Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Assess the Safety, Tolerability, and Pharmacokinetics of MK-1167 Administered to Patients with Alzheimer's Disease Receiving Stable Donepezil Treatment
NCT number:	NCT06285240
Document Date:	14-Jun-2024

TITLE PAGE

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Assess the Safety, Tolerability, and Pharmacokinetics of MK-1167 Administered to Patients with Alzheimer's Disease Receiving Stable Donepezil Treatment

Study Number: 007-02

Compound Code(s): MK-1167

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

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	N/A
EU CT	N/A
EudraCT	N/A
jRCT	N/A
WHO/UTN	N/A
IND	164154

Approval Date: 14 June 2024

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
Amendment 2	14-JUN-2024	Addition of Panel B
Amendment 1	23-FEB-2024	Update Exclusion Criteria
Original Protocol	05-JAN-2024	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

The primary rationale for Amendment 02 is to add an additional panel (Panel B) where participants will receive multiple doses of 6 mg MK-1167/placebo.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
1.3 Schedule of Activities and Throughout	A second SoA table was added to reflect the addition of Panel B where participants will receive 6 mg of MK-1167/placebo.	To address the addition of a panel in order to study a higher dose.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.
1.1 Synopsis: Estimated Duration of Study	Updated estimated duration of study from 4 to 5 months.	Addition of Panel B necessitates update to estimated timelines for study conduct.
1.1 Synopsis: Intervention Groups and Durations	For Panel B added arm name, intervention name, unit dose strength(s), dosage level(s), route of administration, regimen/treatment period/vaccination regimen, and use.	Addition of Panel B necessitates updates to intervention groups and duration for study conduct.
1.1 Total Number of Intervention Groups/Arms	Updated text (‘2 arm’) to include the following detail: ‘There will be 2 panels (A and B) with approximately 16 participants each.’	Addition of Panel B necessitates inclusion of the number of participants for Panel B for study conduct.
1.1 Synopsis: Duration of Participation	Added 16-week time frame for Panel B.	Addition of Panel B necessitates addition of 16-week timeframe for study conduct.

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema	Updated Table 1 Study Design to included schema for Panel B. Added Figure 2 Study Schema for Panel B to reflect schema for Panel B.	Addition of Panel B necessitates update to Table 1 Study Design and addition of Figure 2 Study Schema for Panel B for study conduct.
2.2.1 Pharmaceutical and Therapeutic Background	Added information about preliminary safety data from Panel A of this study.	Addition of information about preliminary safety data for Panel A of this study supports addition of Panel B.
2.2.2 Preclinical and Clinical Studies	Updated to include new safety data from clinically completed Phase 1 studies, including MK-1167 PN003, PN004, and PN006. Updated to include preliminary PK data from 1167 PN006.	Several Phase 1 studies have completed clinical investigation since publication of initial protocol.
2.2.3 Ongoing Clinical Studies	Updated to include new safety data from ongoing Phase 1 study MK-1167 PN007.	One Phase 1 study has additional data since publication of initial protocol.
4.1 Overall Design	Updated to include addition of Panel B to the study design.	Addition of Panel B necessitates update to the overall design for study conduct.
4.2 Scientific Rationale for Study Design	Updated to include addition of dosing and dosing duration for Panel B.	Addition of Panel B necessitates update to scientific rationale for study design for study conduct.
4.2.1.1 Safety Endpoints	Updated to include safety data from Phase I studies, including MK-1167 PN001, PN002, PN004, PN006, and PN007 Panel A.	Several Phase I studies have additional data since publication of initial protocol.
4.3 Justification of Dose	Updated to provide PK projections for Panel B based on MK-1167 PN001, PN002, and PN004 Panel A PK data to inform justification of dose for Panel B. Updated to include information about MK-1167 PN003 to support dose of Panel B. Updated Table 2 to reflect addition of PN004 Panel A data used to inform exposure projections.	Addition of Panel B necessitates update to justification of dose for study conduct.
4.3.1 Rationale for Dose Interval and Study Design	Updated to include rationale for Panel B dose interval and study design	Addition of Panel B necessitates update to rationale for dose interval and study design for study conduct.
5.2 Exclusion Criteria	The first sentence of Exclusion Criterion 5 correctly states the estimated eGFR value of ≤60 mL/min/1.73 m^2. The final sentence in the same section incorrectly states “80 mL/min” for CrCl and “80 mL/min/1.73m^2” for eGFR. The correct value is indeed 60 mL/min” for CrCl and “60 mL/min/1.73m^2” for eGFR.	The values in this section were inconsistent due to a typographical error.
5.3.1.1 Diet Restrictions	Updated to include full PK sampling days for Panel B.	Addition of Panel B necessitates update to diet restrictions for study conduct.
5.3.1.2 Fruit Juice Restrictions	Updated to include full PK sampling days for Panel B.	Addition of Panel B necessitates update to fruit juice restrictions for study conduct.
5.3.2.1 Caffeine Restrictions	Updated to include full PK sampling days for Panel B.	Addition of Panel B necessitates update to caffeine restrictions for study conduct.
6.1 Study Intervention(s) Administered – Table 3	Updated to include intervention information for Panel B. Updated to include donepezil 5 mg as medication for potential dechallenge for Panels A and B.	Addition of Panel B necessitates update to Table 3. Potential need to down titrate donepezil dose necessitates update to Table 3.

Section Number and Name	Description of Change	Brief Rationale
6.3.1 Intervention Assignment	Added Table 5 to illustrate the allocation of participants to treatment for Panel B.	Addition of Panel B necessitates addition of Table 5 for study conduct.
8.1.8.1 Timing of Dose Administration	Updated to include donepezil dosing information for Panel B.	Addition of Panel B necessitates update to timing of dose administration for study conduct.
8.1.11 Domiciling	Updated timing of participant reporting to CRU to the evening on Day -4	This change was made to address erroneous text in this section
8.3.2.2 Orthostatic Vital Signs	When considering repeating orthostatic vital signs (VS) measurements, Section 8.3.2.2 should be followed, including the instructions that participants should be semi recumbent for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.	The process for repeat measurements for orthostatic vital signs was erroneously omitted in this section.
8.4.7 Events of Clinical Interest	Updated the location/bulleting of the study-specific ECIs	This change was made to enhance how the text is presented in this section
8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure	Updated study intervention administration for Panel B. Updated Table 7 CCI [redacted].	Addition of Panel B necessitates update to timing of procedures for study conduct. CCI [redacted]
9.5.1 Statistical Methods for Pharmacokinetic Analyses	Updated to include model-based PK and C24 estimation information for Panel B.	Addition of Panel B necessitates update to statistical methods for PK analyses for study conduct.
10.1.3 Appendix 1: Data Protection	Added the following language: The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.	This change was made to reflect an update to the Data Protection language.
10.8 Appendix 8: Blood Volume Table	Updated donepezil sampling in the blood volume table for Panel A. Added blood volume table for Panel B.	This change was made to address the addition of Panel B.
10.13 Appendix 13: List of Abbreviations	Addition of 'COVID-19' and 'DBL' per use in Sec. 2.2.2 and 'EU' per use in updated Data Protection.	Addition to Preclinical and Clinical Studies data and Data Protection warrants update.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Assess the Safety, Tolerability, and Pharmacokinetics of MK-1167 Administered to Patients with Alzheimer's Disease Receiving Stable Donepezil Treatment

Short Title: Clinical Trial to Evaluate MK-1167 in AD Patients Taking Donepezil

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

The study population consists of patients with mild to moderate AD, 50 to 90 years of age.

Primary Objective	**Primary Endpoint**
Evaluate the safety and tolerability of MK-1167 when administered to patients with mild to moderate Alzheimer's Disease on stable doses of oral donepezil 10 mg daily	Adverse events, discontinuation due to Adverse events
Secondary Objectives	**Secondary Endpoints**
Evaluate the pharmacokinetic profile of MK-1167 when administered to patients with mild to moderate Alzheimer's Disease on stable doses of oral donepezil 10 mg daily Estimation: [redacted]	AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F, t1/2

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Dementia Alzheimer's type
Population	Patients with mild to moderate cognitive impairment associated with Alzheimer's Disease
Study Type	Interventional
Intervention Model	Sequential This is a multi site study
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects, Investigator, and Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 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:

For Panel A, approximately 16 participants will be allocated/randomized such that 12 evaluable participants complete the study as described in Section 9.8. For Panel B, approximately 12 participants will be allocated/randomized as described in Section 9.8.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Panel A	MK-1167	5 MG, 1 MG	6 MG	Oral	CCI loading doses QD Days 1 to 7	Test Product
Panel A	MK-1167	1 MG	3 MG	Oral	CCI maintenance doses QD Days 8 to 21	Test Product
Panel A	Donepezil	10 MG	10 MG	Oral	QD dosing during entire treatment period	Comparator
Panel A	Placebo to MK1167	0 MG	All Dosage Levels	Oral	CCI QD Days 1 to 21	Placebo
Panel B	MK-1167	5 MG, 1 MG	6 mg	Oral	CCI QD Days 1 to 31	Test Product
Panel B	Donepezil	10 MG	10 mg	Oral	QD dosing during entire treatment period	Comparator
Panel B	Placebo to MK-1167	0 MG	All Dosage Levels	Oral	CCI QD Days 1 to 31	Placebo

Total Number of Intervention Groups/Arms	There will be 2 panels (A and B). Panel A will have approximately 16 participants, and Panel B will have approximately 12 participants.
Duration of Participation	Each participant will participate in the study for approximately 11 weeks for Panel A and 12 weeks for Panel B from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening period of up to 4 weeks, each participant will be receiving assigned study intervention for approximately 21 days for Panel A and 31 days for Panel B. CCI [redacted]

Study Governance Committees:

Executive Oversight Committee	No
External Data Monitoring Committee	No
Clinical Adjudication Committee	No

Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 13.

1.2 Schema

The study design is depicted in Table 1, and the study schema in Figure 1 and Figure 2.

Table 1 Study Design

Panel A [a,b,c] (n≤16)			Panel B [a,c,d] (n≤12)	
Loading Dose MK-1167/Placebo 6 mg QD Days 1 to 7	Maintenance Doses MK-1167/Placebo 3 mg QD Days 8 to 21	CCI	All Doses MK-1167/Placebo 6 mg QD Days 1 to 31	CCI
Donepezil 10 mg QD throughout treatment period			Donepezil 10 mg QD throughout treatment period	

CCI

Figure 1 CCI

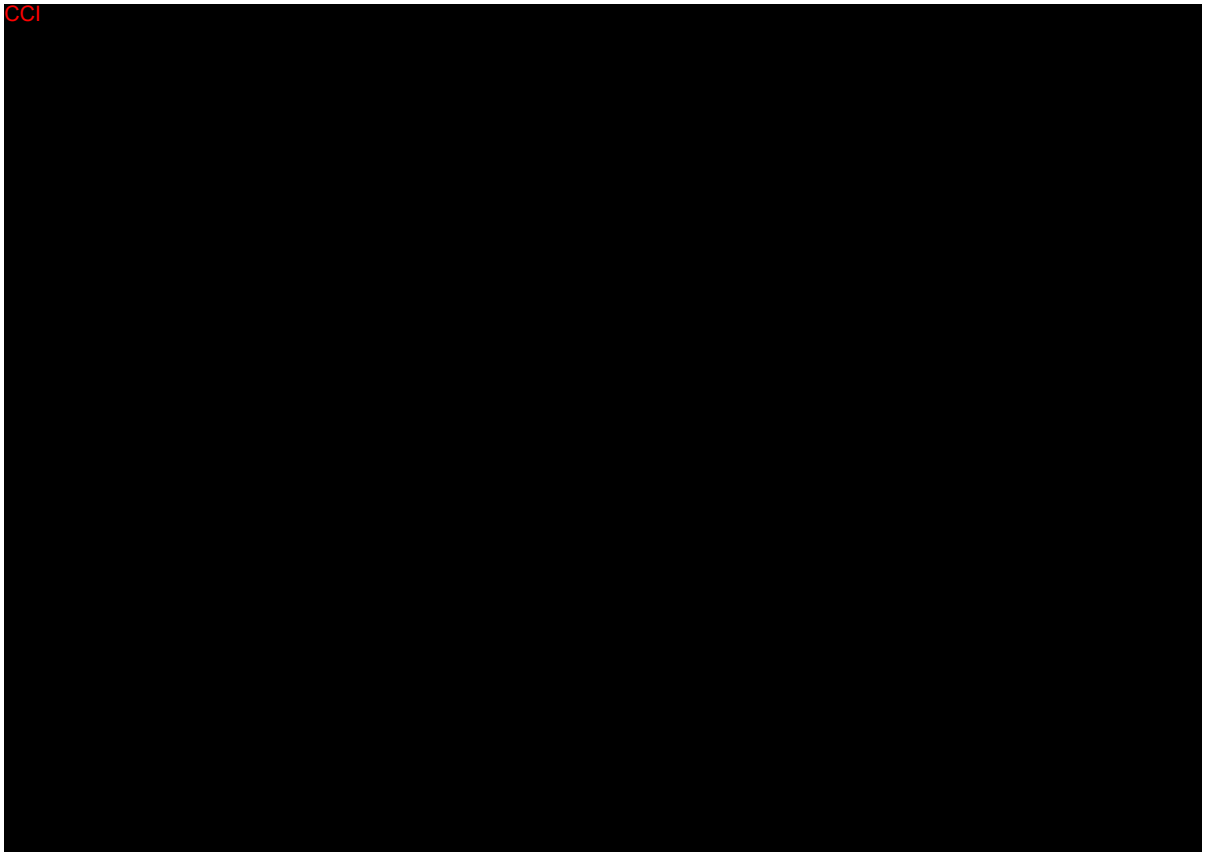
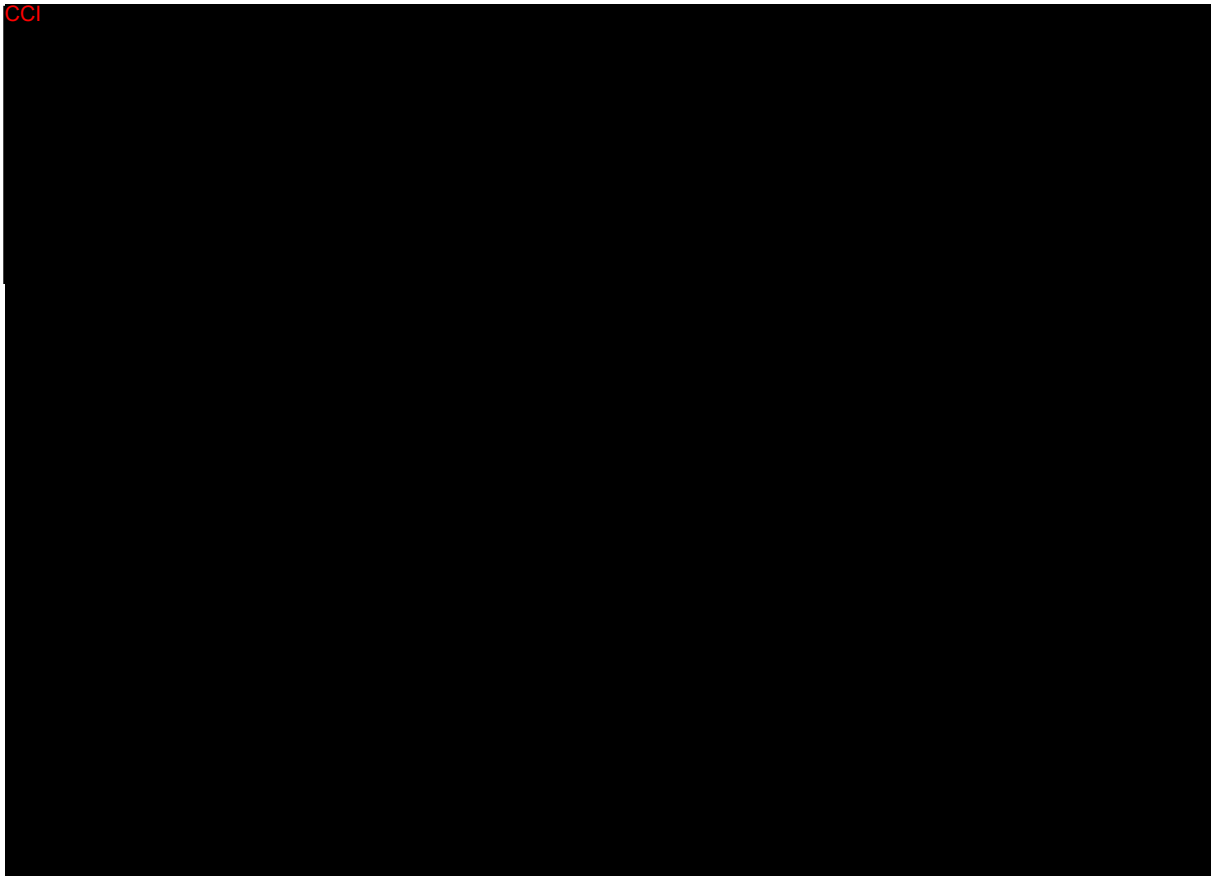


Figure 2 CCI



1.3 Schedule of Activities

Panel A																	
Study Period	**Screening[a]**	CCI														**Poststudy[b]**	**Notes**
Study Day																	
Administrative/Study Procedures																	
Informed Consent	X																Sections 5.1, 8.1.1.1
Informed Consent for FBR	X																Sections 5.1, 8.1.1.2
Participant ID Card	X																Section 8.1.3
Inclusion/Exclusion Criteria	X			X	X												Reviewed at Screening, Day -1, and after completion of Day 1 predose procedures. Sections 5.1, 5.2, 8.1.2
Medical History	X																Includes medical history of illicit drugs, alcohol, tobacco, and caffeine use. Section 8.1.4
Prior/Concomitant Medication Review	X ----------X																Sections 5.2, 6.5, 8.1.5
Assignment of Screening Number	X																Section 8.1.6
Assignment of Treatment/Randomization Number					X												Sections 5.5, 8.1.7
MK-1167/Placebo Administration					X	X	X	X	X								Section 8.1.8, 8.10.5
Donepezil Administration[c]	X ---------- X																Section 8.1.8, 8.10.5
Standard Meals[d]		X	X	X	X	X	X	X	X	X							Meals and snacks will be provided. Section 5.3.1

Panel A																	
Study Period	**Screening[a]**	CCI														**Poststudy[b]**	**Notes**
Study Day																	
Domiciling		X	X	X	X	X	X	X	X	X							Participants will report to the CRU in the evening of Day -4. CCI At the discretion of the investigator, participants may be requested to remain in the CRU longer. Section 8.1.11
Safety Procedures																	
Full Physical Examination	X			X[e]			X		X								Screening: anytime. CCI Section 8.3.1.
Full Neurological Examination	X															X	Section 8.3.5, Appendix 12
Targeted Neurological Examination				X[e]			X		X								Section 8.3.5, Appendix 12
Height	X																Section 8.3.1.
Weight	X			X[e]	X												BMI to be taken only at Screening. Day 1: predose. Section 8.3.1.
Resting VS (Semi Recumbent): Heart Rate and Blood Pressure	X				X		X		X							X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.1.

Panel A																
Study Period	**Screening[a]**	CCI													**Poststudy[b]**	**Notes**
Study Day																
Orthostatic VS: Heart Rate and Blood Pressure	X				X		X		X						X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.2.
VS: Respiratory Rate and Body Temperature	X				X		X		X						X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.
12-lead ECG[g]	X				X	X[h]	X		X				X[i]		X[i, j]	Screening: anytime. CCI Section 8.3.3, Appendix 9
Serum FSH (PONCBP only)	X															Appendices 2, 5, 8
Urine or Serum Pregnancy Test (POCBP only)	X	X														Urine test will be collected. Serum test will be collected in the event that urine test is positive or cannot be confirmed. Section 5.1, Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X															Section 5.2, Appendices 2, 8

Panel A																	
Study Period	**Screening[a]**	CCI														**Poststudy[b]**	**Notes**
Study Day																	
UDS/BDS (per site SOP)	X	X[e]															Drug screen is mandatory at Screening; any additional drug screen(s) is/are conducted per site SOP. Section 8.3.4, Appendix 2
Alcohol Screen	X	X															Breathing test. Section 5.2, Appendix 2
Clinical Safety Assessment (Hematology, Urinalysis, and Chemistry)	X	X			X		X		X							X	Screening, Day -3, and Poststudy visits: anytime. CCI Section 8.3.4, Appendices 2, 8
AE/SAE Review	X ---------- X																Section 8.4, Appendix 3
MMSE-2	X								X[k]							X	Sections 5.1, 5.2, 8.3.6
DSST[l]	X			X		X[h]		X[m]	X							X	Sections 4.2.1.3, 8.3.7, 8.7
C-SSRS Baseline[n]	X																Sections 4.2.3, 5.2, 8.3.8
C-SSRS Since Last Assessment[n]					X		X		X							X	Sections 4.2.3, 8.3.8

Panel A																
Study Period	**Screening[a]**	CCI													**Poststudy[b]**	**Notes**
Study Day																
Pharmacokinetics																
Blood for Plasma MK-1167 and Metabolites Assaying					X	X	X	X	X	X[i]	X[i]	X[i]	X[i]	X[i]	X[i, j]	CCI
Blood for Plasma Donepezil Assaying[o]		X	X	X					X							Day CCI: 24 hours postdose[f]. Day CCI: 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose[f] Day CCI: predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours postdose Section 8.10.5, Appendix 8.

Panel A																	
Study Period	**Screening[a]**	CCI														**Poststudy[b]**	**Notes**
Study Day																	
Biomarkers																	
Blood for Genetic Analysis					X												Predose from enrolled participants only. Section 8.8, Appendix 8.
CCI	X																Sections 8.8, 8.10.1, and Appendix 8.

AE=adverse event; BDS=blood drug screen; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; DSST=Digit Symbol Substitution Test; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; ID=identification; MMSE-2=Mini-Mental State Examination Edition 2; PK=pharmacokinetic(s); POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

[a] Screening should occur within 4 weeks prior to Day 1.

[b] The Poststudy Visit will occur at approximately C CI days after last dose.

[c] Donepezil will be administered in the mornings at approximately the same time as MK-1167/placebo. If participants do not usually take their donepezil in the mornings, they should be instructed to start taking it in the morning starting on Day -7 until Day -4. CCI

[d] Standardized meals/snacks to be provided on all days during domiciling at ~ 2 (breakfast), ~ 4 (lunch), ~ 7 (snack), ~ 10 (dinner), and ~ 13 (snack) hours postdose or equivalent (Section 5.3.1).

[e] Can be conducted within 24 hours prior to first dose.

[f] 24-hour timepoint will be collected at predose when dosing occurs on the day of collection.

[g] ECG measurements to be obtained in triplicate and performed before any blood sample for each timepoint.

[h] Day 2 only.

[i] Participants will return to the clinic for collection of MK-1167 plasma samples and ECG recordings at the hours/days specified in the Schedule of Activities.

[j] CCI will be collected before any Poststudy Visit procedures.

[k] Give within 12 hours of morning dose.

[l] A practice assessment will be administered at Screening. The assessment given on Day -1 will provide the baseline value. On Days CCI, assessments should be given within 4 hours after the morning dose. See Study Operation's Manual for specific instructions on test administration.

[m] Days 17 to 20 only.

[n] C-SSRS Baseline version to be used at Screening Visit, and all other visits use the C-SSRS Since Last Assessment version.

[o] Donepezil 24-hour postdose samples CCI will be analyzed; remaining donepezil blood samples will be archived.

[p] CCI

Panel B																					
Study Period	**Screening[a]**	CCI																		**Poststudy[b]**	**Notes**
Study Day																					
Administrative/Study Procedures																					
Informed Consent	X																				Sections 5.1, 8.1.1.1
Informed Consent for FBR	X																				Sections 5.1, 8.1.1.2
Participant ID Card	X																				Section 8.1.3
Inclusion/Exclusion Criteria	X			X	X																Reviewed at Screening, Day -1, and after completion of Day 1 predose procedures. Sections 5.1, 5.2, 8.1.2
Medical History	X																				Includes medical history of illicit drugs, alcohol, tobacco, and caffeine use. Section 8.1.4
Prior/Concomitant Medication Review	X ----------X																				Sections 5.2, 6.5, 8.1.5
Assignment of Screening Number	X																				Section 8.1.6
Assignment of Treatment/Randomization Number					X																Sections 5.5, 8.1.7
MK-1167/Placebo Administration					X ---------- X																Section 8.1.8, 8.10.5
Donepezil Administration[c]		X ---------- X																			Section 8.1.8, 8.10.5
Standard Meals[d]		X ---------- X																			Meals and snacks will be provided during domiciling. Section 5.3.1
Domiciling		X ---------- X																			Domiciling for Panel B is optional. Participants may choose to travel to and from the CRU or they can choose to domicile at the CRU. Section 8.1.11

Panel B																				
Study Period	**Screening[a]**	CCI																	**Poststudy[b]**	**Notes**
Study Day																				
Safety Procedures																				
Full Physical Examination	X			X[f]			X	X[e]	X				X							Screening: anytime. CCI Section 8.3.1.
Full Neurological Examination	X																		X	Section 8.3.5, Appendix 12
Targeted Neurological Examination				X[f]			X	X[e]	X				X							CCI Section 8.3.5, Appendix 12
Height	X																			Section 8.3.1.
Weight	X			X[f]															X	BMI to be taken only at Screening. Section 8.3.1.
Resting VS (Semi Recumbent): Heart Rate and Blood Pressure	X				X	X[r]	X	X[s]	X				X						X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.1.
Orthostatic VS: Heart Rate and Blood Pressure	X				X	X[r]	X	X[s]	X				X						X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.2.
VS: Respiratory Rate and Body Temperature	X				X		X	X	X				X						X	Screening and Poststudy visits: anytime. CCI Section 8.3.2.

Panel B																					
Study Period	**Screening[a]**	CCI																		**Poststudy[b]**	**Notes**
Study Day																					
12-lead ECG[h]	X				X	X[i]	X		X				X				X[j]		X[j,k]		Screening: anytime. CCI Section 8.3.3, Appendix 9
Serum FSH (PONCBP only)	X																				Appendices 2, 5, 8
Urine or Serum Pregnancy Test (POCBP only)	X	X																			Urine test will be collected. Serum test will be collected in the event that urine test is positive or cannot be confirmed. Section 5.1, Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X																				Section 5.2, Appendices 2, 8
UDS/BDS (per site SOP)	X	X[f]																			Drug screen is mandatory at Screening; any additional drug screen(s) is/are conducted per site SOP. Section 8.3.4, Appendix 2
Alcohol Screen	X	X																			Breathing test. Section 5.2, Appendix 2
Clinical Safety Assessment (Hematology, Urinalysis, and Chemistry)	X	X			X		X		X				X							X	Screening, Day -3, and Poststudy visits: anytime. CCI Section 8.3.4, Appendices 2 and 8
AE/SAE Review	X ---------- X																				Section 8.4, Appendix 3
MMSE-2	X								X[l]											X	Sections 5.1, 5.2, 8.3.6
DSST[m]	X			X		X[i]	X		X			X[n]	X							X	Sections 4.2.1.3, 8.3.7, 8.7
C-SSRS Baseline[o]	X																				Sections 4.2.3, 5.2, 8.3.8
C-SSRS Since Last Assessment[o]					X		X	X[e]	X		X		X							X	Sections 4.2.3, 8.3.8

Panel B																				
Study Period	**Screening[a]**	CCI																	**Poststudy[b]**	**Notes**
Study Day																				
Pharmacokinetics																				
Blood for Plasma MK-1167 and Metabolites Assaying					X	X	X	X	X	X	X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j,k]		CCI Sections 8.6.1, 8.10.5, Appendix 8
Blood for Plasma Donepezil Assaying[p]		X	X	X									X								Day CCI: 24 hours postdose[g]. Day CCI: 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose[g]. Day CCI: predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours postdose. Section 8.10.5, Appendix 8

Panel B																					
Study Period	**Screening[a]**	CCI																		**Poststudy[b]**	**Notes**
Study Day																					
Biomarkers																					
Blood for Genetic Analysis					X																Predose from enrolled participants only. Section 8.8, Appendix 8.
CCI	X																				Sections 8.8, 8.10.1, and Appendix 8

AE=adverse event; BDS=blood drug screen; BMI=body mass index; CRU=Clinical Research Unit; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; DSST=Digit Symbol Substitution Test; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; ID=identification; MMSE-2=Mini-Mental State Examination Edition 2; PK=pharmacokinetic(s); POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

[a] Screening should occur within 4 weeks prior to Day 1.

[b] The Poststudy Visit will occur at approximately C CI days after last dose.

[c] Donepezil will be administered in the mornings at approximately the same time as MK-1167/placebo. If participants do not usually take their donepezil in the mornings, they should be instructed to start taking it in the morning starting on Day -7 until Day -4. On Days CCI , donepezil will be dispensed and administered by site staff.

[d] Standardized meals/snacks will be provided on all days during domiciling at ~ 2 (breakfast), ~ 4 (lunch), ~ 7 (snack), ~ 10 (dinner), and ~ 13 (snack) hours postdose or equivalent (Section 5.3.1).

[e] Day 16 only.

[f] Can be conducted within 24 hours prior to first dose.

[g] 24-hour timepoint will be collected at predose when dosing occurs on the day of collection.

[h] ECG measurements to be obtained in triplicate and performed before any blood sample for each timepoint.

[i] Day 2 only.

[j] Participants will return to the clinic for collection of MK-1167 plasma samples and ECG recordings at the hours/days specified in the Schedule of Activities.

[k] Day C CI scheduled study procedures CCI will be collected before any Poststudy Visit procedures.

[l] Within 12 hours of morning dose.

[m] A practice assessment will be administered at Screening. The assessment given on Day -1 will provide the baseline value. On Days CCI assessments should be given within 4 hours after the morning dose. See Study Operation's Manual for specific instructions on test administration.

[n] CCI

[o] C-SSRS Baseline version to be used at Screening Visit, and all other visits use the C-SSRS Since Last Assessment version.

[p] Donepezil 24-hour postdose samples (Days CCI will be analyzed; remaining donepezil blood samples will be archived.

[q] CCI

[r] Day 4 only.

[s] On both Days 12 and 16.

2 INTRODUCTION

2.1 Study Rationale

This study investigates MK-1167 CCI [redacted]

MK-1167 is a PAM of the α7 nAChR and is not considered a compound with high potential for risk of harm to participants [European Medicines Agency 2017]. MK-1167 is not a biological molecule, does not exhibit species-specific action, and is not directed towards immune system targets. CCI [redacted]

The purpose of this study is to evaluate the safety and tolerability, and effect of multiple doses of donepezil on the multiple dose PK of MK-1167 in patients with AD. Donepezil is an AChEI, and 10 mg daily is the standard of care for patients with mild to moderate AD. CCI [redacted]

2.2 Background

Refer to the IB for detailed background information on MK-1167.

2.2.1 Pharmaceutical and Therapeutic Background

MK-1167 is a PAM of the α7 nAChR. The compound is being developed for the treatment of cognitive deficits associated with CNS disorders, with a primary focus on AD.

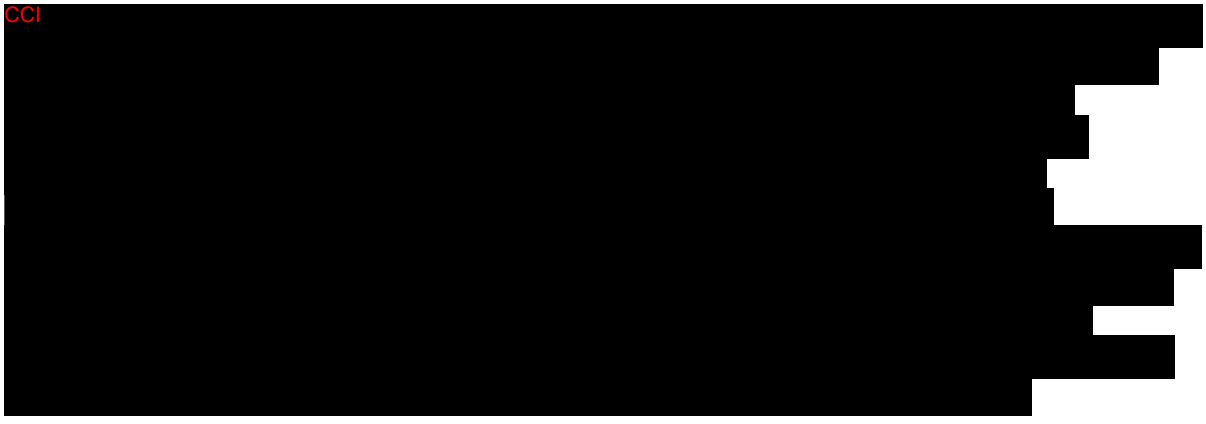
AD is the leading cause of dementia in elderly people and affects an estimated 35 million individuals worldwide, several which is escalating because of increased lifespan. AD is a

progressive neurodegenerative disorder in which cognitive deficits gradually worsen over time. Characteristics of the disease include degeneration of cholinergic neurons in the basal forebrain and reduction of cholinergic innervation of the cerebral cortex, hippocampus, and other regions of the brain.

It has been hypothesized that cholinergic hypofunction contributes to the cognitive deficits of patients suffering from AD. This hypothesis is supported by the fact that AChEIs, which inhibit hydrolysis of ACh, provide symptomatic benefit and have been approved for the treatment of the cognitive impairments in AD. However, AChEIs produce only modest efficacy so a treatment that significantly improves cognition as an adjunctive therapy would represent an important advance.

The α7 nAChR is a ligand-gated ion channel that is highly expressed in brain regions associated with cognitive function. The expression level of α7 nAChRs can be affected by several pathological conditions, including AD. In addition, genetic evidence supports the involvement of the α7 nAChR in cognitive function since both large deletions to Chromosome 15q13.3, as well as smaller deletions to the gene for the α7 nAChR, CHRNA7, frequently produce cognitive deficits in addition to other phenotypes. Positive clinical data in AD patients with α7 nAChR agonists further support the rationale that drugs that enhance α7 nAChR activity have therapeutic potential. Most notably, an α7 nAChR partial agonist, encenicline (Forum Pharmaceuticals, Inc), produced significant effects in a Phase 2 AD study but was discontinued during Phase 3 due to profound GI side effects. These side effects are believed to be due to off-target activity, namely serotonin 5-HT3 receptor antagonism. Furthermore, encenicline, as well as other α7 agonists, cause desensitization of the α7 receptor and produce an inverted U-shaped dose-effect function in a variety of preclinical assays. This profile is thought to limit the efficacy of α7 nAChR agonists and/or require exposures to be in a very specific range to produce efficacy.

PAMs of the α7 nAChR are hypothesized to exhibit an improved clinical profile in comparison to α7 nAChR agonists and be devoid of the tolerability issues that halted encenicline. In contrast to α7 nAChR agonists, PAMs do not promote receptor desensitization. Furthermore, α7 nAChR PAMs demonstrate efficacy over a much wider range of concentrations in several assays (no inverted U) and maintain efficacy upon repeated dosing. Additionally, α7 nAChR PAMs exhibit improved selectivity over related channel targets, presumably through binding to a nonconserved region of the α7 nAChR.



CCI [redacted]

2.2.2 Preclinical and Clinical Studies

Refer to the IB for detailed preclinical studies for MK-1167.

CCI [redacted]

MK-1167-001 (PN001)

Study MK-1167-001 was a randomized, placebo-controlled, double-blind, single ascending dose study to evaluate the safety, tolerability, and PK of MK-1167 in healthy male participants. The study consisted of 4 alternating panels (A, B, C, and D) consisting of 8 participants, each of whom were administered single-oral doses of MK-1167 or placebo (3:1 ratio as an on-site formulation (oral suspension). A total of 32 participants were enrolled, of whom 30 received single-oral doses of MK-1167 (3 to 100 mg). Overall, single-oral doses of MK-1167 up to 76 mg were generally well tolerated in healthy male participants. Of the 32 participants, 28 (87.5%) experienced 1 or more AEs during the study: n=25 (83.3%) on MK-1167 and n=8 (57.1%) on placebo. The most frequently reported AEs (>1 participants) after MK-1167 intervention were headache (11), dizziness (7), fatigue (5), diarrhea, sunburn (4 each), back pain, postural dizziness, gastrointestinal pain, oropharyngeal pain (3 each), dyspepsia, hematoma, skin irritation, and vomiting (2 each). Most AEs were mild to moderate in intensity.

CCI [redacted] Decreases in orthostatic BP persisted for approximately 5-hours postdose and then resolved spontaneously. No changes to resting BP or HR were observed in this participant, or in any other study participant in semirecumbent testing at any dose. Subsequent doses in the study were adapted such that doses ≥100 mg were not administered to study participants following the observation of this AE.

There were no serious AEs, ECIs or deaths reported in the study and no participant discontinued from the study due to an AE. There were no clinically meaningful trends observed as a function of study intervention for laboratory safety tests, VS, or ECGs.

MK-1167-002 (PN002)

Study MK-1167-002 was a randomized, placebo-controlled, single site, double-blind study of MK-1167 in healthy participants to assess the safety, tolerability, and PK of multiple doses of MK-1167. This study completed 4 sequential panels (A, B, C, and D) with 8 healthy participants in each panel who received multiple doses of MK-1167 (n=6) or placebo (n=2) in a randomized, blinded fashion. In Panel A, participants received a 4-mg loading dose of MK-1167 or placebo on Day 1 followed by 1 mg maintenance doses every other day on Days 3, 5, 7 and 9. In Panel B, participants received a 20-mg loading dose of MK-1167 or placebo on Day 1 followed by 2 mg QD (maintenance dose) for 9 consecutive days (Days 2 to 10). In Panel C, participants received a 40-mg loading dose of MK-1167 or placebo on Day 1 followed by 4 mg qd (maintenance dose) for 9 consecutive days (Days 2 to 10). In Panel D, participants received a 22-mg loading dose of MK-1167 or placebo qd for Days 1 to 4 followed by 8 mg qd (maintenance dose) starting on Day 5 and for 6 consecutive days.

Based on unblinded data from PN002, single oral loading doses of MK-1167 up to 40 mg and multiple oral doses of MK-1167 (1 to 8 mg) were generally well tolerated in healthy male participants. Of the 32 participants included in the study analysis set, 12 (37.5%) experienced 1 or more AEs during the study: n=10 (41.7%) on MK-1167 and n=2 (25.0%) on placebo. The most frequently reported AE (>1 participant) after MK-1167 intervention was abdominal discomfort (n=3). After placebo intervention, there were no AEs reported by >1 participant. All AEs were mild to moderate in severity, limited in duration, and all resolved without intervention. There were no clinically meaningful trends in laboratory safety measurements, vital signs, physical and neurological examinations, C-SSRS or ECGs. No participant was discontinued or withdrew participation due to an AE.

MK-1167-003 (PN003)

Study MK-1167-003 was a single-blind, placebo-controlled, 2-period, fixed sequence investigation of the ability of a single, oral dose of MK-1167 to modify glutamatergic neurotransmission in the prefrontal cortex of healthy adult males using selPOCE-13C-MRS to measure MK-1167 induced changes in the FE of ^{13}C-glutamate (^{13}C-glu) and ^{13}C-glutamine (^{13}C-gln) relative to placebo (baseline) treatment. This study is clinically complete and DBL was achieved on 09-MAY-2024. A total of 26 participants were enrolled in this study, of whom 11 received single doses of MK-1167 1 mg and 15 received single doses of MK-1167 6 mg. Overall, single doses of MK-1167 1 mg and 6 mg were generally well tolerated in healthy male participants. Of the 15 participants who received single doses of MK-1167 6 mg, 9 (58%) experienced 1 or more AEs during the study. The most frequently reported AEs (>1 participants) after MK-1167 6 mg intervention were catheter site or venipuncture pain (3) and panic attack (2). The episodes of panic attack were attributed to study-specific procedures in PN003, specifically the requirement in this study to participate in MRS imaging without movement for an extended period of time. All AEs were mild to moderate in intensity and resolved without intervention.

There were no serious AEs, ECIs or deaths reported in the study and no participant discontinued from the study due to an AE. There were no clinically meaningful trends observed as a function of study intervention for laboratory safety tests, VS, or ECGs.

MK-1167-004 (PN004)

Study MK-1167-004 was a randomized, placebo-controlled, single-site, double-blind study of MK-1167 in 2 panels of healthy elderly male and female participants, conducted in conformance with GCP. The primary objective of the study was to assess the safety, tolerability, and to characterize the PK of multiple doses of MK-1167 in healthy elderly study participants before administration in patients with AD in later studies. In this study, approximately 8 participants received single-day oral loading doses of MK-1167 10 mg/PBO following by maintenance doses of oral doses of MK-1167 1 mg/PBO daily for 16 days (Panel A), and approximately 8 participants received multiple-day oral loading doses of MK-1167 10 mg/PBO for 3 days following by maintenance doses of oral doses of MK-1167 3 mg/ PBO daily for 13 days (Panel B). This study is clinically complete, but DBL has not yet been achieved. A total of 16 participants were enrolled in this study, all of whom received multiple oral doses of MK-1167/PBO. Preliminary data indicate that the multiple-dose administration of MK-1167/PBO was generally well tolerated in healthy male and female elderly study participants. Of the 8 participants in Panel A, 5 (62.5%) experienced 1 or more AEs during the study. The most frequently reported AE (>1 participants) after MK-1167/PBO intervention in Panel A was headache (2). CCI [redacted] All AEs for both panels were mild to moderate in intensity.

There were no serious AEs, ECIs or deaths reported in the study and no participant discontinued from the study due to an AE. There were no clinically meaningful trends observed as a function of study intervention for laboratory safety tests, VS, or ECGs.

MK-1167-006 (PN006)

Study MK-1167-006 was an open-label, fixed-sequence, 2-period study to evaluate the safety, tolerability, and PK profile of a single oral dose of MK-1167 coadministered with diltiazem, a calcium channel blocker that has been extensively characterized as an inhibitor of CYP3A4 and frequently used as a perpetrator in DDI studies. The study was performed to assess the effect of MK-1167 on safety, PK, and interaction with CYP3A4 inhibitors in healthy male and female (of non-childbearing potential) study participants prior to introducing the treatment in patients with AD. This study is clinically complete and DBL was achieved on 27-FEB-2024. On Day 1 of Period 1, a single dose of MK-1167 3 mg was administered. PK sampling was performed predose and up to 600 hours postdose. There was a washout of at least 35 days between dosing in Period 1 and the first dose in Period 2. In Period 2, diltiazem was administered QD for 49 consecutive days with a single dose of MK-1167 3 mg coadministered on Day 3. PK sampling for MK-1167 was performed predose and up to 1128 hours post MK-1167 dosing. Predose blood samples were also collected for

diltiazem PK. Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

A total of 16 participants were enrolled in this study, of whom 14 completed the study and received 2 single doses of MK-1167. These participants received a single dose of MK-1167 3 mg alone on Day 1 of Period 1 and a single dose of MK-1167 3 mg coadministered with diltiazem on Day 3 of Period 2. Two participants were discontinued from the study due to AEs (positive COVID-19) on Day -1 of Period 2; these 2 participants received 1 single dose of MK-1167 3 mg alone on Day 1 of Period 1. Overall, single doses of MK-1167 3 mg were generally well tolerated in healthy study participants when administered alone or with diltiazem. Of the 16 study participants, 6 (38%) experienced 1 or more AEs during the study. The most frequently reported AEs (≥2 participants) after MK-1167 intervention were dry mouth, COVID-19, and headache, each reported by 2 (13%) participants. All AEs were mild to moderate in intensity.

There were no serious AEs, ECIs or deaths reported in the study. There were no clinically meaningful trends observed as a function of study intervention for laboratory safety tests, VS, or ECGs.

MK-1167-001, and MK-1167-002 were conducted in Belgium (PN001, PN002) and MK-1167-003 was conducted in the Netherlands (PN003). MK-1167-004 and MK-1167-006 were conducted in the US (PN004, PN006) under the MK-1167 IND.

PK

The PK of MK-1167 in plasma and blood were determined following single oral doses in healthy adult male participants of CCI [redacted] Given that the t1/2 estimates were generally equivalent in plasma and blood, these results suggest that the partitioning between the blood and plasma is rapid and reversible. In a comparison of fed and fasted participants following administration of 12-mg MK-1167, the PK exposures in plasma and whole blood were equivalent to one another indicating no relevant food effect on MK-1167 PK.

CCI [redacted]

CCI [redacted]

Additional safety and PK information is available in the IB.

2.2.3 Ongoing Clinical Studies

As of 28-MAY-2024, one Phase 1 study including oral doses of MK-1167 is ongoing in addition to MK-1167-007.

MK-1167-005 (PN005)

Study MK-1167-005 is a 2-part, randomized, placebo-controlled, single-site, double-blind study to evaluate the safety, tolerability, and PK of single and multiple doses of MK-1167 in healthy Japanese participants. As of 28-MAY-2024, the study is ongoing, but no clinical data are available. MK-1167-005 is being conducted in Japan.

MK-1167-007 (PN007)

CCI [redacted]

2.2.4 Information on Other Study-related Therapy: Donepezil Hydrocholoride

Donepezil HCl is an AChEI that is indicated for symptomatic treatment of mild-to-moderate AD. Standard dosing is donepezil HCl 10 mg, 1 tablet PO daily. The most common AE of donepezil HCl, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by the cholinomimetic effects of donepezil HCl, including nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These AEs are typically of mild intensity and transient, resolving during continued donepezil HCl treatment without the need for dose modification [Jack, C. R. Jr., et al 2018]. Less commonly observed AEs include depression and sleep disturbances (eg, abnormal

dreams and somnolence). Donepezil HCl is ~ 96% bound to human plasma proteins, mainly to albumins (~ 75%) and alpha-1 acid glycoprotein (about 21%) over the concentration range of 2 to 1000 ng/mL. Donepezil HCl is both excreted in the urine intact and extensively metabolized to 4 major metabolites, 2 of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil HCl is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Donepezil HCl has a Tmax of ~ 3 to 4 hours and t1/2 ~ 70 hours.

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.

CCI [redacted]

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.

The study population consists of patients with mild to moderate AD, 50 to 90 years of age.

Primary Objective	**Primary Endpoint**
Evaluate the safety and tolerability of MK-1167 when administered to patients with mild to moderate Alzheimer's Disease on stable doses of oral donepezil 10 mg daily	Adverse events, discontinuation due to Adverse events
Secondary Objectives	**Secondary Endpoints**
Evaluate the pharmacokinetic profile of MK-1167 when administered to patients with mild to moderate Alzheimer's Disease on stable doses of oral donepezil 10 mg daily Estimation: CCI [redacted]	AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F, t1/2
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Evaluate the changes in cognitive function of Alzheimer's Disease patients by comparing the Mini Mental State Examination and Digit Symbol Substitution Test scores obtained at baseline with those from the last day of dosing.	Mini Mental State Examination scores Digit Symbol Substitution Test scores
CCI [redacted]	Germline genetic variation
Explore the relationships between genetic variation, response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multisite study to evaluate the safety, tolerability, and PK of multiple doses of MK-1167 in participants with Alzheimer's disease maintained on baseline AChEI treatment with donepezil 10 mg PO daily. CCI [redacted]

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.

CCI [redacted]

In Panel A, participants will receive a loading dose of MK-1167 6 mg or matching PBO on Days 1 to 7 followed by QD dosing of MK-1167 3 mg or matching PBO for 14 consecutive days (Days 8 to 21). In Panel B, participants will receive QD dosing of MK-1167 6 mg or matching PBO for Days 1 to 31. CCI [redacted]

4.2 Scientific Rationale for Study Design

CCI [redacted]

CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Safety and tolerability of MK-1167 in male and female participants with AD will be evaluated as the primary objective for this study. CCI [redacted]

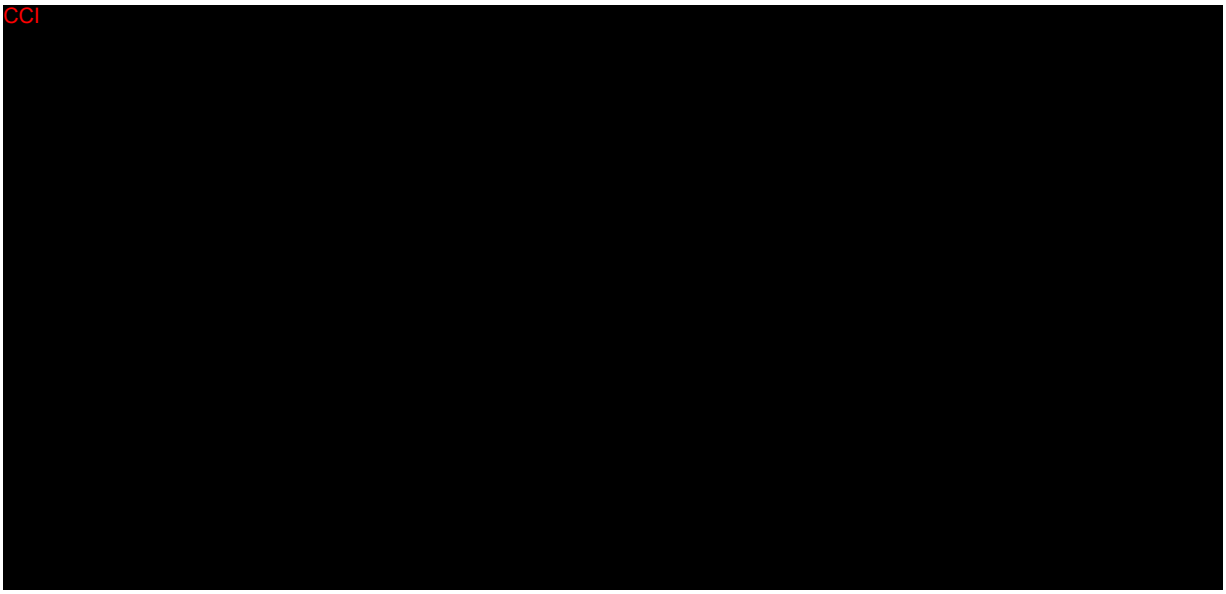
A cholinergic-related AE term has been defined and is composed of the following individual component AEs: nausea, vomiting, diarrhea, and abdominal pain.

Prospective assessment of suicidal ideation and behavior will be performed in this study using the C-SSRS.

Based on data from the preclinical toxicology and safety studies as well as clinical safety data from PN001, PN002, PN004, PN006 and PN007 Panel A (Section 2.2.3), it is expected that multiple-day administration of MK-1167 up to 6 mg daily for 31 days will be well tolerated in study participants with AD maintained on a stable dose of donepezil 10 mg daily.

No specific target organ toxicities have been identified in preclinical studies conducted with MK-1167 to date. In PN001 and PN002, single-dose administration of MK-1167 up to 76 mg and multiple-dose administration up to 8 mg daily was generally well tolerated in healthy younger adult study participants. In PN004, multiple-day oral loading doses of MK-1167 10 mg/PBO for 3 days following by maintenance doses of oral doses of MK-1167/PBO 3 mg daily for 13 days were generally well tolerated in healthy elderly study participants (Section 2.2.2). In PN007 Panel A, multiple-day oral loading doses of MK-1167/PBO 6 mg for 7 days following by maintenance doses of oral doses of MK-1167/PBO 3 mg daily for 14 days were generally well-tolerated in participants with AD maintained on a stable baseline dose of donepezil 10 mg (Section 2.2.3).

CCI [redacted]



4.2.1.2 Pharmacokinetic Endpoints

A secondary objective of this study is to evaluate the plasma PK profile of MK-1167 following multiple doses in male and female participants with AD. To characterize the PK of MK-1167, plasma AUC0-24, Cmax, and C24 will be determined. Other PK endpoints to be evaluated include Tmax, apparent terminal t1/2, apparent CL/F, and apparent Vz/F.

4.2.1.3 Pharmacodynamic Endpoints

Digit Symbol Substitution Test

The DSST, which assess processing speed and working memory, will be used in this study to measure potential effects of MK-1167 on cognition. The DSST is a rapid assessment of cognitive function that will be included in the current study on an exploratory basis to characterize potential effects of MK-1167 on cognition state CCI .

The DSST is one of the oldest and best-established neuropsychological tests and is found in a wide variety of intelligence scales. The test participant is required to associate certain symbols (usually digits) with other non-alpha-numeric symbols, and the speed and accuracy with which the task is performed serve as measures of executive function, specifically attention and processing speed. The task can be administered and performed quickly and because there are several versions of the test, the possibility of learning bias is reduced.

The DSST has been demonstrated to be sensitive to a wide variety of organic brain diseases including AD and has been used previously to demonstrate a treatment effect of encenicline a selective α7 nicotinic acetylcholine receptor partial agonist developed by Forum Pharmaceuticals for cognitive impairment in AD and schizophrenia [Barbier, A. J., et al 2015].

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 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 multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

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 participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Placebo will be used in this study to allow for an appropriate assessment of the safety data of MK-1167 and to maintain study blinding to reduce bias.

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

CCI [redacted]

As this is a Phase 1 assessment of MK-1167 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.6.

For the highest dose of MK-1167 to be tested in this study (Panel B), a dose of MK-1167 6 mg will be administered for approximately 31 days to achieve plasma concentrations that are sufficient to provide data on safety and tolerability over a range of potential doses that may be investigated for efficacy in AD patients in later studies, accounting for both inter-individual PK variability as well as potential DDI effects when MK-1167 is coadministered with CYP3A4 moderate inhibitors.

Preclinical investigations of MK-1167 indicate that participant age should not significantly affect the absorption, distribution, metabolism, or elimination profiles of MK-1167. As a result, PK data from doses previously investigated in healthy young adult participants in PN001 and PN002 as well as healthy elderly participants in PN004 Panel A have been used to anticipate exposures and concentrations for elderly participants in Panels A and B for the present study and are summarized in CCI [redacted]

CCI [redacted]

CCI [redacted]

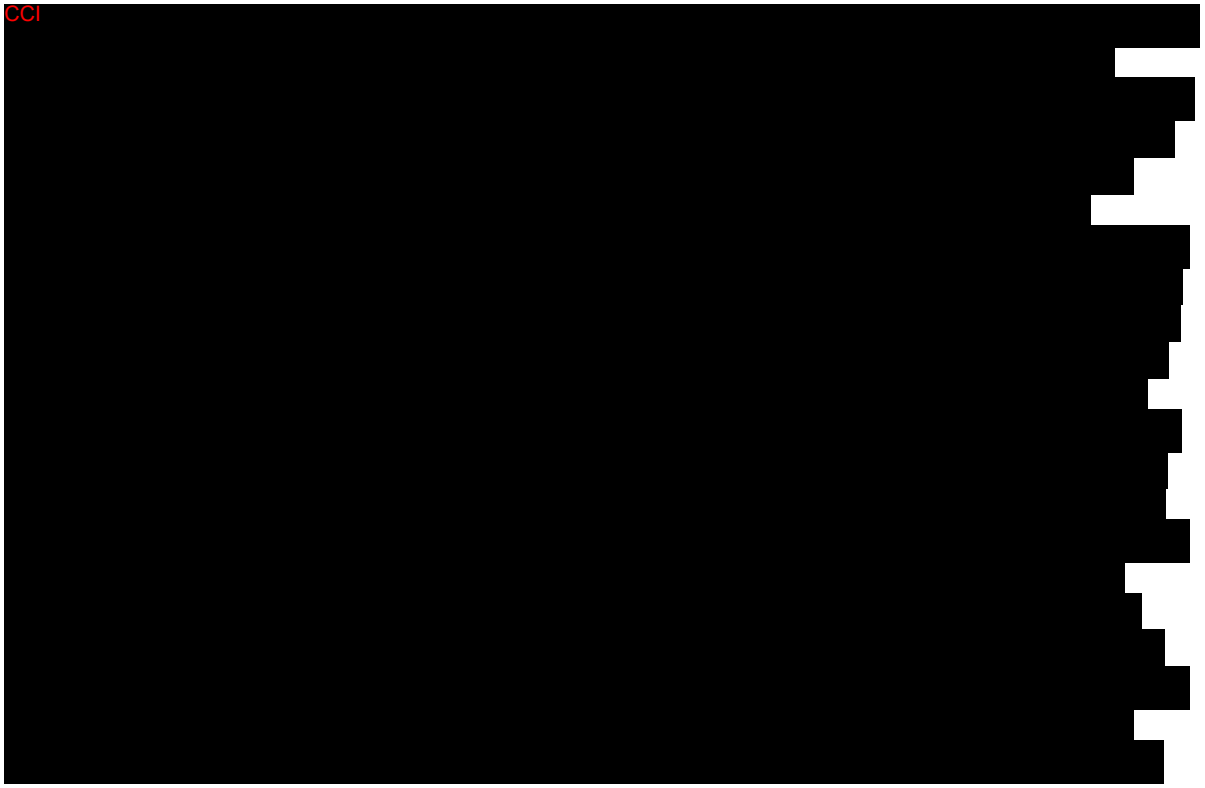
Table 2 CCI [redacted]

CCI [redacted]

CCI

Based on the overall GLP toxicity study findings in the rat and the dog, the dog is considered to be the more sensitive species. For more detailed information regarding results from the rat and dog toxicological studies, please refer to the IB for MK-1167.

CCI



CCI [redacted]

4.3.1 Rationale for Dose Interval and Study Design

MK-1167, an α7 nAChR PAM, is not considered a compound with higher potential for risk of harm to volunteers according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2007). It is not a biological molecule, does not exhibit highly species-specific action, nor is it directed towards immune system targets. Safety assessment toxicity trials and ancillary pharmacology trials with MK-1167 provide no contraindications to the initiation of clinical study in people with this compound via the oral route.

CCI [redacted]

CCI [redacted] and to reach steady state within the duration of the planned treatment in this study, Panel A participants received a loading dose of MK-1167 6 mg or placebo for Days 1 to 7 followed by QD maintenance dosing of MK-1167 3 mg or placebo for Days 8 to 21. This dosing schedule is similar to the multiple-dose administration paradigm previously implemented in healthy young adult participants in PN002 and healthy elderly participants in PN004. CCI [redacted] The loading and daily maintenance doses

and the corresponding projected exposures in a given panel of healthy elderly participants will not exceed the highest multiple dosage/exposures previously obtained in healthy young adult participants in PN002.

CCI [redacted]

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 (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test 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.

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

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

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Be in good health based on medical history, physical examination, VS measurements, and ECGs performed before randomization.
    a. Participants with chronic medical conditions, including but not limited to hypertension, hyperlipidemia, diabetes (Type 1 or 2) or hypothyroidism, which have been well-controlled on a stable dose of medication for the past 2 months and who are not receiving any proscribed medications for treatment may be enrolled if clinically acceptable to the investigator and Sponsor.

   Appendix 9 provides a table of the 12-Lead Electrocardiogram Evaluation Criteria.
2. Be in good health based on laboratory safety tests obtained at the Screening Visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.
3. BMI between 18 and 35 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.
4. Report a history of cognitive and functional decline with gradual onset and slow progression for at least 1 year before Screening, that is either corroborated by an informant who knows the subject well or is documented in medical records.
5. Meet the criteria for a diagnosis of probable AD based on NINCDS-ADRDA criteria for probable AD (Appendix 11).
6. Have a MMSE-2 score between 14 and 28, inclusive, at Screening as confirmed by the investigator. The MMSE-2 should be administered by a certified practitioner alternating the colors (red, blue) of the exam for a given subject to avoid learning effects with repeated administration.
7. Be receiving donepezil 10 mg daily for symptomatic treatment of cognitive impairment associated with AD. The dose level must be stable for at least 2 months prior to Screening. If receiving donepezil via a transdermal system (ie, patch), it should be a 10-mg/day dose and should switch prescription to a 10-mg oral daily dose, before enrollment.

8. Have a reliable and competent trial partner/caregiver who has a close relationship with the participant, has face-to-face contact at least 3 days a week for a minimum of 6 waking hours a week, and is willing to accompany the participant, if desired, to study visits. Overnight stays at the clinic for the partner/caregiver are not required but may be requested at the discretion of investigator after consultation with the Sponsor. The study partner/caregiver should understand the nature of the study and adhere to study requirements (eg, dosing, visit schedules, and nature and number of evaluations).

Demographics

9. Is an individual of any sex/gender, from 50 years to 90 years of age inclusive, at the time of providing the informed consent or assent, as applicable.

Assigned Male Sex at Birth

10. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. CCI [redacted]

    - Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent.

    OR

    - Uses contraception as detailed below 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) as detailed below:
        - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception as a condom may break or leak.

          Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.
        - Contraceptive use by participant capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Assigned Female Sex at Birth

11. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions apply:
    - Is not a POCBP

    OR

    - Is a POCBP and:
        - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. CCI [redacted]
        - The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
        - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for urine test) or 72 hours (for serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
        - CCI [redacted]
        - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

12. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.
13. The reliable and competent trial partner/caregiver who has a close relationship with the participant has provided documented informed consent/assent for the study.

Additional Categories

14. Willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. 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 5 years or suicidal behavior in their lifetime.
2. History of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases that are not under medical control over the past 2 months. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.
3. Has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-5 criteria, including schizophrenia or other psychotic disorder, bipolar disorder, or delirium at the time of the pre-study (screening) visit, or has a history of clinically significant psychiatric disorder of the last 5 years. Candidates may be excluded if they currently manifest neuropsychiatric symptoms of dementia, specifically episodes of aggression, emotional outbursts or agitation. Following consultation between the Investigator and the Sponsor, a history of major depressive disorder, generalized anxiety disorder, and/or insomnia under good control for ≥ 2 months on stable medical therapy may not be exclusionary.
4. History of cancer (malignancy).
    a. Participants with adequately treated disease deemed as “cured,” or who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study, may be enrolled at the discretion of the investigator and Sponsor.

5. Estimated eGFR ≤60 mL/min/1.73 m^2 based on the 2021 CKD-EPI.

CKD-EPI Equation (2021):

$$eGFR_{cr} = 142 \times \min(S_{cr}/K,1)^{\alpha} \times \max(S_{cr}/K, 1)^{-1.200} \times 0.994^{Age} \times 1.012 \text{ [if female]}$$

Where S_{cr} is serum creatinine, K is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of S_{cr}/K or 1, max indicates the maximum of S_{cr}/K or 1.

At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured CrCl of up to10% below of either 60 mL/min (for CrCl) or 60 mL/min/1.73 m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

6. History of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
7. Positive test(s) for HBsAg, hepatitis C antibodies or HIV at the screening visit.
8. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

9. Unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study, until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).
    a. Exception: participants on a stable dose of memantine (at least 2 months prior to Screening) may be included in the study.

CCI [redacted]

Prior/Concurrent Clinical Study Experience

11. Participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

12. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females) at the screening visit or Day -1/pre-dose visit. has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval.

CCI [redacted]

Other Exclusions

14. Under the age of legal consent.
15. The participant is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.
16. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer <354 mL/12 ounces>, wine <118 mL/4 ounces>, or distilled spirits <29.5 mL/1 ounce>) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
17. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
18. The participant is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative drug screen prior to randomization.
19. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
20. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, 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

5.3.1.1 Diet Restrictions

CCI [redacted] Participants will fast from all food and drinks, except water, between study intervention administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the SoA. Participants will fast from all food and drinks, except water, between meals and snacks. Meals do not have to be identical; however, the caloric content and composition of meals will be the same on each full PK sampling day in each panel. The meal content should be

consistent within a given clinical site. [redacted] Approximately 240 mL of water will be provided during study intervention administration. Additional water may be provided in 50-mL increments if required. Water will be restricted 1 hour before and 1 hour after study intervention administration.

On all other days**,** participants will fast from all food and drinks, except water, for at least 8 hours before study intervention administration. Participants will remain fasted between study drug administration and the first scheduled meal. Meals and snacks will be provided by the investigator at time points indicated in the SoA. Meals and snacks will be unrestricted in caloric content, composition, and timing. Each study intervention administration will need to be taken with approximately 240 mL of water. Additional water may be provided in 50-mL increments if required. Water will be restricted 1 hour before and 1 hour after study intervention administration.

5.3.1.2 Fruit Juice Restrictions

[redacted]

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants are advised to refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the Screening Visit. A recheck may be needed if participants did not refrain from consuming caffeinated beverages or xanthine-containing products 12 hours prior to the Screening Visit.

[redacted]

On all other days, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants are advised to refrain from consumption of alcohol 24 hours prior to the Screening Visit and 24 hours prior to initial domiciling on Day -3. A recheck may be needed if participations did not refrain from consuming alcohol 24 hours prior to the Screening Visit.

Participants will refrain from consumption of alcohol during their entire sequester in the CRU. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), and until the poststudy visit.

5.3.4 CCI [redacted]

Since this study intervention may make participants more likely to get sunburn, they will be required to protect their skin from sunlight exposure.

CCI [redacted]

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 may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention or withdraws from the study, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

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 provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. 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 3.

Country-specific requirements are noted in Appendix 7.

CCI

[redacted]

All supplies indicated in CCI 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 (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

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

Participants will be assigned randomly according to a computer-generated allocation schedule.

The sample allocation tables are provided below in Table 4 and Table 5.

Table 4 Allocation of Participants to Treatment For Panel A

Number of Participants	Days 1 to 7	Days 8 to 21
	Treatment	Treatment
n=12	6-mg MK-1167 QD + donepezil	3-mg MK-1167 QD + donepezil
n=4	Placebo to MK-1167 + donepezil	Placebo to MK-1167 + donepezil
n=number of participants in a subset of the study; QD=once daily. The suggested doses may be adjusted downward based on evaluation of safety, tolerability and/or pharmacokinetic data observed in previous treatment periods/panels. Note: Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range		

Table 5 Allocation of Participants to Treatment For Panel B

Number of Participants	Days 1 to 31
	Treatment
n=9	6-mg MK-1167 QD + donepezil
n=3	Placebo to MK-1167 + donepezil
n=number of participants in a subset of the study; QD=once daily. The suggested doses may be adjusted downward based on evaluation of safety, tolerability and/or pharmacokinetic data observed in previous treatment periods/panels. Note: Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range	

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique will be used. MK-1167 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. 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.

Donepezil administration will be conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

See Section 8.1.10 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

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

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention. Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after randomization or intervention allocation) must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

In addition, the following are specifically restricted from concomitant use during the study:

- CCI [redacted]

- CCI [redacted]
- All AChEIs other than donepezil (physostigmine, neostigmine, echothiophate, pyridostigmine, rivastigmine, galantamine, tacrine, edrophonium, succinylcholine, etc.).
- All cholinergic agonist medications (pilocarpine, cevimeline, carbachol, bethanecol, etc.).
- All medications with anticholinergic effects (amantadine, atropine, benztropine, cyclobenzaprine, darifenacin, dicyclomine, diphenoxylate with atropine, hydroxyzine, fesoterodine, glycopyrrolate, hydroxyzine, hyoscyamine, ipratropium, oxybutynin, phenothiazine, prochlorperazine, promethazine, quinidine, scopolamine, tolterodine, tropicamide, trospium, trimethobenzamide, trihexyphenidyl, tricyclic antidepressants [amitriptyline, monoamine oxidase inhibitors], as well as antihistamines cyproheptadine, promethazine, desloratadine, loratadine, diphenhydramine, etc.).
- CCI [redacted]
- Mood stabilizers, anticonvulsants, and typical or atypical antipsychotic medications (eg, lithium, valproic acid, phenytoin, levetiracetam, carbamazepine) Exception: use of pregabalin and gabapentin for neuropathic pain is acceptable.
- Sedatives/benzodiazepines (eg, chlordiazepoxide, clonazepam, diazepam, flurazepam, meprobamate, triazolam). Use of the following non-benzodiazepine medications for sleep may be acceptable if stable for at least 2 months before the Screening Visit, following review by the investigator and Sponsor: trazodone, mirtazapine, zaleplon, zopiclone, eszopiclone, and zolpidem.
- Narcotic analgesics (eg, codeine, morphine, hydromorphone, oxycodone, propoxyphene and combination products that contain a narcotic).
- Stimulant medications (eg, amphetamine, methylphenidate, atomoxetine, modafinil)

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications/vaccinations are permitted:

- CCI [redacted]
- Female participants: Hormonal replacement therapy. The participant must be on a stable treatment regimen for at least 6 months prior to screening.
- Cetirizine and montelukast sodium may be permitted for allergies following consultation with the Sponsor.
- CCI [redacted]

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/Other

Refer to Section 4.3.1 for a discussion on the dose planned for this study.

For both Panels A and B, safety and tolerability of at least 8 participants through at least 24 hours post-last dose will be evaluated to determine if study objectives continue to be met.

6.6.1 Stopping Rules

The following stopping rules will be used during the conduct of this study.

These stopping rules apply to study intervention which refers to relationship to MK-1167/placebo administration.

If any of the below stopping rules are met, the study will be stopped, and no further dosing will occur until the Sponsor has reviewed the totality of data available. Continuation of the study would require an amendment.

- An individual participant reports an SAE, unless clearly not related to study intervention by the investigator.
- Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs unless clearly not related to study intervention by the investigator.

If any of the stopping rules are met, subsequent doses of treatment for remaining participants may be adjusted (maintained at the same level, decreased or halted) based on joint agreement of the Sponsor and investigator after an amendment is implemented.

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 allocation/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 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

This study is blinded, but supplies are provided open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are provided.

6.9 Standard Policies

Not applicable.

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 participate in the study as specified in Section 1.3 and Section 8.1.9, or a PCL (only applicable if not all procedures should be done per Section 1.3).

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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 interrupts study intervention administration for more than 1 consecutive days or has 1 cumulative missed doses.

The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

The participant has a confirmed positive serum pregnancy test.

The participant has a positive drug screen at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

For a participant who are discontinued from study intervention, all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

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.

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.
- Participant is lost to follow-up.

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 8.1.9. 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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

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 providing documented informed consent or assent, when applicable, may be used for screening or baseline purposes provided the procedures meet 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 or assent, when applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in Appendix 8.

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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

Informed consent given by the participant (or their legally acceptable representative) must be documented on a consent form. The form must include the study protocol number, study

protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

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

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. If there are changes to the participant'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

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 dated signature.

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 their 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 identification 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

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 4 weeks or 5 half-lives before screening. CCI [redacted] Participants will be stably maintained on donepezil (10 mg) for at least 2 months prior to Screening.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Participants will be stably maintained on donepezil (10-mg) for at least 2 months prior to screening.

8.1.6 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 Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee.

Study intervention should begin on the day of treatment allocation/randomization or as close as possible to that day.

8.1.8.1 Timing of Dose Administration

The first oral doses of MK-1167/placebo will be administered in the morning at approximately the same time every day. After all pre-dose procedures are completed on the morning of Day 1, either MK-1167 or placebo will be administered, with the time of administration constituting Time "0". All capsules will be distributed and consumed within 10 minutes of the recorded administration time. CCI

[redacted]

[redacted]

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 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.

8.1.10 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, they will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. The emergency unblinding call center will provide the investigator or medically qualified designee the requested information 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 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.

8.1.11 Domiciling

Panel A:

Participants will report to the CRU in the evening on Day −4 before the scheduled day of study intervention administration on Day [redacted] and remain in the unit until all post-dose procedures have been performed on Day [redacted] for Panel A. [redacted]

CCI site. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Participants may be permitted to leave the unit, for emergency situations only, during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

Panel B:

Domiciling for Panel B is optional. If participants choose to travel to and from the CRU on select days, they will need to report to the CRU in the evening on Day −4 before the scheduled day of study intervention administration on Day C CI and remain in the unit until all post-dose procedures have been performed on Day C C per the SoA. On Days 3-31 participants will be required to attend the CRU daily to receive study intervention and complete all activities per the SoA. Participants may also domicile at the CRU on Days 23 and 31, if deemed necessary by the investigator. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

If participants choose to domicile at the CRU for the duration of the study intervention period, participants will report to the CRU in the evening on Day −4 before the scheduled day of study intervention administration on Day 1 and remain in the unit until all post-dose procedures have been performed on 31 for Panel B. Participants can stay in the CRU through 32 for Panel B, if deemed necessary by the investigator. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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8.1.12 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 Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.7.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study

(from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at prespecified timepoints noted in the SoA (Section 1.3). Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body Mass Index

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

Oral, tympanic, or temporal body temperature, PR, RR, and BP will be assessed.

BP and pulse measurements will be assessed in the semi-recumbent and/or standing position with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participant's arm is essential to increase the accuracy of BP measurements.

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-1167/placebo. The mean of these measurements will be used as the baseline to calculate change from baseline for safety

evaluations (and for rechecks, if needed). On all other days indicated in the SoA (See Section 1.3) predose HR and BP will be single measurements. Postdose VS measurements will be single measurements unless there is an out-of-range reading. In this case, at least 3 measures of VS (either resting or orthostatic HR, BP) will be taken within a 15-minute period, or until readings fall into normal range.

Participants will continue to rest semirecumbent from dosing until 2 hours postdose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained. Participants should be semirecumbent for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS. When there is an out-of-range reading, additional measurements should be taken until readings fall into normal range. Participants should be semirecumbent for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.

At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Participants may need to remove interfering garments.

Participants should be resting in the semirecumbent position for at least 10 minutes before each ECG measurement.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing MK-1167. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During each treatment period, if a participant demonstrates a mean increase in QTc interval ≥60 msec compared to the mean predose baseline measurement, the participant will continue to be monitored by at least single repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc interval is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

Postdose ECG measurements will be triplicate measurements.

During each treatment period, if the mean QTc interval is ≥500 msec for postdose measurements, the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the mean QRS interval from any postdose ECG is 20% greater than the mean baseline QRS interval and is >120 msec (and change is not considered rate related or pacing induced) or there appears to be new onset intermittent bundle branch block, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS interval is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If at any time the QRS interval is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc interval is noted, concomitant medications that prolong QTc interval should be held until the QTc interval is within 60 msec of baseline and the QTc interval is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 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 20 days after the last dose of study intervention, 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.

8.3.5 Neurological Exam

The full neurological exam monitors aspects of mental status, cranial nerve function, motor system function, reflexes, coordination and gait and sensory function (Appendix 12) and will be administered at screening and the post-study exam. The targeted neurological exam contains Modules 1, 2 and 5 of the general examination, focusing on arousal, cranial nerve function, and gait.

8.3.6 Mini-Mental State Examination

The MMSE-2 will be administered to the participant in paper form, scored and recorded by the principal investigator or trained designee according to the instructions in the operations manual.

8.3.7 WAIS-IV Digit Symbol Substitution Test

The DSST will be administered to the participant in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the operations manual.

8.3.8 Suicidal Ideation and Behavior Monitoring

8.3.8.1 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 the time points indicated in the SoA. In addition, C-SSRS will be administered at any unscheduled visit where safety assessments are performed. The C-SSRS will not be routinely administered at visits with a

sole purpose of PK sampling and/or witnessed study intervention administration. 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 at screening, 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.

8.3.9 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption, or rash occurrence in determining etiology and study intervention relationship. See Investigator Site Binder for additional guidance.

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 safety 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

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 under any of the following circumstances:

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,

if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention randomization through 14 days after cessation of intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside the period specified in the previous paragraph also 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 6.

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

Table 6 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting 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 (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose				

DILI=drug-induced liver injury; 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. 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). The investigator will also make every attempt to follow 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 toward 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 SAEs) 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

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

A cholinergic-related AE term has been defined and is composed of the following individual component AEs: nausea, vomiting, diarrhea, and abdominal pain.

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:

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  - CCI
  - CCI
  - CCI
  - CCI
- An overdose of Sponsor's product, as defined in Section 8.5.
- Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent). It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any study intervention administered that exceeds the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a non-study intervention dose (eg, rescue or concomitant medication) is to be considered an overdose, in consultation with the Sponsor.

Sponsor does not recommend specific treatment for any overdose. 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

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-1167

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

8.7 Pharmacodynamics

Tools for cognitive assessment, such as the DSST (processing speed and working memory), may be useful to assess effects on cognition. The DSST is a rapid assessment of cognitive function that will be included in the current study CCI [redacted]

8.8 Biomarkers

CCI [redacted]

- Blood for Genetic Analysis
- CCI [redacted]

8.8.1 Planned Genetic Analysis Sample Collection

CCI [redacted] 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 pre-dose on Day 1 but may be collected at the next scheduled visit, 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

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

Leftover samples listed in Section 8.8.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Within approximately 4 weeks; before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Rescreening is defined as a separate screening period and be initiated as needed, by the investigator after consultation with the Sponsor, including for screen failures (Section 5.4).

Participants may be rescreened after consultation with the Sponsor. Rescreening is to include all screening procedures listed in the SoA (Section 1.3), including consent review.

CCI [redacted]

Rescreen procedures cannot be conducted the day prior to intervention randomization if there are Day −1 procedures planned per protocol.

8.10.2 Treatment Period/Vaccination Visit

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

CCI [redacted]

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-1167 is the critical procedure.

At any postdose time point, the blood sample for MK-1167 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

PK Collection as outlined in CCI [redacted]

Table 7 CCI

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Study Intervention Administration:

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Panel A and Panel B - Predose and Postdose Procedures:

Predose standard safety evaluations: VS and ECG within 3 hours; laboratory safety tests and physical examination within 24 hours

Panel A - Postdose standard safety evaluations: VS, ECG, laboratory safety tests, physical/neurological examination, and C-SSRS.

- Prior to 24-hours postdose may be obtained within 30 minutes of the theoretical sampling time
- Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
- CCI postdose may be obtained within 4 hours of the theoretical sampling time
- CCI may be obtained within 30 hours.

Panel B - Postdose standard safety evaluations: VS, ECG, laboratory safety tests, physical/neurological examination, and C-SSRS.

- Prior to 24-hours postdose may be obtained within 30 minutes of the theoretical sampling time
- 24-hours postdose may be obtained within 1 hour of the theoretical sampling time
- CCI may be obtained within 24 hours of the theoretical sampling time
- CCI

8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-1167 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel
- Interchange of doses between panels
- Entire period(s) or panel(s) may be omitted
- Decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, divided doses qd to bid, tid, or vice versa)
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

The PK sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during their participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during their participation in the entire study.

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 KEY STATISTICAL CONSIDERATIONS

This section details the principal statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor.

9.2 Hypotheses/Estimation

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

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Safety: Primary safety endpoints will include all types of adverse events and discontinuation of study intervention due to adverse event(s), in addition to laboratory safety tests, ECGs, C-SSRS and vital signs. Baseline is defined as measurements obtained pre-dose Day 1.

9.3.2 Secondary Endpoints

Pharmacokinetics: The pharmacokinetic variable(s) of plasma MK-1167 [AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F, t1/2] are of secondary interest.

9.3.3 Exploratory Endpoints

MMSE-2, DSST.

9.4 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

9.4.1 All Participants As Treated Population

The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

9.4.2 Per-Protocol (PP) Population

The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit

the effects of treatment, according to the underlying scientific model. 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 prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. 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 from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the pharmacokinetics and pharmacodynamic analyses.

9.5 Statistical Methods

9.5.1 Statistical Methods for Pharmacokinetic Analyses

Model-based PK summary

CCI [redacted]

[redacted]
Kenward and Roger's adjustment to the degrees of freedom will be employed. Ninety-five percent confidence intervals for the least squares means by day will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. A sample code is as follows:

```
proc mixed data=adpp;
class day usubjid;
model lnpk=day /ddfm=kr;
random usubjid;
lsmeans day /alpha=0.05 cl;
run;
```

To assess the accumulation of MK-1167 relative to the loading dose, the least squares mean differences CCI [redacted] and 90% confidence intervals from this model will be back transformed to obtain the geometric mean accumulation ratios (Day 8/Day 1 and Day 21/Day 1) and 90% confidence intervals for CCI [redacted]

CCI [redacted] Kenward and Roger's adjustment to the degrees of freedom will be employed. Ninety-five percent confidence intervals for the least squares means by day will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield

estimates for the population geometric means and confidence intervals about the geometric means on the original scale. A sample code is as follows:

```
proc mixed data=adpp;
class day usubjid;
model lnpk=day /ddfm=kr;
random usubjid;
lsmeans day /alpha=0.05 cl;
run;
```

CCI

[redacted]

CCI

[redacted]

[redacted]

Descriptive Statistics

Individual values will be listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV, calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 × sqrt($\exp(s^2) - 1$), where s^2 is the observed variance on the natural log-scale).

9.5.2 Statistical Methods for Pharmacodynamic Analyses

MMSE-2 scores

In order to evaluate the change in cognitive function of AD patients, descriptive summary statistics of the values and the change from baseline values will be provided for the MMSE-2 scores obtained at baseline (screening) and from the last day of dosing.

WAIS-IV DSST scores

In order to evaluate the change in cognitive function of AD patients, descriptive summary statistics of the values and the change from baseline values will be provided for the DSST scores obtained at baseline (Day -1) and each postdose timepoint by treatment.

9.5.3 Statistical Methods for Safety Analyses

Safety will be evaluated by clinical assessment of AEs, 12-lead ECGs, vital signs, laboratory safety tests, physical/neurological examinations and C-SSRS. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or VS as well as for change from

baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Responses to the C-SSRS will be tabulated and the individual score will be listed.

9.6 Interim Analyses

No interim analysis is planned.

9.7 Multiplicity

Since there is no hypothesis, no adjustments for multiplicity are needed.

9.8 Sample Size and Power Calculations

CCI

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and 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. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. 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. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in 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 and ICH Guidelines. 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. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

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.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record 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 their 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

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 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.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.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 Regulation 536/2014 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 Regulation 536/2014, 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.

10.1.6 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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.7 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.

10.1.8 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.

10.1.9 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 8 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose fasting			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (as needed in PONCBP only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, • cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 nontherapeutic 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 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 study intervention cause the AE?

The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? 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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)

- **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 study intervention 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 study intervention relationship).

- Yes, there is a reasonable possibility of study intervention relationship:
  - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
- No, there is not a reasonable possibility of study intervention relationship:
  - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (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 email 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: Drug–Device Combination Products/Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

Premenopausal 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, Müllerian 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

- 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 participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
- Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Nonparticipant of Childbearing Potential

A nonparticipant assigned female sex at birth is considered fertile and capable of becoming pregnant following menarche until becoming postmenopausal unless permanently sterile (see below):

Nonparticipants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered of CBP:

Premenarchal

Premenopausal with 1 of the following:

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

Postmenopausal

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

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant [a] • IUS [a,b] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception [a,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception [a,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide [d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Penile/external condoms must be used in addition to the POCBP's hormonal contraception [b] IUS is a progestin releasing IUD [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [d] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction) [d]

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 their 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 is 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 that 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 used 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

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
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/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Tables

Panel A

	Pre-Study[a]	Treatment Periods	Post-Study	Total Collections	mL Per Collection	Total mL/Test
Laboratory Safety Tests	1	4	1	6	12.5	75
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
CCI [redacted]	1	0	0	0	5	5
Blood for donepezil PK	11	10	0	21	3	63
Blood for MK-1167 PK	0	51	0	51	4	204
Total Blood Volume per Participant[b]						**360.5**

[a] Pre-Study includes screening and Days -3, -2, and -1.
[b] If additional pharmacokinetic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

Panel B

	Pre-Study[a]	Treatment Periods	Post-Study	Total Collections	mL Per Collection	Total mL/Test
Laboratory Safety Tests including serum hCG (POCBP) or serum FSH (PONCBP) and BDS	1	5	1	7	12.5	87.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
CCI [redacted]	1	0	0	0	5	5
Blood for donepezil PK	11	10	0	21	3	63
Blood for MK-1167 PK	0	61	0	61	4	244
Total Blood Volume per Participant[b]						**413**

[a] Pre-Study includes screening and Days -3, -2, and -1.
[b] If additional pharmacokinetic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia		
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation		
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay		
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female		
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P. Mitrale or P. Pulmonale
Ventricular Abnormalities		
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old		

ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Nonspecific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER		
AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave. Baseline is defined as predose Day 1.		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at pre-study (screening) visit and/or pre-dose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.
B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including repeats if performed), the participant will be excluded from the study.
C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
   - The participant may be excluded from the study.
   - The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
   - The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.
     OR
   - The abnormal test may be repeated (refer to items below for continuation of algorithm for repeated values).
     - If the repeat test value is within the normal range, the participant may enter the study.
     - If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.
D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria for Probable AD

I. The criteria for the clinical diagnosis of PROBABLE AD include:

Dementia established by clinical examination and documented by the Mini-Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;

Deficits in two or more areas of cognition;

Progressive worsening of memory and other cognitive functions;

No disturbance of consciousness;

Onset between ages 40 and 90, most often after age 65; and

Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE AD is supported by:

Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia);

Impaired activities of daily living and altered patterns of behavior;

Family history of similar disorders, particularly if confirmed neuropathologically

III. Other clinical features consistent with the diagnosis of PROBABLE AD, after exclusion of causes of dementia other than AD, include:

Plateaus in the course of progression of the illness;

Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

Seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE AD uncertain or unlikely include:

Sudden, apoplectic onset;

Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

Seizures or gait disturbances at the onset or very early in the course of the illness.

10.12 Appendix 12: General and Targeted Neurological Examinations

The General and Targeted Neurological Examination will be performed at the time points specified in the SoA (Section 1.3).

Note to the investigator: If at any time abnormalities are observed in the General or Targeted Neurological Exams, the investigator should do additional examinations as needed based on medical judgment.

10.12.1 The General Neurological Examination

The General Neurological Examination includes all of the modules listed below and is intended to be a general screening examination.

10.12.1.1 Module 1 – Mental Status Examination

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of impaired attention or concentration. For example, difficulty remembering or following instructions or distractibility may be signs of inattention).

B. Thought Processes and Language (generally assess logic, relevance, organization, and coherence of participant's use of language throughout the interview).

C. Orientation (time, place, person).

D. Attention/Concentration.
Ask the participant to count backwards from 100 by 7's ("Serial 7's") or ask to recite months backwards or spell a 5 unique letter word (eg, "WORLD") backwards.
Note: To avoid learning effects, switch between tests throughout the study.

E. Memory (test registration of 3 objects; then test immediate recall 5 minutes later).
Grade: NORMAL or IMPAIRED and describe abnormality (for each, A to E, above).
Normal performance on Serial 7's is getting to 65 with no more than 1 error.

10.12.1.2 Module 2 – Cranial Nerve Assessment

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus).
Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)

F. VIII – Auditory Acuity (assessed using a bed-side screening test [eg, by rubbing fingers on each side of participant's head or by whispering numbers])

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)
Score: left and right (except for G, H, J)
Grade: NORMAL or IMPAIRED and describe abnormality

10.12.1.3 Module 3 – Motor System

A. Muscle Tone

1. Ask the participant to relax.
Flex and extend the participant's elbows and knees (bilaterally).
There is a small, continuous resistance to passive movement.
Observe for involuntary movements (eg, tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

   Score: left and right

   Grade: NORMAL, INCREASED or DECREASED

B. Muscle Strength

1. Ask the participant to stand up from sitting without using hands

   Grade: NORMAL, IMPAIRED and describe abnormality

   Test proximal limb strength by having the participant flex and extend the knees and elbows against your resistance.
Test bilaterally and compare one side to the other.

   Score: left and right

   Grade:

   5/5: normal
   4/5: movement against resistance impaired
   3/5: movement against gravity but not against resistance
   2/5: visible movement but not against gravity
   1/5: visible contraction
   0/5: no visible activity

   Test distal limb strength by having the participant conduct dorsiflexion and plantar flexion of the participant's feet; finger abduction and handgrip strength against your resistance.
Test bilaterally, and compare one side to the other.

   Score: left and right

Grade:

5/5: normal
4/5: movement against resistance impaired
3/5: movement against gravity but not against resistance
2/5: visible movement but not against gravity
1/5: visible contraction
0/5: no visible activity

C. Pronator Drift

Ask the participant to hold both arms straight forward with, palms up and eyes closed for ≈10 to 15 seconds as tolerated; watch for how well the arm position is maintained. Instruct the participant to keep both arms still while you tap them briskly downward. The participant should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

Score: left and right

Grade: NORMAL or IMPAIRED and describe abnormality

10.12.1.4 Module 4 – Reflexes

A. Biceps

B. Knee

Note: Other deep tendon reflexes may be tested at investigator's discretion (eg, elbow, wrist, or Achilles tendon)

Score: left and right

Grade: NORMAL, INCREASED, DECREASED, or ABSENT

C. Babinski

Score: left and right

Grade: NORMAL or ABNORMAL

10.12.1.5 Module 5 – Coordination and Gait

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the participant to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

   Score: left and right

   Grade: NORMAL or IMPAIRED

   Reminder: If the rapid alternate movements are disturbed, the participant will be asked to strike their hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place. (This test is impaired in cerebellar disease, extra pyramidal disease and upper motor neuron weakness.)

B. Point-to-Point Movements
   1. Ask the participant to touch your index finger and their nose alternately several times. Move your finger about as the volunteer performs this task.

      Score: left and right

      Grade: NORMAL or IMPAIRED

      Reminder: If the point-to-point testing is disturbed, the participant will be asked to place one heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides. (Impaired tests indicate cerebellar disease.)

C. Romberg
   1. Ask the participant to stand with both feet together and eyes closed for 20 to 30 seconds without support.

      Be prepared to catch the participant if they are unstable.

      Grade: NORMAL or IMPAIRED

D. Gait
   1. Ask the participant to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

      Grade: NORMAL or IMPAIRED and describe abnormality

      Ask the participant to walk heel-to-toe in a straight line (tandem gait).

      Grade: NORMAL or IMPAIRED and describe abnormality

10.12.1.6 Module 6 – Sensory

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.
B. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.
C. Temperature: warm or cool object touched to skin of forearms and legs, bilaterally.
D. Vibration: tuning fork vibration detection in hands, feet bilaterally.
E. Position sense: perception of thumb and toe movement, bilaterally.
F. Stereognosis: (identify common objects placed in hand, [eg, coin, key, etc]).

   Score: left and right

   Grade: NORMAL OR IMPAIRED and describe abnormality (for each A to F)

10.12.2 The Targeted Neurological Examination

The Targeted Neurological Examination, which is intended to focus on tests where drug effects can be seen, includes the following tests only:

10.12.2.1 Module 1 – Mental Status Examination

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of

impaired attention or concentration. For example, difficulty remembering or following instructions or distractibility may be signs of inattention)

10.12.2.2 Module 2 – Cranial Nerve Assessment

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)
   1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

10.12.2.3 Module 3 – Motor System

B. Muscle Strength
   1. Ask the participant to stand up from sitting without using hands
      Grade: NORMAL or IMPAIRED and describe abnormality

10.12.2.4 Module 5 – Coordination and Gait

D. Gait
   1. Ask the participant to walk heel-to-toe in a straight line (tandem gait).
      Grade: NORMAL or IMPAIRED and describe abnormality

10.12.2.5 Module 6 – Sensory

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
α7 nAChR	alpha 7 nicotinic acetylcholine receptor
ACh	acetylcholine
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-24	area under the curve from 0 to 24 hours
BDS	blood drug screen
bid	twice daily
BLA	Biologics License Application
BMI	body mass index
BP	blood pressure
C24	concentration at 24 hours
CCU	Cardiac care unit
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL/F	oral clearance
COVID-19	coronavirus of 2019
CrCl	creatinine clearance
CRF	Case Report Form

Abbreviation	Expanded Term
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
CV	coefficient of variation
DBL	database lock
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EM	exposure multiple
EMA	European Medicines Agency
EU	European Union
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FE	fractional enrichment
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice

Abbreviation	Expanded Term
gln	glutamine
CCI [redacted]	CCI [redacted]
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCl	hydrochloride
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
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
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
LAM	lactational amenorrhea method
MBP	mean blood pressure
CCI [redacted]	CCI [redacted]
nAChR	nicotinic acetylcholine receptor
NCS	not clinically significant
NDA	New Drug Application
NHP	nonhuman primate

Abbreviation	Expanded Term
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders - Stroke and the Alzheimer's Disease and Related Disorders Association
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PAM	positive allosteric modulator(s)
PBO	placebo
PCL	Protocol Clarification Letter
PK	pharmacokinetic
PN	protocol number
PO	orally
POCBP	participant/participants of childbearing potential
PONCBP	participant/participants of nonchildbearing potential
PP	per-protocol
PQC	product quality complaint
PR	pulse rate
PS	polysorbate
QD	once daily
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures

Abbreviation	Expanded Term
SPF	sun protection factor
SUSAR	suspected unexpected serious adverse reaction
TEA	Treatment Eligibility Assessment (form)
t1/2	half life
Tmax	time to maximum plasma concentration
UDS	urine drug screen
ULN	upper limit of normal
US	United States (of America)
UTN	Universal Trial Number
Vd	volume of distribution
VAS	Visual Analog Scale
VS	vital signs
Vz/F	apparent volume of distribution
WAIS-IV	Wechsler Adult Intelligence Scale-IV
WBC	white blood cell

11 REFERENCES

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