

Official Protocol Title:	A Multiple Ascending Dose Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-2214 in Adults with Mild Cognitive Impairment or Mild-to-Moderate Alzheimer's Disease
NCT Number:	NCT05466422
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TITLE PAGE

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Protocol Title: A Multiple Ascending Dose Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-2214 in Adults with Mild Cognitive Impairment or Mild-to-Moderate Alzheimer's Disease

Protocol Number: 002-03

Compound Number: MK-2214

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	Not applicable
EudraCT	Not applicable
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	154578

Approval Date: 01 July 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 3	01-JUL-2024	Revised post-randomization CSF collection to Day 29 for all participants in Panels D to F.
Amendment 2	12-DEC-2023	Revised inclusion/exclusion criteria to support study recruitment.
Amendment 1	08-MAY-2023	Extended domiciling period following each dose for additional safety observation
Original Protocol	16-JUN-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

Revised post-randomization CSF collection to Day 29 for all participants in Panels D to F.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3, Schedule of Activities	Revised post-randomization CSF collection to Day 29 for all participants in Panels D to F in footnote 'i'.	This change was made to support characterization of CSF CCl levels at a common timepoint for all participants in Panel D and subsequent panels.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3 Schedule of Activities	Revised the end of infusion assessment timing of local infusion site tolerability. Revised end of infusion PK collection timepoint for dosing days. Updated the notes for Blood for Serum ADA from reference Sec. 8.6.1 to 8.6.3 Revised footnote 'c' to include flexible language for the duration of the infusion.	Provided clarification in the event infusion times are less than 30 minutes, the 0.5h assessment should be moved to the end of the infusion. Provided clarification in the event infusion times are less than 30 minutes, the 0.5h sample should be collected at the end of the infusion instead of at the 0.5hr timepoint. Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6). This language was added to provide flexibility in the infusion time duration in the event a dose requires an infusion time of less than 30 minutes.
4.2.1.2 Pharmacokinetic Endpoints	Revised post-randomization CSF collection to Day 29 for all participants in Panel D to F. “ADAs to MK-2214” subheading and content moved from deleted Section 4.2.1.3 (Pharmacodynamic Endpoints)	This change was made to support characterization of CSF CCI levels at a common timepoint for all participants in Panel D and subsequent panels. Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).
Section 4.2.1.3 Pharmacodynamic Endpoints	This section was removed and the content for CCI was moved to Section 4.2.1.3 (now Planned Biomarker Research) and subsequent sections were renumbered.	Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).

Section Number and Name	Description of Change	Brief Rationale
Section 4.2.1.3 Planned Biomarker Research	Removal of “Exploratory” in this newly renumbered section heading title.	The title of this section was updated to reflect that there are biomarkers that support the primary and exploratory objectives in this section.
Section 4.2.1.3.2 Other Biomarkers	The heading for this section was changed to “Other Biomarkers” and the prior section titled “Exploratory Plasma Diagnostic Biomarkers for Alzheimer’s Disease” is now a subheading for the original content in this section.	Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).
Section 6.3.2 Stratification	Revised post-randomization CSF collection to Day 29 for all participants in Panels D to F.	This change was made to support characterization of CSF CCI levels at a common timepoint for all participants in Panel D and subsequent panels.
Section 8.6.1 Blood Collection for Serum MK-2214	Heading title updated from ‘Blood Collection for Plasma MK-2214’ to ‘Blood Collection for Serum MK-2214’.	This correction was made to align with the appropriate biological matrix used for the PK samples.
Section 8.6.3 Blood for Serum ADA	Created new “Blood for Serum ADA” section heading and added language for handling of serum ADA samples.	Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).
Section 8.7 Pharmacodynamics	Removed original language in this section and created a reference to Section 8.8.	Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).
Section 8.8 Biomarkers	Updated CSF bullet to include CCI and hemoglobin”.	Consolidated samples and rationale to better align placement within the appropriate sections (eg, pharmacodynamic samples under Exploratory Biomarkers which includes pharmacodynamic analyses (4.2.1.4 and 8.8), and ADA collections aligned with PK (4.2.1.2 and 8.6).
Section 9.6 Statistical Methods	Removed the “Exploratory (Pharmacodynamic)” subheading and moved the serum ADA content under the “Exploratory (Pharmacokinetics)” subheading.	Consolidated samples and rationale to better align placement within the appropriate sections.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multiple Ascending Dose Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-2214 in Adults with Mild Cognitive Impairment or Mild-to-Moderate Alzheimer's Disease

Short Title: Multiple Ascending Dose Trial of MK-2214 in Adults with MCI or Mild-to-Moderate AD

Acronym: NA

Hypotheses, Objectives, and Endpoints:

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

This study is to be conducted in male and female participants with MCI or mild-to-moderate AD and healthy older participants (optional).

Primary Objective	Primary Endpoint
Objective: To evaluate the safety and tolerability of multiple ascending doses of MK-2214.	Adverse events and participant discontinuations due to adverse events adverse events.
Objective: To estimate the serum PK profile (eg, AUC0-28, Cmax, Tmax, t1/2) of multiple ascending doses of MK-2214.	Serum AUC0-28, Cmax, Tmax, t1/2 (after the third dose)
Objective: To estimate cerebrospinal fluid exposure (eg, cerebrospinal fluid concentration at Day 85) of multiple ascending doses of MK-2214. Hypothesis (Part 1 only): At a generally well tolerated dose level, the true geometric mean concentration at Day 85 of MK-2214 in cerebrospinal fluid is >0.3 nM.	Cerebrospinal fluid concentration at Day 85
Objective: To evaluate the free phospho-tau in cerebrospinal fluid.	Free phospho-tau in cerebrospinal fluid
Secondary Objectives	Secondary Endpoints
There are no secondary objectives in this trial.	Not Applicable

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Dementia Alzheimer's type
Population	Part 1: Men and women of nonchildbearing potential with MCI or mild-to-moderate AD. Part 2 (optional): healthy older men and women of nonchildbearing potential and/or participants with MCI or mild to moderate AD.
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 Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 2 years 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:

Up to approximately 48 participants will be allocated/randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Active	MK-2214	150 mg/mL	20 mg 100 mg 500 mg 2000 mg	IV Infusion	Panel A Panel B Panel C Panel D Panel E Panel F	Test Product
Placebo	Placebo	0	0 mg	IV Infusion	Panel A Panel B Panel C Panel D Panel E Panel F	Placebo

In this protocol, placebo for MK-2214 is diluent alone (5% Dextrose), diluent is used for blinding purposes and does not contain active ingredients.

Other current or former name(s) or alias(es) for study intervention(s) are as follows:

Total Number of Intervention Groups/Arms	There will be up to 6 panels with up to approximately 48 participants.
Duration of Participation	Each participant will participate in the study for approximately 1 year from the time the participant provides documented informed consent through the final contact. After a screening phase of up to approximately 8 weeks, each participant will receive assigned intervention for approximately 2 months. After the end of treatment each participant will be followed for approximately 8 months.

Study Governance Committees:

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

There are no governance committees in this study. Regulatory, ethical and study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 13.

1.2 Schema

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

Table 1 Study Schema

Part	Panel ^a				
1	A ^b	20 mg IV			
1	B ^b		100 mg IV ^c		
1	C ^b			500 mg IV ^c	
1	D ^b				2000 mg IV ^c
2 (optional)	E ^b	To be determined based on PK from Part 1 ^c (not to exceed 2000 mg)			
2 (optional)	F ^b	To be determined based on PK from Part 1 ^c (not to exceed 2000 mg)			

^a The suggested doses (with the exception of the starting dose) may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic, and/or pharmacodynamic data observed in previous intervention periods. Refer to Section 6.6 (Dose Modification) for the safety, pharmacokinetic, and pharmacodynamic data that will be reviewed prior to dose escalation.

^b Within each intervention period, 6 participants will be randomized to receive MK-2214 and 2 participants to receive matching placebo according to a computer-generated allocation schedule.

^c The assigned intervention will be administered on Days 1, 29, and 57 for each panel.

Figure 1 Part 1 Study Diagram

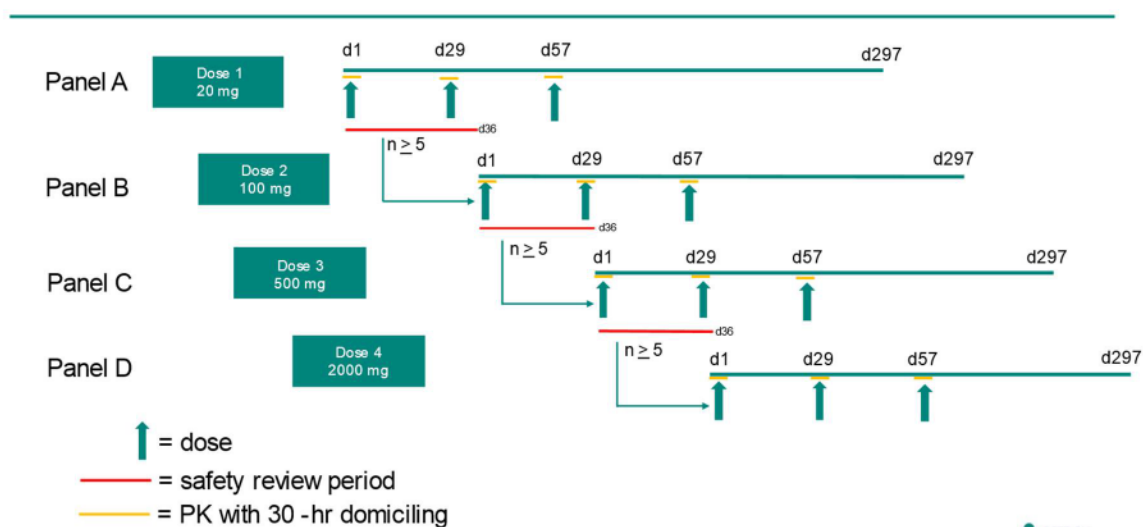
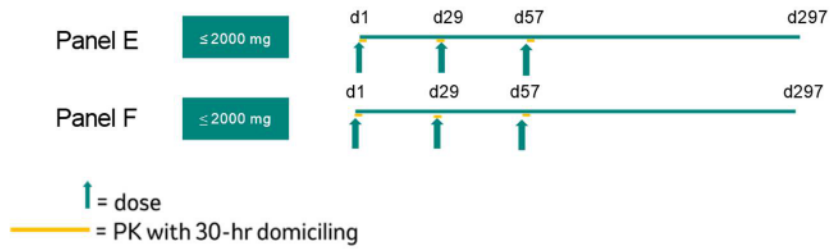


Figure 2 Part 2 (Optional) Study Diagram



1.3 Schedule of Activities

Parts 1 and 2

All Panels																					
Study Period:	Screening		Intervention																	Post-study ^b	Notes
Scheduled Day	Screening ^a	Day -30 to Day -1	Pre-dose Day 1	1	4	8	15	29	36	57	60	64	71	85	113	141	197	247	297	The start of the infusion is t=0; all postdose timepoints are relative to this start time.	
Administrative Procedures																					
Informed Consent	X																			Sec. 5.1, 8.1.1.1	
Informed Consent for FBR	X																			Sec. 5.1, 8.1.1.2	
Participant ID Card	X																			Sec. 8.1.3	
Inclusion/Exclusion Criteria	X	X	X																	Sec. 5.1, 5.2, and 8.1.2 Review of IC/EC at Screening, just prior to prestudy LP, and after Day 1 predose procedures	
Medical History	X	X	X																	Sec. 8.1.4	
Prior/Concomitant Medication Review	X-----X																			Sec. 5.2, 6.5, 8.1.5	
MMSE and MHIS ^m	X																			Sec 8.1.6, 8.1.7	
Assignment of Screening Number	X																			Sec. 8.1.8	
Assignment of Treatment/Randomization Number			X																	Sec. 5.5, 8.1.9	
MK-2214/Placebo Administration ^c				X				X		X										Sec. 8.1.10 All doses of study intervention will be given in the morning at approximately the same time for each dose for a given participant	
Domiciling ^d				X				X		X										Sec. 8.1.13 Days 1, 29, 57: discharge at approximately 30 h postdose	
Safety Procedures																					
Full physical examination	X		X ^{e,f}																X	Sec. 8.3.1	
Height	X																			Sec. 8.3.1	
Weight ^f	X		X ^f							X							X		X	Sec. 8.3.1 BMI at Screening only	
Full Neurological Examination	X		X ^{e,f}																X	Sec. 8.3.2, Appendix 11	

All Panels																						
Study Period:		Screening		Intervention																	Post-study ^b	Notes
Scheduled Day	Screening ^a	Day -30 to Day -1	Pre-dose Day 1	1	4	8	15	29	36	57	60	64	71	85	113	141	197	247	297	The start of the infusion is t=0; all postdose timepoints are relative to this start time.		
Directed Physical Examination				X				X ^f		X ^f							X			Sec. 8.3.1 Predose (Days 29, 57) Days 1, 29, 57: 4, 24h postdose		
Targeted Neurological Examination				X				X ^f		X ^f							X			Sec. 8.3.2, Appendix 11 Predose (Days 29, 57) Days 1, 29, 57: 4, 24h postdose		
VS (HR, BP)	X			X	X	X	X	X	X	X	X			X		X	X	X	X	Sec. 8.3.4 Semirecumbent position Days 1, 29, 57: predose (triplicate), 0.25, 0.5, 1, 2, 4, 8, 12, 24h postdose Other days: single measurement any time of day		
VS (RR and BT)	X			X	X	X		X	X	X	X			X			X		X	Sec. 8.3.4 Days 1, 29, 57: -BT: predose, 0.5, 1, 2, 4, 8, 12, 24h postdose -RR: predose, 4, 24h postdose Other days: single measurement any time of day		
Orthostatic VS (HR and BP)	X			X				X		X										Sec. 8.3.4.2 Days 1, 29, 57: predose, 4 and 24h postdose Other days: single measurement any time of day		
12-lead ECG	X			X ^e		X		X	X	X	X			X			X		X	Sec. 8.3.5, Appendix 9 Semi recumbent position Days 1, 29, 57: predose (triplicate), 4, 24h postdose Other days: single measurement any time of day		
Monitoring for systemic infusion reaction				X				X		X										Sec. 8.3.3 Days 1, 29, 57: 0 through approximately 30h postdose		

All Panels																					
Study Period:	Screening		Intervention																	Post-study ^b	Notes
Scheduled Day	Screening ^a	Day -30 to Day -1	Pre-dose Day 1	1	4	8	15	29	36	57	60	64	71	85	113	141	197	247	297	The start of the infusion is t=0; all postdose timepoints are relative to this start time.	
Assessment of local infusion site tolerability				X	X	X		X	X	X	X									Sec. 8.3.3 Days 1, 29, 57: predose, 0.5, 1, 24h postdose If the planned infusion time is less than 30 minutes the assessment should be performed immediately at the end of the infusion instead of the 0.5 timepoint.	
C-SSRS Baseline/Screening	X																			Sec. 8.3.7	
C-SSRS Since Last Visit			X		X			X		X				X		X	X	X	X	Sec. 8.3.7 Days 29 and 57: 24h postdose Other days: single assessment any time of day	
Safety Follow Up Phone Call															X					Sec 8.3.8	
AE/SAE Review	X-----																		X	Sec 8.4, Appendix 3	
Laboratory Procedures																					
Serum FSH - (WONCBP as needed)	X																			Appendices 2, 5 and 8	
HIV, hepatitis B and C screen	X																			Sec 8.3.6, Appendices 2 and 8	
Drug and alcohol test	X			X ^f				X ^f		X ^f										Sec 8.3.6, Appendix 2 Mandatory at screening and predose Days 1, 29, 57; any additional drug and alcohol tests conducted per site SOP	
Hematology	X			X ^f		X	X	X ^f	X	X ^f	X			X		X	X		X	Sec 8.3.6, Appendix 2 Days 1 29, 57: predose, 24h postdose Other days: single collection any time of day	
Urinalysis	X			X ^f		X	X	X ^f	X	X ^f	X			X		X	X		X	Sec 8.3.6, Appendix 2 Days 1 29, 57: predose, 24h postdose Other days: single collection any time of day	
Chemistry	X			X ^f		X	X	X ^f	X	X ^f	X			X		X	X		X	Sec 8.3.6, Appendix 2 Days 1, 29, 57: predose, 24h postdose Other days: single collection any time of day	
Coagulation tests (PT and INR, aPTT)	X	X ^g						X ^g						X ^g						Sec. 8.3.6, 8.11.5 Appendix 2	

All Panels																				
Study Period:	Screening		Intervention																	Post-study ^b
Scheduled Day	Screening ^a	Day -30 to Day -1	Pre-dose Day 1	1	4	8	15	29	36	57	60	64	71	85	113	141	197	247	297	The start of the infusion is t=0; all postdose timepoints are relative to this start time.
PK/Pharmacodynamics																				
Blood for Serum MK-2214 Assay ^h				X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	Sec. 8.6.1 and 8.11.5 Days 1, 29, 57: blood collections relative to t=0 (start time of infusion) Days 1, 57: predose, 0.5, 1, 2, 4, 8, 12, 24h postdose Day 29: predose, 0.5, 8h postdose The 0.5 h sample must be collected just after the end of the infusion. If the planned infusion time is less than 30 minutes, the sample should be collected immediately at the end of the infusion. All other days: Single blood collection done at any time of day.
Blood for Serum ADA			X				X	X		X				X		X	X	X	X	Sec. 8.6.3, 8.11.5 and Appendix 8 Collections at same time as PK collection Collections on Days 29 and 57 are predose only.
CSF (via LP) ⁱ for: -MK-2214 CCI ^g and Hb -Archive ⁱ		X ^j						X ^{j,h}						X ^{j,k}						Sec 8.6, 8.7, 8.11.5, and 8.11.6
Biomarkers																				
Blood Sample for AD Biomarkers ^{i,n}			X					X ^h						X ^k			X		X	Sec. 8.8 and Appendix 8
Blood for Genetic Analysis				X																Sec. 8.8.1 and Appendix 8 Collect once from enrolled participants only preferably on Day 1

All Panels																				
Study Period:	Screening		Intervention																Post-study ^b	Notes
Scheduled Day	Screening ^a	Day -30 to Day -1	Pre-dose Day 1	1	4	8	15	29	36	57	60	64	71	85	113	141	197	247	297	The start of the infusion is t=0; all postdose timepoints are relative to this start time.
AD=Alzheimer's Disease; ADA=antidrug antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; BMI=body mass index; BT=body temperature; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; EC=exclusion criteria, ECG=electrocardiogram; FBR=future biomedical research; FPE=first patient enrolled; FSH=follicle stimulating hormone; h=hour(s); Hb=hemoglobin; HIV=human immunodeficiency virus; HR=heart rate, IC=inclusion criteria, ID=identification; INR=international normalized ratio; IV=intravenous; LP=lumbar puncture; MHIS=Rosen-Modified Hachinski Ischemic Scale; MMSE=Mini-Mental State Examination; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; RR=respiration rate, SAE=serious adverse event; SOA=Schedule of Activities; SOP=standard operating procedure; VS=vital signs; WONCBP=women of nonchildbearing potential.																				
^a Screening will be conducted within up to approximately 8 weeks before the first dose of study intervention.																				
^d Poststudy visit should occur 240 days following the last dose of intervention (±7 days). If the visit occurs prior to 240 days following the last dose of intervention, a phone call should be made to assess for SAEs on Day 297.																				
^c IV infusion over ~ 30 minutes (t=0-30 minutes). Infusion time duration may be adjusted by the Sponsor based on the dose chosen for each panel, and may increase or pause and restart based upon on tolerability. The start of the infusion is defined as t=0. All Day 1, 29, and 57 postdose timepoints as listed in the SOA are relative to this start time.																				
^f Domiciling is mandatory following dosing on Days 1, 29, and 57 (through approximately 30 hours postdose). Participants may also be domiciled the night prior to dosing and/or the night prior to or following LPs at the investigator's discretion.																				
^g If baseline LP is performed on Day -1 and Day 1 predose PE and/or neurological exams will be performed on Day -1 as well, the predose PE (including weight), neurological exam and ECG must be performed after the LP.																				
^h Day 1, 29 and 57 predose PE (including weight), neurological exam, laboratory safety evaluations, drug and alcohol tests may be conducted/collected upon admission within 24 hours of dosing. If the participant's predose drug/alcohol is performed within 24 hours of dosing, but they are not domiciled overnight prior to dosing, a urine drug and alcohol screen may be repeated on the day of dosing (predose) at the discretion of the Investigator.																				
ⁱ Within ~ 5 days prior to LP.																				
^j On Day 29, predose serum PK/ADA, AD Biomarker, and CSF must be collected on the same day, with the predose PK/ADA and AD Biomarker samples drawn prior to the CSF collection. This may be done on the day prior to dosing, or predose in the morning on the day of dosing.																				
^k Leftover specimens: CSF archive and Blood Sample AD biomarker specimens will be stored for FBR.																				
^l LPs should be performed in the morning. LP and post-LP AE evaluation must be performed prior to Day 29 dosing and may be performed on the day prior.																				
^m On Day 85, serum PK/ADA and AD biomarker collection must be done prior to CSF collection and all must be done on the same day (or all can be collected the day prior to the CSF collection).																				
ⁿ Each participant will undergo 2 LPs. All participants will complete 1 LP on Days -30 to -1; in Panels B and C the first 4 participants randomized will complete 1 LP on Day 29 and the remaining 4 participants will complete 1 LP on Day 85. For participants who randomize in Panel A after implementation of amendment 02, LPs will be assigned equally to Day 29 and Day 85 (in the event of an odd number of participants remaining for Panel A after implementation of this amendment, the last participant randomized in Panel A will be assigned an LP on Day 85). All participants in Panels D to F will complete 1 LP on Days -30 to -1 and 1 LP prior to dosing on Day 29.																				
^o Applicable for Part 1 and Part 2 participants with MCI or mild to moderate AD																				
^p AD Biomarker specimens will be collected in Part 1 and Part 2. For Part 2 participants with MCI or mild to moderate AD, the AD Biomarker specimens will be collected at all specified timepoints; for Part 2 healthy older participants, AD Biomarker specimens will only be collected at Day 1 predose.																				

2 INTRODUCTION

2.1 Study Rationale

MK-2214 is a humanized anti-tau mAb which targets a CCI [REDACTED] that is detected on oligomeric tau species found in the brains of AD patients. It is theorized that the extracellular spread from neuron-to-neuron of pathologic tau species contributes to the progression of AD, and that MK-2214 may reduce this spread and consequently slow the progression of AD.

The purpose of this study is to assess the safety, tolerability, PK and pharmacodynamics of multiple IV doses of MK-2214 in participants with MCI or mild-to-moderate AD. Data from this study, which represents the initial administration of MK-2214 to individuals with MCI or mild-to-moderate AD, will be used to guide the selection of doses and dosing regimens for future clinical studies.

This study may also assess safety, tolerability, PK, and pharmacodynamics of multiple IV doses of MK-2214 in 2 optional panels of healthy older participants and/or participants with MCI or mild to moderate AD. These panels will provide additional data to inform subsequent clinical studies.

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-2214.

2.2.1 Pharmaceutical and Therapeutic Background

In AD, the microtubule-associated protein tau in the brain becomes hyper-phosphorylated, forming aggregates of misfolded proteins, and ultimately aggregating into the disease defining NFTs. These NFTs are closely associated with degenerating neurons and clinical cognitive impairment. Data from longitudinal tau PET tracer studies are consistent with spatio-temporal progression of NFT deposition in AD patients, suggesting that the geographic spread of tau pathology contributes to disease progression [Kreisl, W. C., et al 2021]. Growing evidence supports the hypothesis that spatial propagation of this pathology occurs via neuron-to-neuron spread involving the extracellular transmission of tau species and templating of new pathology in previously healthy cells. Based on this theorized mechanism, the binding of extracellular tau forms is predicted to interfere with the spread of tau pathology and consequently slow the progression of AD.

CCI [REDACTED]

CCI [REDACTED] MK-2214 is being developed to reduce the transmissibility of CCI [REDACTED] believed to contribute mechanistically to disease progression with the intention of slowing the progression of AD. CCI [REDACTED] and are related to MK-2214 reduce seeding/spreading in preclinical models as outlined in the IB.

2.2.2 Ongoing Clinical Studies

As of the date of this protocol amendment there are two ongoing trials with MK-2214 (PN002 and PN003). Refer to the MK-2214 IB for a description of these studies and summaries of available blinded safety data. Two additional SAEs have been reported in ongoing studies since finalization of the most recent MK-2214 IB. One participant in PN002 experienced an SAE of sepsis (severe in intensity) approximately 4 months following their last dose of study intervention which resolved with antibiotic treatment. One participant in PN003 experienced an SAE of patellar fracture due to a fall (moderate in intensity) 13 hours following a single dose of MK 2214 4200 mg IV or placebo which resulted in hospitalization. The investigators considered these SAEs to be not drug related.

2.3 Benefit/Risk Assessment

Participants in this clinical study are not expected to receive direct benefit from treatment during participation as this study is designed to provide information about the safety and properties of an investigational medicine. It has not been established that targeting extracellular phosphorylated tau results in clinical benefit, and the limited duration of MK-2214 dosing in this study would not be anticipated to confer a meaningful benefit for participants with MCI or AD.

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.

This study is to be conducted in male and female participants with MCI or mild-to-moderate AD and healthy older participants (optional).

Primary Objective	Primary Endpoint
Objective: To evaluate the safety and tolerability of multiple ascending doses of MK-2214.	Adverse events and participant discontinuations due to adverse events.
Objective: To estimate the serum PK profile (eg, AUC0-28, Cmax, Tmax, t1/2) of multiple ascending doses of MK-2214.	Serum AUC0-28, Cmax, Tmax, t1/2 (after the third dose)
Objective: To estimate cerebrospinal fluid exposure (eg, cerebrospinal fluid concentration at Day 85) of multiple ascending doses of MK-2214. Hypothesis (Part 1 only): At a generally well tolerated dose level, the true geometric mean concentration at Day 85 of MK-2214 in cerebrospinal fluid is >0.3 nM.	Cerebrospinal fluid concentration at Day 85
Objective: To evaluate the free phospho-tau in cerebrospinal fluid.	Free phospho-tau in cerebrospinal fluid
Secondary Objectives	Secondary Endpoints
There are no secondary objectives in this trial.	Not Applicable
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
Objective: To estimate cerebrospinal fluid exposure relative to serum (eg, cerebrospinal fluid to serum ratio) of multiple ascending doses of MK-2214	Cerebrospinal fluid /serum MK-2214 concentrations
Objective: To evaluate the development of antidrug antibodies after multiple ascending doses of MK-2214.	Serum antidrug antibody

Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-2214.	Molecular (genomic, metabolic, and/or proteomic) determinants using blood.
Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanism of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, single period, sequential panel, double-blind, multisite study in participants with MCI or mild-to-moderate AD (Part 1) and healthy older participants and/or participants with MCI or mild to moderate AD (optional Part 2).

The objectives of this study are to assess the safety and tolerability, and to characterize the PK and pharmacodynamics of multiple ascending doses of MK-2214 in this population. See [Table 1](#) for a summary of the dose escalation scheme; proposed doses may be adjusted lower based on ongoing monitoring of safety and PK data.

This study will include up to 6 panels of 8 participants who will each receive 3 monthly doses of MK-2214 administered IV. Each participant will be assigned to 1 panel and will participate in a single treatment period. Participants will be randomized to receive MK-2214 (n=6) or placebo (n=2) in a blinded fashion. PK will be evaluated in both serum and CSF, and pharmacodynamics will be assessed in CSF. CSF will be collected at 2 timepoints from each participant to characterize central PK and pharmacodynamics of MK-2214. Doses will be administered on Days 1, 29, and 57 and all dosing will occur in clinic.

Dose escalation decisions (the decision to dose the subsequent panel) in Part 1 will be based on review of key safety variables (with summary statistics as needed) including AEs, VS, 12-lead ECGs, laboratory safety tests, neurological and physical examinations, C-SSRS, and local infusion site and systemic reactions through at least approximately 7 days following the second dose (Day 36) from at least 5 participants in the previous panel, as well as other available safety data. The aggregate summaries will be presented in an unblinded manner; no individual participant level results will be provided. Additionally, Serum PK through at least approximately 7 days following the first dose (Day 8) from at least 5 participants in Panel A will be reviewed prior to dosing in Panel C. Serum PK through at least approximately 7 days following the first dose (Day 8) from at least 5 participants in Panel B will be reviewed prior to dosing in Panel D.

Optional panels in healthy older participants and/or participants with MCI or mild to moderate AD (Part 2, Panels E and/or F) will be permitted to dose at dose levels determined by criteria met (as outlined above) in Part 1. In addition, panels in Part 1 may be dosed at dose levels determined by the same criteria being met in Part 2.

As multiple doses of MK-2214 have not previously been administered, and in the context of the monthly dosing interval employed in this study, available safety data from each participant through at least 7 days following the first dose (ie, through Day 8) will be reviewed by the investigator prior to that participant being administered the second dose.

If deemed necessary by the Sponsor, additional operational pauses may occur to allow for additional time for PK or safety assessment.

Because this is a Phase 1 assessment of MK-2214 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written

with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

The study design selected is deemed optimal for the evaluation of safety, tolerability, PK, and pharmacodynamics of MK-2214, a mAb, in individuals with MCI or mild-to-moderate AD and healthy older individuals. Preclinical studies and preliminary blinded single-dose data in healthy participants support this study.

The study employs separate single period panels. Each panel includes 8 participants randomized 3:1 active:placebo, consistent with standard MAD design. Participants are men and WONCBP ages 50 to 80 with MCI or mild-to-moderate AD (Part 1) and healthy men and WONCBP and/or participants with MCI or mild to moderate AD ages 50 to 80 (optional Part 2). Based on prior class experience with anti-tau antibodies and available preliminary blinded data from PN001, multiple participants (>1) within a panel may be dosed on the same day (up to a maximum of all participants within a panel being dosed on the same day). 30-hour domiciling is proposed to facilitate study execution including PK collection and close in-clinic safety monitoring following all doses.

The overall design of the study is intended to support subsequent clinical studies including dose and regimen selection for Phase 2. Part 1 informs on safety, tolerability, PK and pharmacodynamics in a relevant patient population. The optional Part 2 is included in order to collect additional PK and safety data to supplement data collected in Part 1. Part 2 may include characterization of PK at intermediate doses (ie, doses in between those tested in Part 1) or characterization of PK at doses included in Part 1. Part 2 panels may further support characterization of PK and safety at doses to be used in later development.

The dosing interval and duration of PK collection is informed by PK from PN001. In PN001, the serum PK of MK-2214 was approximately dose proportional and is projected to support achieving the target trough CSF drug concentration with monthly dosing. Data collected through [REDACTED] from PN001 suggest that the $t_{1/2}$ of MK-2214 may be approximately [REDACTED]; the duration of PK collection following the final dose in PN002 is 240 days in order to ensure the rigorous characterization of [REDACTED] MK-2214. This study will inform understanding of multiple dose exposure and the potential for ADA development with multiple dose administration of MK 2214. This study will include an assessment of CSF PK and pharmacodynamics in participants to enable a characterization of [REDACTED] target engagement in CSF, a matrix which is a surrogate for brain ISF, the site of action. The number of CSF collections is selected in order to support the assessment of central PK and pharmacodynamics.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

It is anticipated that IV administration of MK-2214 will be generally well tolerated in participants with MCI or mild-to-moderate AD and in healthy older participants based on preclinical safety and toxicological testing in rats and monkeys, as well as based on data from single doses of MK-2214 in healthy participants in PN001 (refer to the MK-2214 IB for detailed information).

As this is the initial clinical investigation in the patient population (following investigation in healthy participants in PN001), and the initial multiple dose administration of MK-2214, safety and tolerability of MK-2214 will be carefully monitored. Physical examinations, neurological examinations, VS, 12-lead ECG, laboratory safety tests (serum chemistry, hematology, and urinalysis parameters), acute systemic reactions, infusion site local tolerability assessments, C-SSRS, and monitoring of AEs will be assessed throughout the dosing intervals, with assessment times optimized based on the projected PK properties of MK-2214 and the typical timing of reactions to mAbs. Specifically, safety will be monitored in the research unit for at least 24 hours following each dose (with 30-hour domiciling).

As with all biologic medications, MK-2214 carries a risk of acute reactions upon exposure, particularly with IV administration. These reactions can be categorized as common acute infusion reactions, acute hypersensitivity reactions and high cytokine release reactions. Common acute infusion reactions are usually mild, can occur even with the first dose and manifest with rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in HR or BP. In addition to signs similar to common infusion reactions, participants may develop urticaria, wheezing, coughing, facial swelling, angioedema, and more significant changes in VS.

Cytokine release reactions are exceedingly rare but severe. They manifest as severe headache, nausea, vomiting, back pain, fever, hypotension and multiorgan failure. The risk of an infusion reaction to MK-2214 is considered low given its profile in preclinical safety studies, the target of MK-2214 is not known to have any physiologic function (it is believed to be purely pathophysiologic), has been generally well tolerated in healthy participants in PN001 without evident cytokine release reactions, and other anti-tau antibodies have been generally well tolerated. Given potential safety risks, participants will be monitored closely during and after the infusion with scheduled VS. In addition to monitoring for acute reactions to MK-2214, the infusion site will be assessed for signs of reactogenicity, including pain, tenderness, erythema, and swelling.

All AEs and SAEs will be monitored throughout the 297-day follow-up period (240 days following the final dose of study intervention).

4.2.1.2 Pharmacokinetic Endpoints

Serum and CSF PK of MK-2214

Serum PK of MK-2214 will be measured in order to characterize C_{max}, exposure, t_{1/2}, and accumulation, with a focus on collection of PK following the first and final doses. CSF PK will additionally be assessed to determine if the trough target of 0.3 nM is achieved 28 days following the third dose at a generally well-tolerated dose of MK-2214. Based on preclinical models and in vitro studies of AD CSF, 0.3 nM is predicted to achieve [REDACTED].

[REDACTED]. While the level of target engagement required for clinical efficacy is not established, [REDACTED]

[REDACTED] Based on a theorized seeding-based spread model of pathologic tau progression, it is scientifically plausible that [REDACTED]

[REDACTED] Additional analyses may be conducted across dose levels to examine the relationship between MK-2214 exposure and reduction in [REDACTED] to further characterize the PK/pharmacodynamic relationship in vivo in participants with MCI and mild to moderate AD.

CSF will be collected 2 times from each participant (baseline and Day 29 or Day 85). All participants will complete 1 LP on Days -30 to -1; in Panels B and C the first 4 participants randomized will complete 1 LP on Day 29 (prior to dosing) and the remaining 4 participants will complete 1 LP on Day 85. For participants who randomize in Panel A after implementation of amendment 02, LPs will be assigned equally to Day 29 and Day 85 (in the event of an odd number of participants remaining in Panel A after implementation of this amendment, the last participant randomized in Panel A will be assigned an LP on Day 85). All participants in Panels D-F will complete 1 LP on Days -30 to -1 and 1 LP prior to dosing on Day 29. Sampling times were selected to maximize the understanding of CSF PK while minimizing the overall number of LPs required. CSF collections are timed and spaced to capture important features of the CSF PK profile (CSF:serum ratio, CSF accumulation) which will inform estimates for the CSF exposure of MK-2214 and determine key CSF PK parameters including the CSF concentration at trough after 3 doses (Day 85 C_{trough}, based on every 4 weeks administration) and the CSF-to-serum ratio.

ADAs to MK-2214

The presence and titer of ADAs will be measured in blood. ADAs can develop to biologics such as MK-2214. ADAs may be clinically inconsequential or may change the PK and/or drug efficacy. Moreover, ADAs may lead to safety events, such as acute or delayed hypersensitivity reactions. Thus, the titer of ADAs will be correlated with PK and safety events. If indicated, positive ADAs may be further evaluated to determine whether they are able to interfere with MK-2214 binding of the target antigen.

4.2.1.3 Planned Biomarker Research

CCI

CCI will be evaluated in CSF samples, and the observed CCI levels will be assessed. This assay has been developed to assess target engagement of MK-2214 by quantifying CCI. This assessment of target engagement will inform dose selection in the further clinical development of MK-2214.

4.2.1.3.1 Planned Genetic Analysis

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

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

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

4.2.1.3.2 Other Biomarkers

Exploratory Plasma Diagnostic Biomarkers for Alzheimer's Disease

The study will collect plasma for exploratory analysis of biomarkers associated with AD pathology (such as NfL, tau and/or phospho-tau) in Part 1 (and in optional Part 2). The evaluation of emerging biomarkers will permit the evaluation of the relationship between these biomarker data and screening cognitive testing (MMSE) and/or treatment with MK-2214. Changes in plasma biomarkers may also be evaluated for longitudinal changes over the course of the study. This exploratory analysis will be carried out on a post-hoc basis, using a plasma biomarker panel or panels that have not been specifically identified at the time of this protocol finalization, but are actively under investigation and are anticipated to be available at the completion of this study.

4.2.1.4 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

Placebo will be used in this trial to allow for an appropriate assessment of the safety data of MK-2214 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

The methods used in calculating doses and estimated exposures are detailed in Section 4.3.1 and Section 4.3.2.

As this is a Phase 1 assessment of MK-2214 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 8.11.6.

4.3.1 Starting Dose for This Study

A dose range of [REDACTED] has been selected based on safety considerations and the desire to reach the PK target as well as to study doses that include the predicted therapeutic dose.

The starting dose of [REDACTED] is selected to achieve approximately [REDACTED]. This dose is projected to result [REDACTED], and approximately [REDACTED].

CCI [REDACTED]

In healthy participants (PN001), single doses of 10 to 4200 mg IV were generally well tolerated. No treatment-related findings were observed in the 6-month GLP repeat dose toxicity study in rats; because there were no test article related findings observed the NOEL was CCI [REDACTED] (the highest dose tested). There were also no treatment-related findings in the 1 month GLP rhesus and rat repeat dose toxicity studies, which tested up to CCI [REDACTED]. Nonclinical toxicology and PN001 data are described further in the MK-2214 IB.

As MK-2214 is a large molecule to be injected intravenously in this study, doses may be compared directly on a mg/kg basis based on the publication “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers” [Food and Drug Administration 2005]. The starting dose of 20 mg, assuming a 60 kg participant, is CCI [REDACTED]. This is CCI [REDACTED] than the CCI [REDACTED] tested in the 6-month GLP rat toxicity study and is expected to result in mean serum Cmax after the third dose of CCI [REDACTED] than the NOEL.

4.3.2 Maximum Dose Exposure for This Study

The planned highest dose level to be tested in this study is 2000 mg IV. This dose has been selected to ensure the dose levels evaluated in this trial bracket exposures of the potential therapeutic dose range. The target engagement required for efficacy is not known, and CCI [REDACTED] may be required to prevent the spread of pathologic tau species. Based on a seeding-type mechanism of spread of pathological tau, it is biologically plausible that CCI [REDACTED] may be required for optimal efficacy.

This top dose is projected to support the assessment of CCI [REDACTED] in CSF at Cmax and 28 days after the third dose, respectively. Cmax following the third dose is expected to be below maximum serum concentrations observed with a single dose of 4200 mg IV in P001. This dose is 4-fold higher than the lowest dose in this study (500 mg) projected to achieve the CCI [REDACTED] of 0.3 nM (ie, CCI [REDACTED] above the lowest study dose projected to reach the anticipated therapeutic exposure range). The 2000-mg proposed maximum dose is projected to achieve serum exposures of CCI [REDACTED] (AUC0-28 after the third dose) and a serum Cmax value of CCI [REDACTED] (based upon projections from PN001 data), however these preliminary predictions may be under-estimated due to uncertainty in the true terminal t1/2. These post-dose AUC0-28 and Cmax projected exposures are approximately CCI [REDACTED], respectively, than the NOEL exposure in the 6-month GLP repeat dose toxicity study in rats.

4.3.3 Rationale for Dose Interval and Study Design

MK-2214, a mAb directed against the [REDACTED], is not considered a compound with a high degree of uncertainty related to the potential risk of harm to participants based upon its mechanism of action, clinical safety data in healthy participants from PN001, and clinical experience from other monoclonal antibodies targeting Tau (including, tilavonemab, gosuranemab, semorinemab and zagotenemab, among others, with safety data published for tilavonemab and gosuranemab) [Boxer, A. L., et al 2019] [Hoglinger, G. U., et al 2021]. Safety assessment toxicity studies and ancillary pharmacology studies with MK-2214, as well as the clinical experience with single doses in PN001, provide no contraindications to the initiation of multiple dose clinical studies in people with this compound. No dose-limiting toxicities were observed in 6-month rat or 1-month rat and rhesus toxicity studies, and substantial preclinical safety margins were obtained over the planned human doses in this study. Additionally, the doses planned for this study do not exceed the doses previously assessed in PN001.

This study includes up to 6 panels (up to 4 panels in Part 1 and up to 2 optional panels in Part 2) of 8 participants each (6 active and 2 placebo). For each panel, all 8 participants are permitted to be administered MK-2214 or placebo on the same day with spaced dosing by Phase 1 Clinical Research standards for compounds not considered to have a high degree of uncertainty related to the potential risk of harm to participants. For panels enrolling participants with MCI or mild to moderate AD, it is not anticipated that more than 1 to 2 participants will be dosed on any given day based on projected recruitment.

Each participant will receive 3 doses of MK-2214 or placebo in this study and be followed through Day 297 (240 days following the final dose). Data collected through 140 days from PN001 suggest that the t_{1/2} of MK-2214 may be [REDACTED], supporting the monthly dosing regimen used in this study. However, this estimated t_{1/2} is based on projections from data collected through [REDACTED] post-dose, and may not accurately support estimation of a t_{1/2}. Therefore, the collection of PK samples through 240 days following the final dose is intended to further inform the t_{1/2} of MK-2214.

Based on the lack of MK-2214 binding in male reproductive tissues and the physiology of the testis-blood barrier limiting the exposure of immunoglobulins in semen, no contraceptive measures are recommended for male participants during clinical trials with MK-2214.

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.

A primary objective of this early Phase 1 study is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

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:

5.1.1 Inclusion Criteria (MCI and Mild to Moderate AD: Part 1 and, if applicable, Part 2)

Type of Participant and Disease Characteristics

1. Be in good health based on medical history, PE, VS measurements, and ECGs performed before randomization.
 - Participants with stable chronic medical conditions, including but not limited to hypertension, hyperlipidemia, Type 2 diabetes and hypothyroidism, which have been well-controlled on a stable dose of medication for at least the past 2 months, and who are not receiving any prohibited medications, may be enrolled if clinically acceptable to the investigator and Sponsor.Appendix 9 provides a table of the 12-Lead ECG Abnormality Criteria.
2. Be in good health based on laboratory safety tests obtained at the prestudy 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. Be able to speak, read, hear, and understand the language of the study staff and the ICF, and possess the ability to respond verbally to questions, follow instructions, and participate in study assessments based on the investigator's judgment (with legal representative input, as applicable).
4. Has laboratory safety test parameter value(s) for platelets and coagulation (INR, PT and aPTT) within normal range or NCS (as determined by the investigator).
5. BMI between 18.5 and 35 kg/m², inclusive at the prestudy visit. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)².
6. Reports a history of cognitive and functional decline with gradual onset and slow progression for at least one year before Screening, that is either corroborated by an informant who knows the subject well or is documented in medical records.
7. Have an MMSE >12 at the prestudy visit.

8. MHIS score <4 at the prestudy visit.
9. If required based on assessment of physical/cognitive independence by investigator, participant and/or trial partner/caregiver: Has 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 trial visits. Overnight stays at the clinic for the partner/caregiver are not required but may be requested at the discretion of investigator. The trial partner/caregiver should understand the nature of the trial and adhere to trial requirements (eg, dosing, visit schedules, and nature and number of evaluations).

Demographics

10. Is an individual of any sex/gender, from 50 years to 80 years of age inclusive, at the time of providing the informed consent.

Female Participants

11. A female participant is eligible to participate if:
She is a WONCBP, as defined in Appendix 5.

Informed Consent

12. The participant 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.

Additional Categories

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

5.1.2 Inclusion Criteria (Healthy Older Participants, Part 2)

Type of Participant and Disease Characteristics

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

Appendix 9 provides a table of the 12-Lead ECG Abnormality Criteria.

2. Be in good health based on laboratory safety tests obtained at the prestudy 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. Has laboratory safety test parameter value(s) for platelets and coagulation (INR, PT and aPTT) within normal range or NCS (as determined by the investigator).
4. BMI between 18.5 and 35 kg/m², inclusive at the prestudy visit. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)².

Demographics

5. Is male or female, from 50 years to 80 years of age inclusive, at the time of providing informed consent.

Female Participants

6. A female participant is eligible to participate if:
She is a WONCBP, as defined in Appendix 5.

Informed Consent

7. The participant 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.

Additional Categories

8. 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:

Exclusion Criteria (Parts 1 and 2)

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 unstable or poorly controlled endocrine, GI, cardiovascular, hematological, hepatic, renal, respiratory, or genitourinary abnormalities or diseases. Participants with chronic well-controlled conditions and/or with a remote history of uncomplicated medical events may be enrolled in the study at the discretion of the Investigator in consultation with the Sponsor.
3. History of clinically significant active neurological disease (except for AD or MCI for participants in Part 1). This includes a history of stroke, chronic ongoing seizure condition, Parkinson's Disease, traumatic brain injury, dementia due to known non-Alzheimer's pathology (e.g. vascular dementia, Lewy body dementia, Creutzfeldt-Jakob disease), etc. Benign nonprogressive neurologic conditions such as essential tremor are permissible.
4. History of clinically significant active autoimmune disease requiring ongoing systemic immunosuppressant therapy. (Note: Prior Hashimoto's thyroiditis, for example, would not be considered an exclusion.)
5. Has significant emotional problem(s) at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.
6. History of cancer (malignancy).
Exceptions: (1) Adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix or (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥ 10 years prior to the prestudy [screening] visit).
7. Estimated eGFR ≤ 50 mL/min/1.73 m² based on the 2021 CKD-EPI Creatinine Equation. This updated equation does not require use of race and a joint National Kidney Foundation (NKF) and American Society of Nephrology (ASN) Task Force strongly recommends immediate implementation of 2021 CKD-EPI equations.

2021 CKD-EPI Creatinine (CKD-EPI_{Cr} R) Equation:

$$eGFR = 142 \times \min(Scr/k, 1)^\alpha \times \max(Scr/k, 1)^{-1.200} \times 0.994^{\text{age}} \times 1.012 \text{ [if female]}$$

where Scr is serum creatinine, k is 0.7 for females and 0.9 males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

eGFR values indexed to BSA 1.73 will be de-indexed by dividing the value obtained from either formula by 1.73 and then multiplying by participant BSA.

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 to 10% below of either 50 mL/min (for CrCl) or 50 mL/min/1.73m² (for eGFR) may be enrolled in the study at the discretion of the investigator.

8. History of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerance (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
9. Positive test(s) for HBsAg, hepatitis C antibodies or HIV. If hepatitis C antibodies are positive, a negative hepatitis C PCR is acceptable for inclusion as confirmation of either treated or naturally cleared HCV.
10. 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.
11. Has a contraindication to lumbar dural puncture, such as coagulopathy, concomitant anticoagulation beyond low dose aspirin, thrombocytopenia, or other factors that could preclude safe lumbar puncture in the opinion of the investigator.
12. Unstable or uncontrolled chronic disease (ie uncontrolled hypertension, etc.) or clinically significant autoimmune disease.
13. Has a history of clinically significant DVT, thrombophlebitis or coagulopathy, or has a family or personal history of hemophilia or any coagulopathy.
14. Has a history of recent clinically relevant infection (eg, meningitis, encephalitis) within past month, or significant immunodeficiency and/or hospitalization (within past year) for any reason considered clinically relevant.
15. Has a recent history (within past year) of recurrent and/or severe migraine headaches (an isolated mild migraine is not a contraindication).
16. Has a known history of stroke or evidence from prior MRI scan (if available) that is clinically important in the investigator's opinion.

Prior/Concomitant Therapy

17. Currently receiving or has received aducanumab or another anti-amyloid therapy within the last 6 months or has history of prior anti-amyloid therapy with ARIA.
18. Has a history (including participant/caregiver recall, if applicable) of receiving biological therapy (including human blood products or monoclonal antibodies, excluding insulin in well-controlled type 2 diabetics) within the last 3 months or 5 half-lives (whichever is longer) or live vaccination within the last 30 days.
19. Has a history (including participant/caregiver recall, if applicable) of receiving any human immunoglobulin preparation such as IVIG or RhoGAM within the last year.
20. Has received any non-live vaccine starting from 14 days prior to first study intervention or is scheduled to receive any non-live vaccine through 14 days following the final dose of study intervention. Exception: COVID-19 and influenza vaccines may be administered; study intervention must be given at least 72 hours following or 7 days prior to vaccination. Other non-live vaccines may be administered at least 72 hours prior to or 7 days after study intervention with joint agreement of Investigator and Sponsor.
21. Anticipates the use of new medications, 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 and throughout the study until the poststudy visit. There may be certain new medications that are specifically permitted (see Section 6.5).

22. Is receiving systemic immunosuppression, including corticosteroids exceeding physiologic replacement doses (approximately 5-10 mg/day prednisone equivalent). (Note: Topical, ophthalmic, and inhaled/nebulized steroids are permitted upon joint agreement with the Sponsor.)
23. Is receiving systemic anticoagulation. (Note: low dose aspirin is permitted.)

Prior/Concurrent Clinical Study Experience

24. 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

25. QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).
26. Is a smoker that does not agree to follow the smoking restrictions as defined by the CRU.
27. Has a tattoo, scar, or other physical finding at the area of the infusion site that would interfere with infusion or a local tolerability assessment.
28. Has an abnormality or PE finding (including a tattoo and/or scar) contraindicating lumbar puncture, either at screening or predose testing.
29. Has a history of severe lumbar osteoarthritis, spinal cord compression, spinal abnormality, or other current abnormality in the lumbar region (eg, skin infection) that would preclude safe LP and CSF collection in the opinion of the investigator.
30. Has a history or signs/symptoms of lumbar spine/disc disease including but not limited to scoliosis, herniation, or previous lumbar spinal surgery or any other contraindication to lumbar puncture.
31. Has a hypersensitivity to lidocaine.
32. 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.
33. 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.
34. A regular user of cannabis or other drugs or has a history of drug (including alcohol) abuse within approximately 1 year of the prestudy visit. A participant who is a recreational user of cannabis or other drugs within the past 2 years can be enrolled as long as recreational use does not meet the definition of drug abuse and participant agrees to refrain from substance use within one week, prior to and following dosing. Except for cannabis, participants must have a negative drug screen prior to randomization and each dose.

Other Exclusions

35. 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

There are no fasting requirements or dietary restrictions. All meals on Days 1, 29, and 57 will be served so as not to interfere with the study procedures. During domiciling meals and snack(s) will be provided by the investigator per CRU standard procedures.

Participants undergoing LP may be fasted or have a light meal prior to the LP.

5.3.1.2 Fruit Juice Restrictions

No restrictions are required.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the prestudy and poststudy visits. On dosing days participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before and after study intervention administration.

At all other times, 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 will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits and outpatient visits with laboratory safety evaluations. On dosing days participants will refrain from consumption of alcohol 24 hours before and 30 hours after study intervention administration.

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

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

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.

5.4 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.

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 (MK-2214 and 5% Dextrose for placebo) 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 2](#).

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Active	Experimental	MK-2214	Biological/Vaccine	Solution	150 mg/mL	20 mg 100 mg 500 mg 2000 mg	IV Infusion	Panel A Panel B Panel C Panel D Panel E Panel F	Test Product	IMP	Centrally by the sponsor
Placebo	Placebo Comparator	Placebo	Biological/Vaccine	Solution	0	0 mg	IV Infusion	Panel A Panel B Panel C Panel D Panel E Panel F	Placebo	NIMP/AxMP	Centrally by the sponsor

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

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

In this protocol, placebo for MK-2214 is diluent alone (5% Dextrose), diluent is used for blinding purposes and does not contain active ingredients.

All supplies indicated in Table 2 will be provided per the “Sourcing” column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (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 8.1.10 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

MK-2214 sterile solution will be prepared and dosed per the instructions outlined in the Pharmacy Manual.

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.

Refer to [Table 3] for a sample allocation schedule.

Table 3 Sample Allocation Table

Panel	Participants ^b	Dose ^a
A	n=6	20 mg IV
	n=2	Placebo IV
B	n=6	100 mg IV
	n=2	Placebo IV
C	n=6	500 mg IV
	n=2	Placebo IV
D	n=6	2000 mg IV
	n=2	Placebo IV
E	n=6	≤2000 mg IV
	n=2	Placebo IV
F	n=6	≤2000 mg IV
	n=2	Placebo IV
IV=intravenous; n=number of participants; PK=pharmacokinetics a The suggested doses may be adjusted downward based on evaluation of safety, tolerability and/or PK data observed with previously administered doses. b Participants will be randomized to receive a single dose (IV) of MK-2214 (n=6) or placebo (n=2) at each dose level.		

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study. The first 4 allocation numbers in Panels B and C will have CSF collected on Day 29 and the last 4 allocation numbers in each panel will have CSF collected on Day 85. For participants who randomize in Panel A after implementation of amendment 02, LPs will be assigned equally to Day 29 and Day 85 (in the event of an odd number of participants remaining in Panel A after implementation of this amendment, the last participant randomized will be assigned an LP on Day 85). All participants in Panels D to F will complete 1 LP on Days -30 to -1 and 1 LP on Day 29.

6.3.3 Blinding

A double-blinding technique will be used. MK-2214 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.

See Section 8.1.12 for a description of the method of unblinding a participant during the study should such action be warranted.

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 identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after randomization or intervention allocation) through Day 85 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. After Day 85, it is recommended to discuss new medications with the investigator and Sponsor before administration.

Paracetamol/acetaminophen, NSAIDs and antacids may be used for minor ailments without prior consultation with the Sponsor. NSAIDs should not be used within 7 days before or 24 hours after LP. Caffeine is permitted for the treatment of post-LP headaches.

Non-live vaccines may only be administered in consultation with the Sponsor prior to or following the receipt of study intervention according to the time frames specified in Exclusion Criteria (Section 5.2).

Exception: COVID-19 vaccine and influenza vaccine may be administered. Study intervention must be given at least 72 hours following or at least 7 days prior to any COVID-19 or influenza vaccination).

Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

6.5.1 Rescue Medications and Supportive Care

Refer to Section 8.3.3 (Infusion Reactions).

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification (Escalation/Titration/Other)

All dose escalation decisions between panels will be made jointly by the investigator and the Sponsor. Members of the Sponsor safety review team will include: the trial clinical director, trial clinical scientist, senior level clinical director, and biostatistician. Additional Sponsor attendees may include a clinical research associate and a pharmacologist. The Sponsor safety review team will obtain input from the investigator regarding his/her evaluation of safety and tolerability from the previous dosing period and his/her recommendation to dose escalate in the next panel.

Each dose escalation decision will occur after at least 5 evaluable participants have completed the second dose of the previous dose level (participants will be randomized to receive MK-2214 or placebo in a 3:1 ratio, respectively).

Dose escalation decisions will be based on key safety variables (with summary statistics as needed) including, VS, 12-lead ECG, laboratory safety tests, neurological and physical exams, systemic and infusion site reactions, C-SSRS and AEs from the previous dose levels up to at least approximately 7 days following the second dose (Day 36) from at least 5 participants in the previous panel, as well as other available safety data. The aggregate summaries will be presented in an unblinded manner; no individual participant level results will be provided. In addition, serum PK through at least approximately 7 days following the first dose from at least 5 participants in Panel A will be reviewed prior to dosing in Panel C and serum PK through at least approximately 7 days following the first dose (Day 8) from at least 5 participants in Panel B will be reviewed prior to dosing in Panel D. Pharmacodynamic data may be included in the dose escalation decisions (Section 4.1 and Section 4.2).

Participants in optional Part 2 panels will be permitted to dose at dose levels determined by criteria met (as outlined above) by panels in Part 1. In addition, panels in Part 1 may be dosed at the dose levels determined by criteria met by panels in Part 2.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, participants may:

- Receive the same dose level to further explore safety and tolerability at that level,
- Receive a lower dose of the study intervention,

- Receive dose with an increased duration of administration, or
- Dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

The investigator will review the participant's safety data through approximately 7 days following the initial dose before administering the second dose to the participant.

6.6.1 Stopping Rules

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

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. To continue the study (on joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study intervention by the investigator.
2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

If any of the below stopping rules are met, subsequent higher doses will be lowered based on joint agreement of the Sponsor and investigator in order for the study to continue.

1. Should the emerging PK (mean) data indicate that the maximum clinical exposure (C_{max} or AUC), as defined in Section 4.3 will be exceeded, subsequent higher doses will be adjusted based on joint agreement of the Sponsor and investigator.

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

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 not provided.

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.12). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.12 for a description of the method of unblinding a participant during the study, should such action be warranted.

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 8.1.11, or if available, a PCL.

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 8.1.11 and Section 8.11.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator 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 (except for cannabis) 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.

7.2 Participant Withdrawal From the Study

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.

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 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the 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 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 500 ml 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) and assent, when applicable, 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

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 his/her legally acceptable representative) and of the person conducting the consent discussion.

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

The initial 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. The participant or his/her 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.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

The participant 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 14 days before the first dose of study intervention/vaccination.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Mini-Mental State Examination (Part 1 and, if applicable, Part 2 participants with MCI or mild to moderate AD)

The paper (standard) version of the MMSE will be administered and scored by an experienced rater at Screening. Additional information regarding administration, scoring and documentation may also be provided in the Study Operations Manual.

8.1.7 Rosen-Modified Hachinski Ischemic Scale (Part 1 and, if applicable, Part 2 participants with MCI or mild to moderate AD)

The MHIS will be completed by an experienced rater at screening.

8.1.8 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant

will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

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

8.1.9 Assignment of Treatment/Randomization Number

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

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

8.1.10 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. Study intervention must be administered in the morning.

Administration of study intervention will be witnessed by the investigator and/or study staff.

If the infusion is interrupted, it should be restarted as soon as possible and must be finished within the stability time specified within the pharmacy manual.

8.1.10.1 Timing of Dose Administration

All doses of study intervention will be given in the morning at approximately the same time for each dose for a given participant.

8.1.11 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 8.11.4 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.

8.1.11.1 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.

8.1.12 Participant Blinding/Unblinding

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

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

8.1.13 Domiciling

It is recommended that participants report to the CRU the evening before the scheduled day of study intervention administration for each dosing day and they must remain in the unit until approximately 30 hours postdose. At the discretion of the investigator, participants may be requested or participant/caregiver may request, to remain in the CRU longer.

Following discharge from the CRU, participants will return at times specified by the protocol, investigator, or site staff for conduct of procedures as defined in the SoA.

Participants undergoing LPs may be domiciled overnight the night prior to and/or after the LP at the discretion of the investigator.

8.1.14 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/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

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. Height and weight will also be measured and recorded as specified in Section 1.3.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

BMI

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m²). Document this BMI to the nearest 0.1 kg/m².

Weigh the participant, after voiding, while in a gown or underwear, without shoes, on a calibrated scale. Document this weight in kilograms (kg) to the nearest 0.1 kg.

Measure the participant's height on a calibrated stadiometer, without shoes. Document this height in meters to the nearest 0.01 meter (0.01 meter = 1 centimeter [cm]).

8.3.2 Neurological Examination

General and Targeted neurological examinations will be conducted according to the procedures outlined in Appendix 11.

8.3.3 Infusion Reactions

8.3.3.1 Management of Infusion Reactions

As outlined in the IB, the risk of infusion reactions to MK-2214 is considered low since the molecule contains primarily human sequences. However, infusion reactions may be observed. The purpose of this study includes characterizing the safety profile of MK-2214. No preclinical toxicity was observed following IV dosing and infusions were generally well tolerated in PN001; one participant in ongoing PN003 experienced a mild infusion reaction following MK-2214 2100 mg IV or placebo which resolved. At this time no prophylactic medications to reduce the risk of infusion reactions are warranted prior to MK-2214 administration.

In rare instances, systemic infusion reactions are severe and may have a fatal outcome. An anaphylactic reaction is a severe type of infusion reaction that is characterized by cutaneous and mucosal symptoms, such as generalized hives, pruritus or flushing, swollen lips-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor or hoarseness) and/or changes in BP (hypotension). Severe infusion reactions, including cytokine release syndrome and hypersensitivity reactions must be promptly treated with interruption of the infusion, medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician should be readily available during the period of drug administration. Less severe infusion reactions may respond to a reduction in the infusion rate and medical management.

All participants should be evaluated for infusion-type reactions. Participants who experience infusion or hypersensitivity reactions in conjunction with the infusion of study drug should receive appropriate supportive care measures as deemed necessary by the treating physician. Participants should be carefully observed until complete resolution of all signs and symptoms if a reaction occurs. Report any adverse events according to the guidelines in Appendix 3.

8.3.3.2 Infusion Reaction Assessment

Monitoring for Systemic Infusion Reactions

Participants will be monitored during intervention administration and for approximately 30 hours after initiation of intervention administration for signs and symptoms of a systemic infusion reaction. This includes, but is not limited to fever, VS changes (tachycardia, hypotension), pruritis, urticaria (hives), lip swelling, angioedema, bronchospasm, stridor, hoarseness, and shortness of breath. Infusion reactions must be assessed and managed promptly. Such assessment and management is discussed in Section 8.3.3.1.

Local Infusion Reaction Assessment

A local infusion site examination will be completed as outlined in Section 1.3 and will include an assessment of any pain, tenderness, erythema/redness, and induration/swelling. These events will be evaluated based upon the investigator's judgement and industry guidance [Table 4]. Infusion reactions must be assessed and managed promptly per site procedure.

Table 4 Local Infusion Reaction Assessment

Local Site Reaction	Mild	Moderate	Severe	Potentially Life-Threatening
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24h or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
ER=emergency room Adapted from FDA Guidance for Industry, "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (SEP-2007).				

8.3.4 Vital Signs

- Oral temperature, HR, RR, BP and orthostatic VS will be assessed.
- BP and pulse measurements will be assessed in a semirecumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Predose VS must be taken before blood collection for laboratory tests.

8.3.4.1 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-2214/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). Screening, postdose, and postdose VS measurements will be single measurements.

Participants will continue to rest semirecumbent from dosing until 4 hours postdose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure (including consumption of a light breakfast).

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.

8.3.4.2 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.

8.3.5 Electrocardiograms

- All 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA [Section 1.3] 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 to 2 minutes apart, but no more than 2 minutes 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. Female participants may need to remove interfering garments.

Participants should be resting in the semirecumbent 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 to 2 minutes apart within 3 hours before dosing MK-2214/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). Screening, postdose and poststudy ECG measurements will be single measurements.

If a participant demonstrates an increase in QTc interval ≥ 60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥ 60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥ 60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If a participant demonstrates a QTc interval ≥ 500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval is ≥ 500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc 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 at any time the QRS duration 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 on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

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

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

8.3.6 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 240 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.

8.3.7 Suicidal Ideation and Behavior Monitoring

8.3.7.1 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.

8.3.8 Safety Follow Up Phone Call

A safety follow-up phone call will be performed at the time point indicated in the SoA.

The safety phone call must be performed by appropriately trained study site staff. If the initial call is unsuccessful, the study site staff should make a total of 3 attempts for the scheduled safety call. All attempts to contact the participant will be recorded in the source documents. The call will facilitate the collection of relevant safety information.

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 240 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 5](#).

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

Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	<u>Reporting Period:</u> Consent to Randomization/ Allocation	<u>Reporting Period:</u> Randomization/ Allocation through Protocol- specified Follow-up Period	<u>Reporting Period:</u> 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	<u>Reporting Period:</u> Consent to Randomization/ Allocation	<u>Reporting Period:</u> Randomization/ Allocation through Protocol- specified Follow-up Period	<u>Reporting Period:</u> 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	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event
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

Information in this section is not applicable since participants are males (partner pregnancy/lactation information is not required) and WONCBP.

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

Not applicable.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by the 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.

3. Suicidal ideation, suicidal behavior.

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 serum and/or CSF 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. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Serum MK-2214

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

8.6.2 CSF Collection for MK-2214

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

8.6.3 Blood for Serum ADA

Sample collection, storage, and shipment instructions for serum ADA samples will be in Operations/Laboratory manual.

8.7 Pharmacodynamics

Refer to Section 8.8 for pharmacodynamic samples.

8.8 Biomarkers

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

- • Blood for genetic analysis
- • CSF (CCI [REDACTED] and hemoglobin)
- • Blood Sample for AD Biomarkers (Part 1 and Part 2)

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does

not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples listed in Section 8.8 Biomarkers

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

Within approximately 8 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 can be initiated, as needed, by the investigator after consultation with the Sponsor, including for screen failures (Section 5.4). Rescreening is to include all screening procedures listed in the SoA (Section 1.3), including consent review. However, the Precivity AD™ assay is not required to be repeated for rescreening. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day –1 procedures planned per protocol.

8.11.2 Treatment Period Visit

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

8.11.3 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 study procedures specified in the SoA (except for the LPs/CSF collection) may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in an official memo.

8.11.4 Poststudy

Participants will be required to return to clinic approximately 240 days (Day 297) after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 240 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 240 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-2214 is the critical procedure.

At any postdose time point, the blood sample for MK-2214 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.

- Blood Collection (for PK and/or ADA and AD Biomarkers), Postdose Safety Measures and Study Visits as outlined in Table 6.
- CSF Collection (for PK, CCl, Hb) as outlined in Table 7.

Table 6 Blood Collection for (PK and/or ADA and AD Biomarkers), Postdose Safety Measures, and Study Visit Windows

Study Timepoints and Visits	PK Collections, Postdose Safety Measures, and Study Visit Window
0 to ≤2 h a	± 5 min
4 to ≤24 h a	± 15 min
Days 4-8 (inclusive)	± 1 day
Day 15	± 2 days
Days 29b and 57	± 3 days
Day 36 (7 days following actual Day 29 date)	± 1 day
Day 60 (3 days following actual Day 57 date)	± 1 day
Day 64 (7 days following actual Day 57 date)	± 1 day
Days 71 (14 days following actual Day 57)	± 2 days
Days 85-297 (inclusive)	± 7 days
a Applicable for sampling on Days 1, 29 and 57	
b The Day 29 predose serum PK sample must be collected on the same day as and prior to the CSF collection.	

Table 7 CSF Collection (for PK, CCI, Hb) Windows

CSF Collection	CSF Collection Window
Day 29 ^a	± 3 days
Day 85	± 7 days
CSF=cerebrospinal fluid; Hb=hemoglobin; LP=lumbar puncture; PK=pharmacokinetics	
^a For participants receiving an LP on Day 29, LP and post-LP AE evaluation must be performed prior to Day 29 dosing and may be performed on the day prior. LPs will be performed at timepoints specified in Section 1.3	

- Predose PK: within 3 hours of dosing, with the exception of Day 29 when LP is performed and predose PK sample must be drawn prior to the LP.
- Predose standard safety evaluations: VS and ECG, and CSSRS within 3 hours; laboratory safety tests, drug and alcohol tests, physical exam, and neurological exam within 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam, neurological exam, CSSRS use windows per [Table 6](#)
- Coagulation test prior to LP: within ~ 5 days of LP

Note: Visit windows defined by ±X day(s) refers to calendar days.

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

This is a Phase 1 assessment of MK-2214 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 panel
- Entire panel(s) may be omitted
- Decrease in the duration of study intervention administration (eg, number of doses)
- IV infusion rate may be adjusted to a slower rate, provided the infusion may be completed within the stability time specified within the pharmacy manual.

- Addition of PK pause
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data
- LPs may be removed from any Panel

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic 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, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her 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 his/her 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 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full detail is in the Statistical Methods (Section 9.6).

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and vital signs 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).

Pharmacokinetics

Model-based Serum PK Summary: Individual PK values for AUC₀₋₂₈ and C_{max} after the first and third dose from Panels A through D will be natural log transformed and analyzed based on a linear mixed effects model containing fixed effects for treatment, day, treatment by day interaction and a random effect for participant. A 95% CI will be constructed for the GMs of MK-2214 AUC₀₋₂₈ and C_{max} at each day and dose level. The GMR (postdose 3/postdose 1) of AUC₀₋₂₈ and C_{max} and their 90% CIs will be calculated for each dose. AUC₀₋₂₈ and C_{max} for Part 2 will be analyzed based on the same model.

Target CSF PK Concentration: The primary hypothesis that at a dose level of MK-2214 that is generally well tolerated, the true GM concentration at the surrogate site of action (CSF) at Day 85 (C_{85d}) >0.3 nM will be tested using a linear fixed effects model having dose as a fixed effect. Individual MK-2214 CSF C_{85d} values from Panels A through D will be natural log transformed prior to analysis. For participants who do not provide a sample for CSF PK on Day 85, the C_{85d} value will be calculated from their observed serum C_{85d} and the observed Day 85 GMR of CSF to serum concentration from participants who do provide a CSF PK sample on Day 85. A posterior distribution for the true GM MK-2214 CSF C_{85d} on the log scale will be generated for each dose level using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level, the posterior probability that the true GM MK-2214 CSF C_{85d} >0.3 nM will be calculated for each dose. A >80% posterior probability for at least 1 dose level that is also generally well tolerated will satisfy the primary PK hypothesis. Point estimates and 95% CIs of MK-2214 CSF C_{85d} GM will be provided by dose level.

Pharmacodynamics

CC1 Descriptive statistics for CC1 level will be provided by treatment and day.

9.2 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.

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 CSR.

9.3 Hypotheses/Estimation

Hypothesis (Part 1 only): At a generally well-tolerated dose level, the true GM C85d concentration of MK-2214 in CSF is >0.3 nM.

9.4 Analysis Endpoints

Primary Endpoints

Safety:

AEs and participant discontinuations due to AE(s), raw laboratory safety tests, ECGs, and vital signs as well as for change from baseline, as deemed clinically appropriate.

Responses on the C-SSRS are classified according to 11 prespecified categories as described in Appendix 12. The most severe treatment-emergent event within each of three broad categories (suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior) reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it either newly emerged or is more severe than the most severe event reported to have occurred in the trial-defined pre-treatment reference period.

Pharmacokinetics: The PK variables of MK-2214 AUC₀₋₂₈, C_{max}, T_{max}, and t_{1/2} (after the third dose) in serum, as well as MK-2214 C85d in CSF are of primary interest.

When observed C85d in CSF are not collected, predicted values derived by multiplying the serum concentrations at Day 85 by the CSF to serum ratio will be used.

Pharmacodynamics: CCI levels in CSF.

When observed CCI levels are BLOQ, the lower limit of quantification will be used.

Exploratory Endpoints:

Pharmacokinetics: CSF/serum MK-2214 concentrations.

Pharmacodynamics: Serum ADA.

9.5 Analysis Populations

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

All Participants as Treated (APaT): 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.

Per-Protocol (PP): 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 PK and pharmacodynamic analyses.

9.6 Statistical Methods

Analysis Overview

All references within this data analysis section to the log transformation or log function pertain to the natural log. If log transformation is used, the CIs for the means (mean differences) will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means (mean differences) and lower and upper limits of these confidence intervals will yield estimates for the population GMs (population GMRs) and confidence intervals about the GMs (GMRs) on the original scale.

If linear mixed modeling is employed for an analysis and statistical inferences are based on t-statistics, Kenward & Roger's approximation will be used to compute the degree-of-freedom.

Data will be examined for departures from the assumptions of the statistical model(s) as appropriate; eg, heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

Primary (Safety)

Incidence of AEs will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the VS, ECG parameters, and selected laboratory safety parameters for participants, 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). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary (Pharmacokinetics)

Model-based Serum PK Summary: Individual PK values for AUC0-28 and Cmax after the first and third dose from Panels A through D will be natural log transformed and analyzed based on a linear mixed effects model containing fixed effects for treatment, day, treatment by day interaction and a random effect for participant. A 95% CI will be constructed for the GMs of MK-2214 AUC0-28 and Cmax at each day and dose level. The GMR (postdose 3/postdose 1) of AUC0-28 and Cmax and their 90% CIs will be calculated for each dose. AUC0-28 and Cmax for Part 2 will be analyzed based on the same model.

Target CSF PK Concentration: The primary hypothesis that at a dose level of MK-2214 that is generally well tolerated, the true geometric mean concentration at the surrogate site of action (CSF) at Day 85 (C85d) >0.3 nM will be tested using a linear fixed effects model having dose as a fixed effect. Individual MK-2214 CSF C85d values from Panels A through D will be natural log transformed prior to analysis. For participants who do not provide a sample for CSF PK on Day 85, their C85d value will be calculated from the observed serum C85d and the observed Day 85 GMR of CSF to serum concentration from participants who do provide a CSF PK sample on Day 85. A posterior distribution for the true GM MK-2214 CSF C85d on the log scale will be generated for each dose level using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level, the posterior probability that the true GM MK-2214 CSF C85d >0.3 nM will be calculated for each dose. A $>80\%$ posterior probability for at least one dose level that is also generally well tolerated will satisfy the primary PK hypothesis. Point estimates and 95% CIs of MK-2214 CSF C85d GM will be provided by dose level.

Descriptive Statistics: Individual values will be listed for each serum and CSF 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 CV (calculated as $100 \times \text{standard deviation} / \text{arithmetic mean}$), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale).

Primary (Pharmacodynamics)

CCI Descriptive statistics for CCI level will be provided by treatment and day.

Exploratory (Pharmacokinetics)

Serum and CSF Concentration Comparison: Descriptive statistics of the observed CSF concentration, serum concentration, and CSF to serum ratio on common days will be reported by dose level and day.

Serum ADA data will be summarized by dose level and visit.

Other PK parameter summaries and listings

Assessment of Dose Proportionality (Pharmacokinetics): The assessment of dose proportionality will be conducted for the third dose in Part 1 in an exploratory manner. The primary assessment of dose proportionality for MK-2214 AUC₀₋₂₈ in serum will be performed using the power law model with $\ln(\text{AUC})$ as the dependent variable and $\ln(\text{dose})$ as an explanatory variable. A point estimate of the slope associated with $\ln(\text{dose})$ will be provided together with a 95% CI from the power law model.

A plot of the observed PK data versus dose will be provided along with an estimated regression line on the raw scale and a 95% Schéffe confidence band. The assessment of the dose proportionality of MK-2214 C_{max} in serum will be carried out in the same manner as that used for MK-2214 AUC₀₋₂₈.

9.7 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (PK, pharmacodynamic, biomarkers and/or safety [labs, VS, ECGs, C-SSRS]) will be prepared as needed to support decision-making meetings such as dose escalation meetings. The aggregate summaries will be presented in an unblinded manner. No individual participant level results will be provided. There are no planned interim analyses to test any formal hypotheses.

9.8 Multiplicity

Since Bayesian approach is used for the primary PK hypothesis, no multiplicity adjustment is necessary. However, a step-down procedure will be utilized when assessing the posterior probability that the true GM CSF C85d >0.3 nM for at least one multiple dose level in Part 1 that also exhibits acceptable safety and tolerability. Specifically, the highest multiple dose level that exhibits acceptable safety and tolerability profile will be assessed first. If there is $<80\%$ posterior probability that the true GM CSF C85d >0.3 nM then the primary PK hypothesis will not be met, and no other multiple doses will be assessed. If there is $\geq 80\%$ posterior probability that the true GM CSF C85d >0.3 nM, then the second highest multiple dose level that also exhibits acceptable safety and tolerability will be assessed. Assessment will continue sequentially in this manner until $<80\%$ posterior probability is observed, or until all multiple dose levels are assessed.

9.9 Sample Size and Power Calculations

No estimates of between-subject variability are available for CSF C85d following multiple dosing of MK-2214. Estimates of the CSF C85d variability was obtained from the population pharmacokinetics model based on CSF data from MK-2214-001. With 6 participants in the MK-2214 treatment group at each dose level, using the geometric standard deviation of 1.28, and a posterior probability of 80%, if the true GM CSF C85d is more than 0.38 nM (predicted to correspond to a dose level between 100 mg and 500 mg), there will be at least 90% probability that the hypothesis that true GM MK-2214 CSF C85d >0.3 nM is supported.

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 his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

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

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

10.1.6 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 Indices: MCV MCH Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate (or CO2)	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Coagulation ^a	PT and INR	aPTT		
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 WONCBP) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines); also conducted prior to each dose. Additional testing per site SOP • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • All study-required laboratory assessments will be performed by a local laboratory			
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; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential				
^a Screening and prior to LP				

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

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.”

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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research^{3, 4}

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

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

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

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

3. Summary of Procedures for Future Biomedical Research^{3, 4}

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. **eCRF Documentation for Future Biomedical Research Specimens**

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

d. **Future Biomedical Research Specimen(s)**

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

4. Confidential Participant Information for Future Biomedical Research^{3,4}

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

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10.7 Appendix 7: Country-specific Requirements

Not Applicable.

10.8 Appendix 8: Blood Volume Table

All Panels	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Blood for FSH (WONCBP as needed)	1	0	0	1	4.5	4.5
HIV/Hepatitis Screen	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
Blood Sample for AD Biomarkers ^b	0	4	1	5	20	100
Laboratory Safety Tests	1	13	1	15	12.5	187.5
Coagulation Tests ^b	1	2	0	3	3	9
Blood for serum MK-2214 PK	0	21	1	22	4	88
Blood for serum MK-2214 PK + ADA	0	8	1	9	6	54
Total Blood Volume per Female Participant (Part 1 and Part 2 participants with MCI or AD) ^a						456.5 mL
Total Blood Volume per Male Participant (Part 1 and Part 2 participants with MCI or AD) ^a						452 mL
Total Blood Volume per Female Participant (Part 2 healthy older participants) ^a						376.5 mL
Total Blood Volume per Male Participant (Part 2 healthy older participants) ^a						372 mL
AD=Alzheimer's Disease; ADA=antidrug antibodies; aPTT=activated partial thromboplastin time; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; INR=international normalized ratio; MCI=mild cognitive impairment; PK=pharmacokinetic; PT=prothrombin time; WONCBP=women of nonchildbearing potential ^a If additional PK/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained. ^b Part 1 and Part 2 participants with MCI or Mild to moderate AD will have 5 total collections, Part 2 healthy older participants will have 1 predose collection only						

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
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	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
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	QRS ≥ 130 ms	QRS ≥ 130 ms + Increase of ≥ 10 ms
QTc (B or F)		
Male	QTc ≥ 470 ms	QTc ≥ 500 ms or Increase of ≥ 60 ms From Baseline
Female	QTc ≥ 480 ms	QTc ≥ 500 ms or Increase of ≥ 60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P. Mitrale or P. Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
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	No exclusion	All
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, PR=pulse rate; 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 prestudy (screening) visit and/or predose 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 a repeat 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:

Select the appropriate option below for item C:

- a. The participant may be excluded from the study.
- b. 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).
- c. 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

- d. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
 - a. If the repeat test value is within the normal range, the participant may enter the study.
 - b. 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: 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.

10.11.1 The General Neurological Examination

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

10.11.1.1 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.

10.11.1.2 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

10.11.1.3 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

10.11.1.4 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

10.11.1.5 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

10.11.1.6 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)

10.11.2 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:

10.11.2.1 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)

10.11.2.2 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

10.11.2.3 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

10.11.2.4 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

10.11.2.5 Module 6 – Sensory

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

10.12 Appendix 12: Mapping Between the 11 Categories of Suicidal Ideation and Behavior and the CSSR-S

Category	C-SSRS Question (from eCRF) ^a
Suicidal ideation	
1. Passive	1. Wish to be dead
2. Active: Nonspecific (no method, intent, or plan)	2. Non-specific active suicidal thoughts
3. Active: Method, but no intent or plan	3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active: Method and intent, but no plan	4. Active suicidal ideation with some intent to act, without specific plan
5. Active: Method, intent and plan	5. Active suicidal ideation with specific plan and intent
Suicidal behavior	
6. Preparatory actions toward imminent suicidal behaviors	Preparatory acts or behavior
7. Aborted attempt	Aborted attempt
8. Interrupted attempt	Interrupted attempt
9. Suicide attempt	Actual attempt
10. Completed suicide	Completed suicide
Self-injurious behavior, no suicidal intent	Has participant engaged in non-suicidal self-injurious behavior?
^a Data are "yes" or "no"	

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
AD	Alzheimer's Disease
ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-28	area under the concentration time curve from 0 to 28 days
AUC0-inf	area under the concentration time curve from 0 to infinity
BLA	Biologics Licensing Application
BLOQ	below limits of quantification
BMI	body mass index
BP	blood pressure
BSA	body surface area
BT	body temperature
C85d	concentration at Day 85
CCU	cardiac care unit
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CS	compound symmetry
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctrough	trough concentration
CV	coefficient of variation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EC	exclusion criteria
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate

Abbreviation	Expanded Term
EMA	European Medicines Agency
FBR	future biomedical research
Fc	crystallizable fragment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPE	first patient enrolled
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GM	geometric mean
GMR	geometric mean ratio
h	hour(s)
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLE	half-life extension
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC	inclusion criteria
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
ID	identification
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	interstitial fluid
IV	intravenous
IVIG	intravenous immunoglobulin
LP	lumbar puncture
mAb	monoclonal antibody
MAD	multiple ascending dose
MCI	mild cognitive impairment
MHIS	Rosen-Modified Hachinski Ischemic Scale
MMSE	Mini-Mental State Examination

Abbreviation	Expanded Term
N/A	not applicable
NCS	not clinically significant
NDA	New Drug Application
NfL	neurofilament light chain protein
NFTs	neurofibrillary tangles
NIMP	non investigational medicinal product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAIDS	non-steroidal anti-inflammatory drugs
PCL	Protocol Clarification Letter
PCR	polymerase chain reaction test
PE	physical examination
PET	positron emission tomography
PK	pharmacokinetic
PN	protocol number
CCI	
PT	prothrombin time
CCI	
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SC	subcutaneous
SCr	serum creatinine
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
Tmax	time to maximum plasma concentration
t1/2	half life
UDS	urine drug screen
ULN	upper limit of normal
VS	vital signs
WBC	white blood cell
WONCBP	woman/women of nonchildbearing potential

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