose of study intervention
- Have a baseline measurement (for those analyses that require a baseline measurement) and at least 1 valid postrandomization observation for the analysis endpoint after at least one dose of study intervention
    - For analyses by time point, a valid postrandomization observation is an observation which 1) is collected within an analysis window and 2) does not occur after an intercurrent event (for those analyses in which such observations are to be excluded).

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention.

- For analyses conducted by time point, participants must have a baseline measurement and at least 1 valid postrandomization observation for the analysis endpoint after at least one dose of study intervention.
    - For analyses by time point, a valid post-treatment observation is an observation which 1) is collected within an analysis window and 2) does not occur after the relevant window pertaining to cessation of study intervention (for those analyses in which such observations are to be excluded).

Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

9.5.3 Pharmacokinetic Analysis Populations

The PP Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to show the effects of treatment. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible. Any participants or data values

excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data will be included in the PP dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type-1 error control strategy are described in Section 9.8. Nominal p-values and 95% CIs will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analysis

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

A separate modeling and simulation analysis plan will be used to describe methods used to evaluate the exploratory objective to assess the effect of MK-1942 on ADAS-Cog11 at the item-level over time.

Data from all 3 treatment groups through Week 12 will be used to contrast the treatment comparisons/time points of interest for the primary efficacy endpoints. The primary analysis is based on a longitudinal ANCOVA model including the change from baseline in ADAS-Cog11 Total score at each planned post-randomization visit up to Week 12. The longitudinal ANCOVA model will handle missing data assuming a missing-at-random missing data mechanism. This model will be used to generate confidence intervals and p-values (compared with placebo). This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time (ie, week) is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include categorical terms for treatment, time, APOE4 status (positive, negative), and geographic region (US/Canada, LATAM, Japan/South Korea, Europe/Australia/NZ) as well as continuous terms for baseline, baseline MMSE score, years since diagnosis, and age. In addition, the model will also include the interaction terms of time-by-treatment and time-by-baseline. The treatment difference in terms of the mean change from baseline in the ADAS-Cog11 Total score at a given time point will be estimated, and as appropriate, tested from the model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger approximation will be used to compute the degrees of freedom [Kenward, M. G. and Roger, J. H. 1997].

If the model fails to converge, the following respective steps will be taken until the model does converge: 1) geographic region will be collapsed from 4 levels to 2 levels (US/Canada and Rest of World), 2) APOE 4 status will be removed from the model, 3) geographic region will be removed from the model.

The same analysis strategy and model used for the primary efficacy endpoint will also be used for the other continuous efficacy endpoints. It is noted that the ADCS-CGIC scores essentially measure the change from baseline at each postdose visit and that no baseline value for the ADCS-CGIC scores exists. As such, the analysis of this measurement will model the postdose score (as opposed to the CFB score) and will not include terms for baseline and the interaction of time-by-baseline in the model.

As outlined in Table 5, supportive analyses will be performed for the primary and secondary hypotheses to assess the robustness of the primary findings with respect to (1) the impact of intercurrent events; and (2) the handling of missing data. Details related to supportive analyses will be provided in the sSAP.

Summary statistics will be computed for all efficacy endpoints over time. This minimally includes means and standard deviations for continuous endpoints and counts and percentages for categorical endpoints.

Table 5 Analysis of Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Analysis[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
CFB in ADAS-Cog11 Total score at Week 12	P	Longitudinal ANCOVA[b] with TPS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA[b] with HS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA with TPS Estimand and CBMI[b]	FAS	CBMI
Secondary Endpoints				
ADCS-CGIC Overall score at Week 12	P	Longitudinal ANCOVA[c] with TPS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA[c] with HS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA with TPS Estimand and CBMI[c]	FAS	CBMI
CFB in ADCS-ADL Total score at Week 12	P	Longitudinal ANCOVA[b] with TPS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA[b] with HS Estimand	FAS	Model-based
	S	Longitudinal ANCOVA with TPS Estimand and CBMI[b]	FAS	CBMI

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Analysis[a]	Statistical Method	Analysis Population	Missing Data Approach
ADAS-Cog11=Alzheimer's Disease Assessment Scale-11-item cognitive subscale; ADCS=Alzheimer's Disease Cooperative Study; ADL=activities of daily living; ANCOVA=analysis of covariance; APOE=apolipoprotein E; CBMI=Control-Based Mean Imputation; CFB=change from baseline; CGIC=Clinical Global Impression of Change; FAS=full analysis set; HS=hypothetical strategy; MMSE=Mini-Mental State Examination; TPS=treatment policy strategy [a] P=Primary approach, S=supportive approach [b] Longitudinal ANCOVA model with categorical terms for treatment, time, APOE4 status, and region, as well as continuous terms for baseline, baseline MMSE score, years since diagnosis, and age. In addition, the model will include the interaction terms of time-by-treatment and time-by-baseline. [c] Longitudinal ANCOVA model with categorical terms for treatment, time, APOE4 status, and region, as well as continuous terms for baseline MMSE score, years since diagnosis, and age. In addition, the model will also include the interaction term of time-by-treatment.				

The strategy to address multiplicity issues regarding multiple treatment comparisons, multiple efficacy endpoints, and an interim analysis is described in Section 9.7 (Interim Analyses) and Section 9.8 (Multiplicity).

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters including laboratory tests, vital signs, and ECG measurements.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE; and a discontinuation from study intervention due to an AE. Point estimates and 95% CIs for the differences between treatment groups (ie, MK-1942 dose groups compared with placebo) in the percentages of participants with the event will be provided.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs for the differences between treatment groups (ie, MK-1942 dose groups compared with placebo) in the percentages of participants with specific AEs will be provided for AEs that occur in at least 4 participants in any treatment group. This threshold for the number of participants with AEs was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences. Similar information will be provided for each SOC.

CIs for between-treatment group differences will be provided using the M&N method (1985) [Miettinen, O. and Nurminen, M. 1985]. None of the CIs that will be generated to evaluate safety endpoints will be adjusted for multiplicity. As such, these CIs should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in at least 4 participants in any treatment group. Point estimates and 95% CIs will be provided for the percentage of

participants with safety parameters that meet predefined limits of change based on the same threshold criteria described above for the specific AEs.

For continuous safety measures, such as change from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

9.6.2.2 Assessment of Safety Topics of Special Interest

The following are considered safety topics of special interest in this study (details pertaining to the exact AE terms considered as AEs of special interest will be included in the sSAP):

- AEs of dizziness that are rated by the investigator as moderate or severe in intensity
- AEs related to gait disturbance, independent of feelings of moderate or severe dizziness
- AEs of falls, independent of feelings of moderate or severe dizziness
- AEs of suicidal ideation
- AEs of suicidal behavior
- AEs of non-suicidal self-injurious behavior

The rationale for considering these as safety topics of special interest in this study is provided in Sections 2.2.2, 2.3, and 4.2.3. The safety topics of special interest will be summarized by the number and percentage of participants with an event. Point estimates and 95% CIs for between-group differences will be provided for these events using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Additionally, for the C-SSRS, the 11 prespecified categories of suicidal ideation and behavior will be summarized. Participant counts (and cumulative counts) for each category will be based on the most severe treatment-emergent event observed during the assessment period.

In constructing the treatment-emergent C-SSRS analyses, a pretreatment reference period is required, from which a baseline score for each of the 3 categories (ideation, behavior, non-suicidal self-injury) is derived. For this study, the baseline score for each of the 3 categories will be taken as the maximum score arising from all predose C-SSRS administrations, within the relevant timeframe. The first predose administration references lifetime history. Each subsequent predose administration references the timeframe since the last predose administration.

It is noted that the first predose administration actually consists of 2 separate administrations; one using lifetime as the reference period and another using fixed-time intervals (6 months for behavior and 2 months for ideation).

For this study, separate analyses will be conducted using 2 defined pretreatment reference periods:

- Lifetime – Baseline score is the maximum score over all predose assessments.
- Fixed-Time-Interval – Baseline score is the maximum score over all predose assessments, excluding the Lifetime History assessment.

Table 6 summarizes the analysis strategy for safety endpoints in this study.

Table 6 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI	Graphical Display
Overall Safety Assessment	Any AE	X	X	
	Any serious AE	X	X	
	Any drug-related AE	X	X	
	Any serious drug-related AE	X	X	
	Discontinued study treatment due to AE	X	X	
	Death due to AE	X	X	
	Specific AEs (incidence ≥ 4 participants in any treatment group)	X	X	X
	SOCs, PDLCs (incidence ≥ 4 participants in any treatment group)	X	X	
	Specific AEs, SOCs or PDLCs (incidence <4 participants in all treatment groups)	X		
	Change from Baseline Results (Laboratory test results, ECGs, Vital Signs)	X		
Assessment of Safety Topics of Special Interest	Dizziness AEs of moderate or severe intensity	X	X	
	Gait disturbance AEs (independent of feelings of dizziness)	X	X	
	AEs of falls (independent of feelings of dizziness)	X	X	
	AEs of suicidal ideation, suicidal behavior, or non-suicidal self-injurious behavior	X	X	
	11 prespecified categories of suicidal ideation and behavior (from C-SSRS)	X		

AE=adverse event; CI=Confidence Interval; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; PDLC=Predefined Limit of Change; SOC=System Organ Class

9.6.3 Statistical Methods for Pharmacokinetic Analysis

Plasma concentrations will be summarized by nominal time point using the following (non-model-based) descriptive statistics: N (number of participants with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt (exp(s^2) -1), where s^2 is the observed variance on the natural log-scale).

9.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Two types of interim analyses may be performed in this study. Results will be reviewed by an eDMC.

The first type of interim analysis will be for safety only and will be conducted approximately every 4 to 6 months, with the frequency subject to change per eDMC recommendation.

In addition, a nonbinding interim futility analysis may be performed at the discretion of the Sponsor when approximately the first 50% of randomized participants have had the opportunity to receive study intervention for 12 weeks (ie, the IA will occur 12 weeks after the randomization of the 204th participant). The endpoints, timing, and purpose of the interim analysis are summarized in Table 7 below.

Table 7 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Safety endpoints as requested by eDMC	Interim safety analyses will be reviewed initially every 4-6 months (approximately) by the eDMC. The eDMC may change the frequency of these analyses based on the results of these analyses.	Safety
Change from baseline at Week 12 in ADAS-Cog11 score (MK-1942 5 mg versus placebo) Change from baseline at Week 12 in ADAS-Cog11 score (MK-1942 15 mg versus placebo)	At the discretion of the Sponsor, after the first 50% of randomized participants have had the opportunity to treat for 12 weeks (ie, the IA will be based on a data cutoff that is 12 weeks after the randomization of the 204th participant).	Assess futility

ADAS-Cog11=Alzheimer's Disease Assessment Scale-11-item cognitive subscale; eDMC=external Data Monitoring Committee, IA=interim analysis

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators before the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no responsibilities associated with the conduct or design of the study.

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Treatment-level results from the interim analysis will be provided to the eDMC by the unblinded statistician. Before final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits. This approach to include all available information is in line with the ICH-E9 guideline, the ITT principle and the CHMP guideline on adaptive designs.

Should the futility IA be conducted, then the decision of whether to terminate the study for futility will be based on the Bayesian predictive conditional probability, ie, the likelihood of correctly detecting a treatment difference at the end of the study given the results at the interim, corresponding to the primary hypotheses. The Bayesian predictive conditional probabilities will be computed assuming that the observed trend at the interim will continue to the end of the study. Details pertaining to the computation of the Bayesian predictive conditional probabilities are included in the sSAP. The interim analysis will include data for participants who completed the study or dropped out, as well as the partial data of ongoing participants. Additional details regarding the calculation of the Bayesian predictive conditional probability will be described in the sSAP.

Traditional conditional power [Lan, K. K. G. 1988] computes the probability of success by fixing the portion of data already observed and by assuming the distribution of the remaining data, with this assumption typically rooted in what has been observed in the study thus far (ie, assuming the "current trend"). The first step in calculating the Bayesian predictive conditional probability is to replace the assumption of the "current trend" used to calculate the conditional power, with an assumption that is centered around the "current trend." This is accomplished by replacing the observed model-based mean and variance with a randomly sampled normal variate (generated using the observed model-based mean and variance). This process is repeated 500 times, and the Bayesian predictive conditional probability is taken as the average of these computed conditional powers. The resultant Bayesian predictive conditional probability is less prone to extreme values (ie, conditional powers <0.01 or >0.99). If the Bayesian predictive conditional probability is <15% for both primary hypotheses, the study may be stopped for futility.

The operating characteristics of the interim futility analysis (calculated via simulation) are provided in Table 8. The probability that the study will meet futility criteria if both null hypotheses are true (ie, the true mean CFB treatment difference (MK-placebo) of both doses is equal to 0) is approximately 70%. The probability that the study will meet futility criteria if the true mean CFB treatment difference (MK-placebo) for both doses is equal to 0.5 (a difference thought not to be clinical meaningful) is approximately 47%.

Table 8 Operating Characteristics of the Interim Futility Analysis

Assumed Week 12 CFB Trt. vs. Pbo (8 mg, 30 mg)	**P (Stop at IA)[a]**
(0.0, 0.0)	69.7
(0.5, 0.5)	47.4
(2.0, 2.0)	2.1

CFB=change from baseline; IA=interim analysis; P=probability; Pbo=placebo; Trt=treatment

Based on 5000 simulations conducted under the same assumptions and design parameters (dropout rate, assumed variances, α) as were used to simulate the power calculations corresponding to the primary hypotheses.

[a] P (Stop at IA) is equal to the probability that both doses have a Bayesian predictive conditional probability less than 15% at the time of the IA.

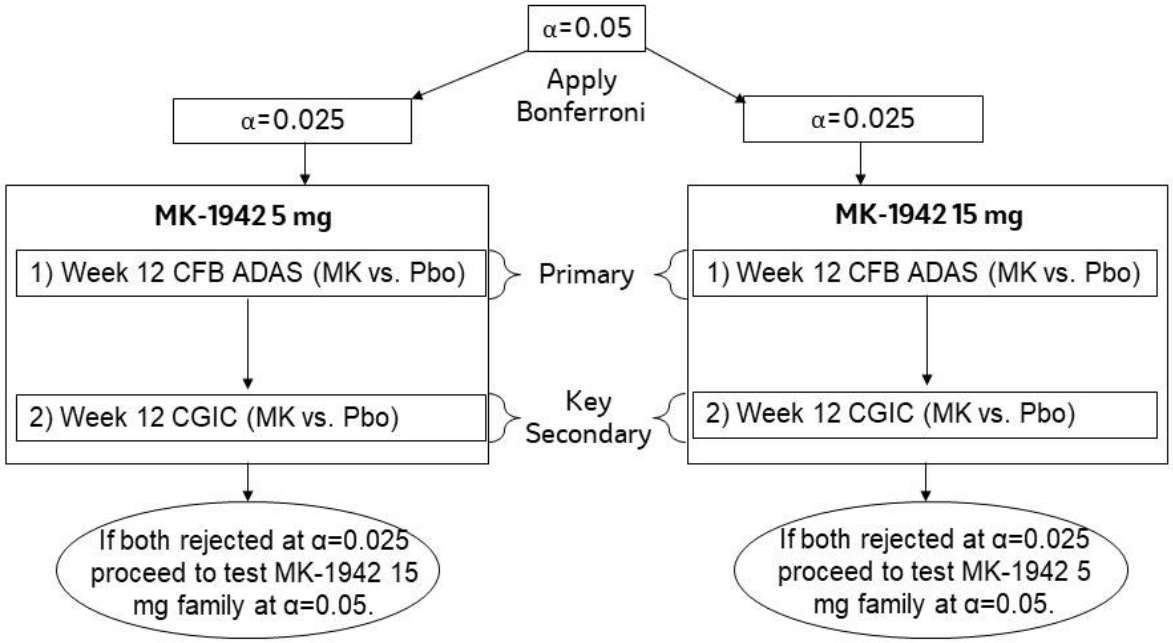
9.8 Multiplicity

The overall Type-I error among the 2 dose comparisons to placebo for the primary and key secondary endpoints will be controlled at the two-sided 5% significance level by utilizing a Bonferroni (Step-down) Procedure in conjunction with a closed testing sequential approach as shown in Figure 2.

Specifically, a separate hypothesis family will be created for each of the MK-1942 5-mg and MK-1942 15-mg doses. Each family will be comprised of 1 hypothesis for the primary endpoint and 1 hypothesis for the key secondary endpoint.

No multiplicity adjustments will be made for other endpoints.

Figure 2 Formal Hypothesis Testing Strategy



9.9 Sample Size and Power Calculations

9.9.1 Efficacy Parameter Estimates

Variance estimates were based on data from MK-7622 P012 (restricted to exclude MMSE values outside the range of MK-1942 P008), which was a similarly designed study in a mild to moderate AD population. Simple summary statistics were computed (variance at each time point, correlation matrix across all time points). The upper bound of a 90% CI for the variance was used to represent the variance at each time point in constructing the power simulations. Though not directly used in the simulations, the corresponding assumed variance for the Week 12 CFB standard deviation can be computed using these upper bounds and the computed correlations. This information is found in Table 9.

The assumed dropout rate (20%) was determined using data from MK-7622 P012 in conjunction with a wide range of literature references [Fullerton, T., et al 2018], [Gault, L. M., et al 2015], [Gault, L. M., et al 2016], [Haig, G. M., et al 2014], [Atri, A., et al 2018], [Olin, J. T. 2002], [Rockwood, K., et al 2001], [Wilkinson, D. 2001] while also factoring in the potentially higher dropout due to the COVID-19 pandemic.

The assumed CFB mean treatment difference for ADAS-Cog11 Total score is not based on prior MK-1942 data, but rather on what treatment difference is considered clinically meaningful. Similarly, the assumed mean treatment difference for CGIC score is not based on prior MK-1942 data, but rather on what effect size is considered clinically meaningful.

Table 9 Assumed Variances and Correlations Used in the Power Simulations

Endpoint	Baseline SD	Week 12 SD	UB of 90% CI for Baseline SD	UB of 90% CI for Week 12 SD	Corr (Baseline, Week 12)	Week 12 CFB SD Using UB of 90% CI
ADAS-Cog11	7.76	8.25	8.47	9.12	0.844	4.95
CGIC[a]	NA	0.91	NA	1.00	NA	NA

ADAS-Cog11=Alzheimer's Disease Assessment Scale-Cognitive Subscale (11);CFB=change from baseline; CGIC=Clinical Global Impression of Change; CI=confidence interval; Corr=correlation; NA=not applicable; SD=standard deviation; UB=upper bound.

[a] Since the CGIC is intrinsically captured as a change score, no baseline or CFB values exist.

9.9.2 Sample Size and Power for Efficacy Analyses

The sample size of 136 per arm was selected to provide approximately 90% power for success for at least one of the MK-1942 dose comparisons (vs placebo) pertaining to the primary hypothesis (Table 10).

Table 10 Power Calculations for ADAS-Cog11 Total Score and CGIC

Endpoint	Assumed Mean CFB. Trt. Diff vs. Pbo (8 mg, 30 mg)	Assumed Week 12 CFB SD	P (Success for at least one dose)	P (Success at a given dose)
ADAS-Cog11[a]	(2.0, 2.0)	4.95	89.7	77.7
CGIC[b]	(0.3, 0.3)	1.00	NC	48.9

ADAS-Cog11=Alzheimer's Disease Assessment Scale-Cognitive Subscale (11); CFB=change from baseline; NC=not computed (since only the marginal power was computed); Pbo=placebo; SD=standard deviation; Trt=treatment

136 randomized participants per arm

All calculations/simulations assume a 20% dropout rate at Week 12.

[a] Computed using 5000 simulations, according to the prespecified multiplicity strategy (see Section 9.8) at an overall two-sided α=0.05 level.

[b] Marginal power was calculated (not simulated) absent regard to the multiplicity approach using α=0.025. The formal power is lower than that presented in the table, as success on ADAS-Cog11 is required within a given dose family in order for testing to proceed. Since the CGIC is intrinsically captured as a change score, the assumed means and SDs presented are not CFB.

9.9.3 Sample Size and Power for Safety Analyses

The probability of observing at least one event for any safety endpoint in this study depends on the number of participants treated and the underlying percentage of participants with a specific AE in the study population. If the underlying incidence of one event on a safety endpoint is 0.8% (1 of every 136 participants receiving the study intervention), there is a 66.5% chance of observing at least one AE among 136 participants in the study intervention group. If no such AEs are observed among the 136 participants in a treatment group, this study will provide 95% confidence that the underlying percentage of participants with that AE is <3% in the treatment group.

9.10 Subgroup Analyses

To assess whether the treatment effect with respect to the primary and key secondary endpoints is consistent across various subgroups of the study population, the between-treatment group effect (with a nominal 95% CI) will be estimated and plotted (Forest plot) within each subgroup of the following classification variables.

- Age group (<65, 65-74, 75-90)
- Gender (female; male)
- Race (white; other)
- Geographic Region (US/Canada, Europe/Australia/NZ, Rest of World)
- Years since diagnosis (<median; ≥median score)
- Baseline MMSE total score (MMSE score ≤19; MMSE score ≥20)
- Baseline BMI (<median; ≥median value)
- APOE4 status (positive, negative)
- Memantine use at baseline (yes, no)

The consistency of the treatment effect will be assessed in the context of the primary (or key secondary, as appropriate) efficacy analysis model using only the data for a specific subgroup. CIs will only be produced for a subgroup if both treatment groups (MK-1942 dose group and placebo) have at least 15 participants (approximately 10%) within the subgroup; summary statistics for subgroups will be provided regardless of sample size.

In addition to conducting the subgroup analyses above (which are all based on pre-randomization characteristics), an additional subgroup analysis will be conducted on a post-randomization factor: low PK versus normal PK. The criteria for inclusion in the “low PK” group will be defined separately for each treatment arm, noting that all participants randomized to the placebo arm will belong to the “normal PK” arm. The criteria for inclusion

in the 2 respective groups will be defined in the sSAP. For further information regarding PK variability, refer to Section 6 of the IB.

These subgroups will be interpreted with caution, as inclusion in the subgroups themselves may be subject to the effect of the drug in ways that cannot be measured or perceived, rendering between-treatment comparisons within these subgroup levels as suspect.

9.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each participant, the number of capsules remaining in study packaging will be counted, reviewed, and recorded at regular intervals. Study intervention records will be used to calculate participant compliance.

A day within the study will be considered an "On-Therapy" day if the participant takes the intended number of capsules.

For a participant who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study intervention.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (N, mean, median, SD). Additionally, the total number of days each participant took a particular total daily dose of study intervention will be identified and summarized (as participant counts and percentages) within duration categories).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.2 Scientific Advisory Committee

This study was developed in collaboration with a SAC. The SAC comprises both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.3 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each

of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory.
- Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. Screening laboratory test results can also be repeated locally if a laboratory error is suspected. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. For Visit 9, if a participant cannot attend the in-person site visit, scheduled safety laboratory assessments may be performed at a local laboratory, and other nonlaboratory assessments will be performed by TC. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Screening laboratory tests should NOT to be repeated if the initial results are exclusionary, except where repeat tests are allowed in the eligibility criteria (Section 5.2). Rescreening may be performed after a participant's laboratory abnormality initially leading to exclusion resolves (information on rescreening is provided in Section 8.11.1). Laboratory criteria for study intervention discontinuation are in Section 7.1 and below.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.
- The approximate amount of blood collected from each participant over the duration of the study is 128 ml.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- All laboratory tests should be performed after all efficacy assessments are completed at each visit, except for Visit 6, where laboratory tests will be done with first PK draw and before efficacy assessments.

  The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Table 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	WBC	WBC count with differential (absolute, percentage): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
	Platelets		
	RBC	Morphology, MCV, RDW	
	Hemoglobin	MCH, MCHC	
	Hematocrit		
Chemistry	Creatinine (includes eGFR calculation) Phosphorus Calcium CK Sodium Potassium Chloride CO_2 or bicarbonate	AST (SGOT) ALT (SGPT) Albumin Total protein Alkaline phosphatase Lactate Dehydrogenase Gamma-Glutamyl Transpeptidase Globulin Urea Nitrogen Uric Acid Total bilirubin Indirect bilirubin Direct bilirubin	Glucose
Urinalysis	Color and clarity Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (reported if detected), includes bacteria, casts, crystals, epithelial cells, RBC, WBC, yeast, oval fat bodies, fat, mucous, sperm, trichomonas		
Other Tests	INR at Visit 2 (randomization) only TSH with reflex FT4 FSH – female only, if applicable Biomarkers Genotyping for CYP2C19/APOE4 Serology (HIV antibody, HbsAg, and hepatitis B, C virus antibody) • Serologies are at the discretion of the investigator (except for country-specific requirements [Appendix 7]) Serum vitamin B12, folate, homocysteine, methylmalonic acid		

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CK=creatine kinase, eGFR=estimated glomerular filtration rate, FSH=follicle-stimulating hormone, FT4=free thyroxine T4, HbsAg=hepatitis B surface antigen, HDL=high density lipoprotein, INR=international normalized ratio, LDL=low density lipoprotein, MCH=Mean corpuscular (or cell) hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, RBC=red blood cell, RDW=red blood cell distribution width, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamate-pyruvate transaminase, TSH=thyroid-stimulating hormone, WBC=white blood cell

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity /toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Childbearing Potential (WOCBP) Nonparticipant Only

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

- Women in the following categories are not considered WOCBP:
  - Premenarchal
  - Premenopausal female with 1 of the following:
  - Hysterectomy

- Bilateral salpingectomy
- Bilateral oophorectomy
- Permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity.

• Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

10.5.2 Contraception Requirements

As WOCBP are not eligible to participate in this study, there are no contraceptive requirements for female participants in this study. Contraceptive use by men is described in Section 5.1.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

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3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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10.7 Appendix 7: Country-specific Requirements

Argentina-specific Requirements

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

United Kingdom-specific Requirements

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 5.2 for information on COVID-19 vaccines.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ACC	American College of Cardiology
AChEIs	acetylcholinesterase inhibitors
ADAS-Cog11	Alzheimer's Disease Assessment Scale-11-item cognitive subscale
ADAS-Cog13	Alzheimer's Disease Assessment Scale-13-item cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study Clinical Global Impression of Change
ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	All-Participants-as-Treated
APOE	apolipoprotein E
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
bid	twice daily
BLA	Biologics License Application
BMI	body mass index
BP	blood pressure
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFB	change from baseline
CG	Cockcroft-Gault
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
COWAT	Controlled Oral Word Association Test
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
CYP2C19	cytochrome P450 2C19
DC	discontinuation

Abbreviation	Expanded Term
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DxV	diagnostic verification form
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eDMC	External Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EM	exposure margin
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	End of Treatment
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
FT4	Free T4 test
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hypothetical strategy
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IE1	Intercurrent Event 1
IE2	Intercurrent Event 2
IE3	Intercurrent Event 3
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous

Abbreviation	Expanded Term
LATAM	Latin America
M&N	Miettinen and Nurminen
MDRD	Modification of Diet in Renal Disease
CCI [redacted]	
MHIS	Modified Hachinski Ischemia Scale
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
CCI [redacted]	
NDA	New Drug Application
NfL	neurofilament light protein
NIA-AA	National Institute on Aging and Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	neuropsychiatric symptoms
NZ	New Zealand
PDLC	predefined limits of change
PK	pharmacokinetic
po	orally
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
QoL	quality of life
QTcF	QTc using the Fridericia formula
RNA	ribonucleic acid
RO	receptor occupancy
SAC	Scientific Advisory Committee
SAE	serious adverse event
SD	standard deviation
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
T_{max}	time to maximum plasma concentration
TPS	treatment policy strategy
TSH	Thyroid-stimulating hormone
t1/2	half-life
ULN	upper limit of normal
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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