Official Protocol Title:	A Randomized Clinical Study to Evaluate the Safety and Tolerability of MK-8189 in Participants with Alzheimer's Disease with or without Symptoms of Agitation-Aggression and/or Psychosis
NCT number:	NCT05227118
Document Date:	21-Jul-2022

Title Page

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Protocol Title: A Randomized Clinical Study to Evaluate the Safety and Tolerability of MK-8189 in Participants with Alzheimer's Disease with or without Symptoms of Agitation-Aggression and/or Psychosis

Protocol Number: 017-04

Compound Number: MK-8189

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	159736

Approval Date: 21 July 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	21-JUL-2022	Exclusion criterion #22 was modified to clarify the use of permitted prescribed medications, which could generate a positive UDS, is not exclusionary.
Amendment 03	03-MAY-2022	Per FDA feedback, inclusion criteria were updated to include specific criteria for hypertension and orthostatic hypotension assessments. Exclusion criteria were updated to exclude participants with a family history of prolonged QTc syndrome.
Amendment 02	25-FEB-2022	Based on newly available preliminary pharmacokinetic data, the first dosing regimen to be evaluated has been modified such that participants will be titrated up to MK-8189 16 mg/placebo as opposed to initially titrating participants up to MK-8189 24 mg/placebo.
Amendment 01	28-JAN-2022	Added the Columbia Suicide Severity Rating Scale (C-SSRS) to every visit.
Original Protocol	10-DEC-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

Exclusion criterion #22 was modified to clarify the use of permitted prescribed medications, which could generate a positive UDS, is not exclusionary.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	The following bolded statement was added to Exclusion #22: Participants must have a negative UDS (with the exception of cannabis **and/or prescribed medications permitted at the discretion of the PI and Sponsor**) prior to randomization.	As the intention of this criterion is to exclude participants using illicit drugs or participants with a history of drug abuse, participants may be included if using permitted prescribed medications which generate a positive UDS.
5.1 Inclusion Criteria	Inclusion #1 and Inclusion #9 were updated to include clarifications per PCL #1.	N/A
6.5 Concomitant Therapy	Added the continued use of medications that may cause somnolence must be discussed between the investigator and Sponsor prior to MK-8189 administration.	As adverse events of transient somnolence have been reported following administration of MK-8189, the investigator and Sponsor will discuss the continued use of other medications known to cause somnolence to minimize the potential for additive somnolent effects.

Section # and Name	Description of Change	Brief Rationale
8.3.2.1 Resting Vital Signs	Wording was updated to clarify Day 1 predose vital signs should be taken within 3 hours **prior to** dosing.	The language is now consistent with the Schedule of Activities footnote.
10.2 Appendix 2: Clinical Laboratory Tests	A sentence was added to indicate routine urinalysis and urine pregnancy tests will be done locally at the site.	The central lab vendor will only be sent urinalysis samples if a microscopic examination is required.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized Clinical Study to Evaluate the Safety and Tolerability of MK-8189 in Participants with Alzheimer's Disease with or without Symptoms of Agitation-Aggression and/or Psychosis

Short Title: MK-8189 Safety and Tolerability in Participants with Alzheimer's Disease with or without Symptoms of Agitation-Aggression and/or Psychosis

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

In male or female participants with Alzheimer's Disease with or without symptoms of agitation-aggression and/or psychosis.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple ascending doses of MK-8189 in participants with Alzheimer's Disease with or without symptoms of agitation-aggression and/or psychosis	• Adverse events • Adverse experiences leading to discontinuation of study intervention
Secondary	
• Not applicable	

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Neuropsychiatric Symptoms in Dementia
Population	Male and female participants, 65-85 years of age, inclusive, with clinically probable Alzheimer's Disease with or without symptoms of agitation-aggression and/or psychosis
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Investigator, Care Provider, Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 16 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to approximately 28 participants will be allocated/randomized such that at least 16 evaluable participants complete the study as described in Section 9.

Note: Greater than 16 participants may be required to complete the study if additional study data are needed to further understand the safety and tolerability profile of MK-8189 in the AD population.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Active	MK-8189	4 mg & 12 mg	QD	Oral	**Titration 1** 4 mg x 2 tablets Days 1-3; 4 mg x 1 tablet & 12 mg x 1 tablet Days 4-28 **Titration 2** 4 mg x 2 tablets Days 1-3; 4 mg x 1 tablet & 12 mg x 1 tablet Days 4-6; 12 mg x 2 tablets Days 7-28 **Titration 3** 4 mg x 1 tablet Days 1-3; 4 mg x 2 tablets Days 4-6; 4 mg x 1 tablet & 12 mg x 1 tablet Days 7-9; 12 mg x 2 tablets Days 10-28	Experimental Treatment
Placebo	Placebo	0 mg	QD	Oral	**Titration 1 & 2** 2 tablets Days 1-28 **Titration 3** 1 tablet Days 1-3; 2 tablets Days 4-28	Control

Abbreviations:
QD=Once a day

Total Number of Intervention Groups/ Arms	2
Duration of Participation	Each participant will participate in the study for approximately 3 months from the time the participant provides documented informed consent through the final contact. After a screening phase of 42 days, each participant will receive assigned intervention for approximately 28 days. After the end-of-treatment each participant will be followed for 14 days.

Study Governance Committees:

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

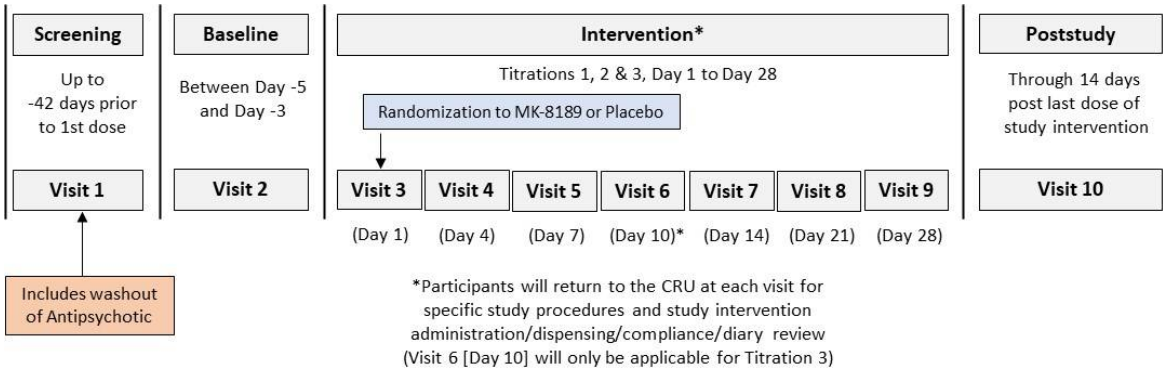
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



1.3 Schedule of Activities

	Screening	Baseline	Intervention							Poststudy[a]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[i]**	**10**	
Scheduled Visit Day plus Window	**Up to -42**	**-5 to -3**	**1**	**4**	**7**	**10[j]**	**14**±1	**21**±1	**28**+1	**LD+14**+2	
Administrative Procedures											
Informed Consent – Study Participant	X										Section 8.1.1.1
Informed Consent – Trial Partner	X										Section 8.1.1.1
Informed Consent for FBR	X										Section 8.1.1.2
Participant ID Card	X										Section 8.1.3
Inclusion/Exclusion Criteria	X	X									Section 5.1 & Section 5.2 Specific criteria may be reviewed before randomization
Medical History (includes psychiatric history and substance usage)	X										Substances: Drugs, alcohol, tobacco, and caffeine Section 8.10.2
Prior/Concomitant Medication Review	X----------									----------X	Section 6.5, Section 8.10.2
Assignment of Treatment/Randomization Number			X								
Study Intervention Administration[b]			X----------							----------X	The last dose will be on Day 28 regardless of the Study Day Visit 9 falls on.
Study Intervention Dispensing/Review			X	X	X	X	X	X	X		Collect prior medication bottle before dispensing new one.
Study Intervention Diary Dispensing/Review			X	X	X	X	X	X	X		Review diary upon participants return to the CRU.
Daily Phone Call[c]			X----------							----------X	
Optional Domiciling			X----------							----------X	See Section 8.1.12
Safety Procedures											
Full physical examination	X	X								X	
Height	X										

	Screening	Baseline	Intervention							Poststudy[a]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[l]**	**10**	
Scheduled Visit Day plus Window	**Up to -42**	**-5 to -3**	**1**	**4**	**7**	**10[j]**	**14**±1	**21**±1	**28**+1	**LD+14**+2	
Weight	X	X								X	BMI to be calculated only at Screening
Full Neurological Exam	X	X									Section 10.10
Targeted Neurological Exam[d]					X		X	X	X	X	Section 10.10
Vital Signs (pulse rate, blood pressure) [e, f]	X		X	X	X	X	X	X	X	X	Section 8.3.2.1
Orthostatic Vital Signs (pulse rate, blood pressure)[e]	X		X	X	X	X	X	X	X	X	Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X		X		X		X	X	X	X	Section 8.3.2.1
12-lead ECG[e, f]	X		X		X		X	X	X	X	Section 8.3.3
Serum hCG Pregnancy Test (as needed in WOCBP only)	X										Section 5.1 & Section 8.3.5
Urine hCG Pregnancy Test (as needed in WOCBP Only)		X			X		X	X	X	X	Section 5.1 & Section 8.3.5
Serum FSH (as need in WONCBP only)	X										
HIV, Hepatitis B and C Screen (per site SOP)	X										
UDS/BDS (per site SOP)	X	X									
Laboratory Safety Tests (hematology, chemistry, urinalysis)[g]	X	X			X		X	X	X	X	Section 10.2
Columbia Suicide Severity Rating Scale (C-SSRS) – Baseline Version	X										Section 8.3.6.1
Columbia Suicide Severity Rating Scale (C-SSRS) – Since Last Assessment Version[d]		X	X	X	X	X	X	X	X	X	Section 8.3.6.1
Neuropsychiatric Inventory (NPI)[d, h]	X								X		Section 8.3.10 & Section 8.10.2
Mini Mental State Examination (MMSE-2)[d]	X								X		Section 8.3.9

	Screening	Baseline	Intervention							Poststudy[a]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[l]**	**10**	
Scheduled Visit Day plus Window	**Up to -42**	**-5 to -3**	**1**	**4**	**7**	**10[j]**	**14**±1	**21**±1	**28**+1	**LD+14**+2	
Rosen-Modified Hachinski Ischemic Score (MHIS)	X										Section 8.3.8
Barnes Akathisia Rating Scale (BARS)[d, i]		X			X		X	X	X	X[i]	Section 8.3.11
Abnormal Involuntary Movement Scale (AIMS)[d, i]		X			X		X	X	X	X[i]	Section 8.3.11
Simpson Angus Scale (SAS) [d, i]		X			X		X	X	X	X[i]	Section 8.3.11
AE/SAE review	X----------									----------X	
Pharmacokinetics											
Blood for Plasma MK-8189 and/or Metabolites Assay			X		X		X	X	X		On days noted, 2 blood samples will be collected: 1) prior to dosing (fasted) 2) 2-4 hours post dose Note: If Visit 9 occurs on Day 29, , only 1 blood sample will be collected as there will be no dose on this day.
Blood for Plasma Donepezil Assay[k]			X		X		X	X	X		Blood collected prior to dosing (fasted).
Blood for Plasma Memantine Assay[k]			X		X		X	X	X		Blood collected prior to dosing (fasted)
Biomarkers											
Blood for Exploratory Plasma Biomarkers for AD Diagnosis			X								See Section 8.8.2
Blood for Genetic Analysis[m]			X								Collect predose from enrolled participants only.

	Screening	Baseline	Intervention							Poststudy[a]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[l]**	**10**	
Scheduled Visit Day plus Window	**Up to -42**	**-5 to -3**	**1**	**4**	**7**	**10[j]**	**14**±1	**21**±1	**28**+1	**LD+14**+2	

AE=adverse event; BDS=blood drug screen; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; ID=identification; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Poststudy visit procedures should also be performed for participants who discontinued early from study intervention.
b. QD dosing at approximately the same time each morning (Days 1-28) either in the CRU or at home. During scheduled CRU visits, participants should be administered study intervention fasted in the CRU. At home study intervention administration will be with or without food and will be recorded in study intervention diary by the participant/trial partner. Participants will be supervised for at least 6 hours following the first administration of study intervention and following the first administration of each study intervention titration (see Section 8.1.8).
c. While participants are outpatient, site staff will call participants daily to check study administration compliance, review AEs, and remind participants of their next scheduled visit (if applicable).
d. Collected after dosing and an optional light breakfast on study treatment administration days.
e. Collected prior to dosing on study treatment administration days.
f. Vital sign measurements at Screening will be taken in triplicate. Day 1 ECGs and vital sign measurements will be taken in triplicate within 3 hours prior to dosing. Single ECGs and vital sign measurements will be collected on all other days.
g. Safety laboratory Baseline results will be reviewed prior to Day 1 dosing. All safety laboratory collection will be fasted and prior to dosing on study treatment administration days.
h. For participants that must washout of prior antipsychotic treatment at Screening, the NPI is to be repeated prior to randomization after a minimum 2-week washout or 5 half-lives, whichever is longer.
i. Poststudy assessment required only if clinically meaningful changes on Day 28.
j. Visit 6 (Day 10) will only occur for Titration 3.
k. Sample will only be taken for participants currently taking donepezil and/or memantine.
l. Every effort should be made to have participants return for Visit 9 on Day 28 however if necessary, participants may return on Day 29 to have all Visit 9 assessments completed. Participants will not be dosed on Day 29.
m. This sample will be drawn for CYPC29 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYPC29. Leftover extracted DNA will be stored for FBR if the participant (or legally acceptable representative) provides documented informed consent for FBR.

2 INTRODUCTION

2.1 Study Rationale

MK-8189, a PDE10A inhibitor, is being developed for the treatment of neuropsychiatric symptoms in dementia. Prior to conducting a larger proof of concept study, this study will explore the safety and tolerability of MK-8189 in the Alzheimer's disease population with or without agitation-aggression and/or psychosis.

2.2 Background

Refer to the IB for detailed background information on MK-8189.

2.2.1 Pharmaceutical and Therapeutic Background

MK-8189 is a potent and selective inhibitor of PDE10A being developed as a novel therapeutic for the treatment of schizophrenia as well as neuropsychiatric symptoms in dementia. In a Phase 2a study, POC has been established for the schizophrenia indication. The objective of this first study is to evaluate safety and tolerability in a similar patient population (participants with or without agitation-aggression and/or psychosis associated with Alzheimer's disease) prior to conducting a larger POC study. Current treatment for neuropsychiatric symptoms associated with dementia often involves the off-label use of atypical antipsychotics (AAPs). However, AAPs have a black box warning in the US with regards to the increased risk of death among elderly patients with dementia-related psychosis, which ultimately creates a therapeutic unmet need in elderly patients with dementia-related agitation and aggression [Marcinkowska, M., et al 2020]. Increased availability of D2 and D3 receptors in the striatum as well as cortical dysfunction have been implicated in the pathophysiology of AAD [Kales, H. C., et al 2015]. The PDE10A enzyme metabolically inactivates the ubiquitous second messengers, cAMP and cGMP [Bender, A. T. and Beavo, J. A. 2006] and is highly expressed in the target nucleus of the corticostriatal pathway, the striatum and to a lesser extent the cortex and hippocampus [Seeger, T. F., et al 2003]. Preclinical pharmacology studies demonstrate that PDE10A inhibition increases cAMP/cGMP signaling in the striatum which results in activation of the D2 pathway and potentiation of cortical striatal signaling leading to increased behavioral control [Grauer, S. M., et al 2009] [Schmidt, C. J., et al 2008].

PDE10A inhibitors have also been shown to decrease psychomotor activity, reverse deficits in pre-pulse inhibition, and inhibit conditioned avoidance responding in assays that are hypothesized to translate to efficacy on psychosis, agitation, and aggression [Smith, S. M., et al 2013] [Grauer, S. M., et al 2009]. In addition, PDE10A inhibitors have beneficial effects on preclinical measures of cognitive performance in nonhuman primates [Smith, S. M., et al 2013] [Vardigan, J. D., et al 2016]. In the Phase 2a POC study, in an exploratory analysis, MK-8189 showed nominal improvement in the PANSS Marder Factor Hostility/Excitement Symptom Score and Disorganized Thought Symptom Score. Thus, based on preclinical and clinical evidence, MK-8189 will be evaluated for the treatment of neuropsychiatric symptoms in dementia.

2.2.2 Preclinical and Clinical Studies

Preclinical and clinical study information can be found in the MK-8189 IB.

Summary of Completed Clinical Studies

As part of the Phase 1 program, three single-dose clinical studies, one DDI study, and two multiple-dose clinical studies have been completed with MK-8189. Overall, 146 participants have received at least one dose of MK-8189; 71 healthy participants and 75 participants with schizophrenia. Single doses of MK-8189 up to 6 mg have been given to 48 healthy men, 22 with an IR formulation and 26 with a CR formulation. Ten healthy male and female participants received multiple doses titrated up to 12 mg over 14 days (P003 Part 3) and 12 healthy male and female participants received doses titrated up to 24 mg over 18 days (P007 Panel A). Thirty-three male and female participants with schizophrenia were titrated up to doses of 16 mg over 14 days (P003), 25 participants with schizophrenia were titrated up to 24 mg over 18 days (P007 Panels B and C) and 17 participants with schizophrenia were titrated up to 48 mg over 15 days (P007 Panel D). All multiple-dose studies were conducted with a CR formulation.

MK-8189 was generally well tolerated across the Phase 1 studies. The most common treatment-related adverse events [AEs] (≥5%) following treatment of MK-8189 (n=146) across the completed 6 Phase 1 studies in healthy participants and participants with schizophrenia were headache (16.4%), somnolence (12.3%), decreased appetite (10.3%), nausea (9.6%), fatigue (8.9%), dizziness (8.9%), vomiting (6.2%), diarrhea (6.2%), akathisia (6.2%), and anxiety (6.2%). Most AEs were mild to moderate in severity. There were no deaths and 2 SAEs. One healthy participant experienced an SAE of gastroenteritis in P003 which was not considered treatment related. The other SAE of severe treatment-related psychosis occurred in a participant with schizophrenia following titration up to and administration of the 36 mg dose (P007). The participant discontinued MK-8189 treatment, was hospitalized, and received treatment with an antipsychotic and anxiolytic. The SAE resolved within 6 days.

In the Phase 2 study, P005, most episodes of dystonia lasted less than one day, with three events lasting one or more days. Only one participant discontinued due to an AE of dystonia. In summary, eight participants (8.9%) had an AE of dystonia and 2 participants (2.2%) had an AE of oromandibular dystonia. The intensities of the dystonia AEs were mild and moderate with most reported as mild. Onset of dystonia occurred mostly during the intervention titration period at the 4 mg, 8 mg, and 12 mg dose levels with a duration range of less than 1 day for most events and up to six days. One participant discontinued study intervention due to dystonia. Two participants experienced 2 episodes of dystonia each during the intervention titration period. One participant experienced both events during the 8 mg dose level (mild, moderate), while another participant experienced one event during the 4 mg (moderate) and one during the 8 mg (mild) dose level. The AEs of dystonia, except for one incident, were considered related to study intervention by the investigators.

Individual studies are summarized in the IB.

Summary of MK-8189 Pharmacokinetics

Following multiple doses of the controlled release formulation, MK-8189 exposure increased approximately proportionally with dose over the range of doses tested (2 to 48 mg) in all populations. Median Tmax of MK-8189 as monotherapy ranged from 10 to 24 hours with a t1/2 of approximately 10.9 hours. Based on completed studies, data suggest that the exposures at steady state for a given dose are generally comparable between healthy participants and participants with schizophrenia administered MK-8189 as monotherapy.

Preliminary results from the ongoing study P011 (described in 2.2.3) suggest that PK exposures in elderly participants with and without schizophrenia are similar to one another and similar to those observed in adult participants < 60 years of age with schizophrenia. While there was significant overlap in the individual PK parameter values for elderly and non-elderly participants, in healthy elderly participants, on average, C24 values were approximately 50% higher than C24 values in non-elderly adults and elderly participants with schizophrenia.

MK-8189 is a CYP3A substrate and in a DDI study (P006) the coadministration of extended release 240-mg diltiazem, a moderate CYP3A inhibitor, increased MK-8189 AUC and Cmax by approximately 2-fold and 1.3-fold, respectively. In another ongoing DDI study (P015, described in 2.2.3) the coadministration of itraconazole, a strong CYP3A inhibitor, increased MK-8189 AUC and Cmax by approximately 1.2-fold and 1.14-fold, respectively, and were generally consistent with the results observed in the diltiazem study. Collectively, these results confirm that MK-8189 is a CYP3A substrate.

2.2.3 Ongoing Clinical Studies

As of October 29, 2021, three Phase 1 trials and one Phase 2 trial are ongoing. All data presented are preliminary.

2.2.3.1 Protocol 011

P011 is a Phase 1 multiple-dose randomized (Panels A/B/C/D/E - 3 active:1 placebo; Panel F/G - 5 active:1 placebo), double-blind, placebo-controlled, multicenter, 2-part study. Part 1 (Panel A/B/C) is evaluating the safety and tolerability of different titration regimens or initiating MK-8189 treatment without titration in participants ≤60 years of age with schizophrenia. Part 2 is evaluating the multiple dose safety, tolerability, and PK of MK-8189 in elderly participants with schizophrenia (Panel D and Panel E) and healthy elderly participants (Panel F and Panel G) between 61 and 80 years of age (inclusive). Panel E and Panel G will explore safety and tolerability at different titration regimens and will only be initiated after a safety and tolerability review from Panel D and Panel F, respectively.

In Part 1, Panel A, participants with schizophrenia initiated dosing with 16 mg of MK-8189/placebo for 3 days and then were escalated to 24 mg/placebo for 4 days. In Panel B, participants with schizophrenia initiated dosing with 24 mg of MK-8189/placebo (no titration) for 7 days. Part 1 is clinically complete and all data are preliminary and blinded. No SAEs or deaths were reported.

In Panel A, all 8 participants enrolled completed treatment. Most AEs were mild, and no AEs were severe in intensity. All AEs resolved. Of the 8 participants, one participant did not dose escalate to 24 mg/placebo due to moderate somnolence which lasted for 3 days. For the duration of the somnolence AE, the participant was also receiving hydroxyzine, a sedating antihistamine. Two participants reported an AE of dystonia. One participant reported mild transient dystonia which began 14 hours after the first dose and lasted 2 days. The dystonia was treated with benztropine until it resolved. The participant continued dosing with MK-8189/placebo without recurrence of dystonia. Another participant reported mild transient dystonia which began 6.5 hours following the first dose and resolved in 22 hours. While experiencing dystonia the participant was treated with benztropine. The participant continued to dose with MK-8189/placebo and escalated to 24 mg/placebo without a recurrence of dystonia. AEs reported (including those already discussed) considered related to study drug included decreased appetite (n=2), dystonia (n=2) somnolence (n=2), nightmare (n=1), worsening psychosis (n=1), and insomnia (n=1).

In Panel B, enrollment and dosing are complete. Participants received MK-8189 24 mg/placebo Days 1-7. Eighteen participants were randomized and 14 completed treatment per protocol. Of the 4 participants that discontinued treatment, 3 withdrew consent and 1 participant discontinued due to AEs of nausea and vomiting that were not considered related to treatment. This participant had a history of gastroesophageal reflux disease that was ongoing throughout the trial. The other participants withdrew consent. No AEs were considered severe and the majority of AEs were mild. Except for an unrelated AE of ligament sprain, all AEs resolved. AEs considered related to treatment included somnolence (n=2), hypertonia (n=1), decreased appetite (n=1), musculoskeletal stiffness (n=1) and increased ALT (n=1). The participant with the AE of elevated ALT had an elevated screening value of 61 IU/L (normal range 7-52 IU/L). The Day -1 predose ALT value was also elevated (98 IU/L) and continued to increase on Day 7 (116 IU/L) and Day 9 (133 IU/L). At the poststudy the ALT was still elevated but below the predose value (71 IU/L). ALP (normal range 34-104 IU/L) followed a similar pattern with elevations at screening (130 IU/L), Day -1 predose (136 IU/L), Day 7 (143 IU/L), Day 9 (134 IU/L) and at the poststudy visit (124 IU/L). While AST was within the normal range (13-39 IU/L) at screening (26 IU/L) and Day -1 predose (37 IU/L), values were elevated above the normal range on Day 7 (44 IU/L) and Day 9 (51 IU/L). At the post study visit, AST was within the normal range (26 IU/L). Bilirubin was normal throughout the study. Preliminary data suggest initiation of MK-8189 at a 16 mg or 24 mg dose was generally well tolerated. No AEs of akathisia or dystonia were reported.

Panel C was not conducted per protocol since the regimens in Panel A and B were generally well tolerated.

Treatment is ongoing in Part 2. Panel D is currently enrolling elderly participants with schizophrenia. Participants will receive MK-8189 8 mg/placebo Days 1-3, MK-8189 16 mg/placebo Days 4-6 and MK-8189 24 mg/placebo Days 7-13. Twelve participants have been dosed to date. No deaths or SAEs have been reported. Most AEs were mild or moderate and 1 AE was severe (described below). All AEs reported to date have resolved except an

AE of a small forehead bump considered not treatment related. Four participants have discontinued the trial:

One participant withdrew consent, and no treatment-related AEs were reported for this participant.

One participant reported an AE of severe somnolence which began following the 8 mg/placebo dose and resolved on Day 3 following administration of the 8 mg/placebo dose. On Day 3 following treatment with 8 mg/placebo, the participant had an AE of moderate dystonia which resolved in 2 days with a single-dose of cyclobenzaprine. This participant reported moderate akathisia following treatment with 8 mg/placebo which continued for 3 weeks. This participant had drug interrupted and subsequently discontinued following the second 16 mg/placebo dose due to moderate treatment-related AEs of dermatitis and conjunctivitis. No other treatment-related AEs were reported.

One participant experienced dystonia of the throat after the Day 3 16 mg/placebo dose which was treated with benztropine and alleviated the participant's difficulty to swallow. The participant continued to have tightness of throat muscles which the investigator considered to be mild dystonia which persisted for 2 weeks. The participant discontinued treatment prior to the Day 4 dose. The participant had also reported hypoesthesia, dizziness, dysgeusia and ear discomfort which were considered treatment related.

Another participant discontinued due to an AE of internal restlessness in the predawn hours of Day 7. This participant also reported involuntary movement of lower extremities the evening prior. These AEs led the participant to withdrawal from the study and the participant discontinued dosing prior to the first dose of 24 mg/placebo. This panel is still actively dosing and the following treatment related AEs have been reported to date (includes AEs which have been reported above); dystonia (n=2), internal restlessness (n=2), somnolence (n=1), akathisia (n=1), conjunctivitis (n=1), dermatitis (n=1), dizziness (n=1), dysgeusia (n=1), ear discomfort (n=1), oral hypoesthesia (n=1) and involuntary movement of lower extremities (n=1)

Panel F is clinically complete and enrolled 6 healthy elderly participants. The treatment regimen was the same as Panel D. Most AEs were mild in intensity and no severe AEs were reported. No deaths or SAEs have been reported. Except for hyponatremia (discussed below), all other reported AEs resolved. One subject discontinued the trial due to treatment related AEs of nausea, vomiting, dyspepsia, and hyponatremia. This participant also reported diarrhea prior to the onset of nausea and vomiting. The hyponatremia was resolving at the time of participant discharge. One participant was down-titrated from 24 mg/placebo to 16 mg/placebo following the onset of moderate EPS. The EPS had a duration of approximately 2 weeks and was managed intermittently with benztropine. This participant completed treatment and the study. The treatment-related AEs reported (including those discussed above) were decreased appetite (n=1), dizziness (n=1), nausea (n=1), vomiting (n=1), dyspepsia (n=1), hyponatremia (n=1), somnolence (n=1), involuntary muscle contractions (n=1), tremor (n=1), extrapyramidal disorder (n=1) and salivary hypersecretion (n=1).

Panel G completed dosing in healthy elderly participants. Participants received MK-8189 16 mg/placebo Days 1-3, MK-8189 24 mg/placebo Days 4-10. Fifteen participants were enrolled. No deaths or SAEs were reported. Most AEs were mild and 3 AEs were severe (2 participants with severe somnolence and 1 participant with severe hypnagogic hallucination) and are described below. All AEs resolved. Three subjects discontinued due to treatment related AEs. The evening of Day 7, following 2 days of dosing with MK-8189 24 mg/placebo, through the early morning hours of Day 8, one participant reported mild akathisia (~20 hour), moderate tactile hallucinations (15 min), mild palpitations (2 min) and bilateral hand hyperhidrosis (5 hour) and in the predawn hours the participant reported severe hypnagogic hallucinations (5 min). The participant did not report these AEs until the morning of Day 8, at which time the dose was held and the participant received treatment with benztropine and all AEs resolved. Later in the afternoon of Day 8, the participant had a recurrence of akathisia, bilateral hand hyperhidrosis, tactile hallucinations and reported sinus tachycardia, all which resolved with the treatment with benztropine. On Day 8 the participant discontinued treatment due to these AEs. This participant also had a brief episode (~30 min) of mild oral mandibular dystonia on Day 1 (16 mg/placebo) that resolved spontaneously.

Another subject discontinued due to an AE of mild akathisia (~24 hour) following treatment with 16 mg/placebo dose on Day 3 which resolved with benztropine.

One subject discontinued after 2 days of dosing at the 24 mg/placebo dose (Day 5) due to moderate oromandibular dystonia (~6 hours) and moderate anxiety (<24 hours duration); both AEs responded to treatment.

In addition to the participant with the brief but severe hypnagogic hallucination, 2 participants were reported to have severe somnolence. In both participants the somnolence began within 2 hours of their first dose of study intervention (16 mg/placebo) and resolved in ≤ 10 hours. All treatment related AEs reported (including those discussed above) were somnolence (n=4), akathisia (n=3), oromandibular dystonia (n=2), myalgia (n=2), tremor (n=2), headache (n=2), involuntary muscle contractions (n=2), tactile hallucination (n=1), palpitations (n=1), bilateral hand hyperhidrosis (n=1), hypnagogic hallucination (n=1), sinus tachycardia (n=1), restlessness (n=1), dyspepsia (n=1), vomiting (n=1), paresthesia (n=1), insomnia (n=1), apathy (n=1) dysphonia (n=1), salivary hypersecretion (n=1), anxiety (n=1), bilateral hands rapid alternating movements (n=1) and smell sensitivity (n=1).

2.2.3.2 Protocol 012

P012 is an open-label single-dose Phase 1 study to evaluate the safety, tolerability, and PK in participants with hepatic impairment and matched healthy participants. To date 6 participants with moderate hepatic impairment have received a single 4 mg dose of MK-8189. No SAEs or deaths have been reported. The following treatment related AEs (duration) have been reported by 3 participants: One participant had mild AEs of a hot flush (40 min), vomiting (1 episode) and leg cramps (10 min). One participant had a mild AE of dizziness (<1 day) which resulted in a fall. One participant had mild AEs of headache (<1 day), anxiety (30 min) and affect lability (30 min).

2.2.3.3 Protocol 015

P015 is a DDI trial to evaluate the effect of multiple-doses of itraconazole, a strong CYP3A inhibitor, on the single-dose PK of MK-8189. In Period 1, 14 participants received a single dose of 4 mg of MK-8189. In Period 2, participants received a loading dose of itraconazole of 200 mg BID on Day 1 and received 200 mg QD on Days 2 to 8. On Day 4, participants were coadministered 4 mg of MK-8189 with itraconazole. No deaths or SAEs have been reported. Of the 14 participants, 7 have reported at least one AE considered related to MK-8189 and/or itraconazole (duration). One participant discontinued due to AE of mild rash (2 days) to itraconazole. In Period 1 on Day 1, one participant reported mild AEs of somnolence (1 day) and dizziness (8.5 hours) considered related to MK-8189. In Period 2 on Day 4, this same participant reported mild restlessness (20 hours) and an ECI of dystonia (12 hours) of moderate severity considered related to MK-8189 and itraconazole. The dystonia resolved without treatment. Following a blood draw, two other AEs, mild presyncopal event (5 min) and mild faint sensation (12 min), were also reported by this participant but neither were considered related to study intervention. One other participant reported an AE of mild dystonia (~ 2 days) which began in Period 2 on Day 5. The dystonia resolved without treatment and was considered related to MK-8189 and itraconazole. One participant had mild AEs of somnolence (2 days) and diarrhea (9 days). The somnolence began in Period 1 on Day 1 and was considered related to MK-8189, and the diarrhea began in Period 2 prior to co-dosing of MK-8189 and was considered related to itraconazole. Three other participants reported mild diarrhea (5 hours, 3 days and 6 days) which began in Period 2 prior to MK-8189 administration.

2.2.3.4 Protocol 008

P008 is an ongoing Phase 2B randomized, double-blind, placebo- and active controlled trial of the efficacy and safety of MK-8189 in adult participants 18 to 50 years of age who are experiencing an acute episode of schizophrenia according to DSM-V™ criteria.

A total of 576 participants from approximately 80 sites across the USA, Europe and Asia will be recruited into this trial. Treatment duration will be for a period of 12 weeks and includes a 6-week acute treatment period followed by a 6-week extension period. Eligible participants will be randomized to receive one of five treatment sequences with target doses of MK-8189 (8 mg, 16 mg, and 24 mg QD), risperidone (6 mg QD), or placebo. Placebo completers at 6 weeks will be allocated to receive MK-8189 24 mg for the remainder of the trial. This trial is being conducted in a hospital/acute care setting followed by an outpatient setting.

Recruitment was initiated in December 2020.

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

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

There are no hypotheses for this study.

In male or female participants with Alzheimer's Disease with or without symptoms of agitation-aggression and/or psychosis.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple ascending doses of MK-8189 in participants with Alzheimer's Disease with or without symptoms of agitation-aggression and/or psychosis	• Adverse events • Adverse experiences leading to discontinuation of study intervention
Secondary	
• Not applicable	
Tertiary/Exploratory	
• To evaluate the trough exposures of MK-8189	• C24hr
• To investigate the relationship between CYP2C9 genetic polymorphs and the PK of MK-8189. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study	• Germline genetic variation in CYP2C9 and association to clinical data collected in this study
• To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study	• Germline genetic variation and association to clinical data collected in this study
• To explore changes in cognitive functioning, neuropsychiatric status and extrapyramidal symptomatology	• MMSE-2 and NPI, BARS, AIMS, SAS

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of MK-8189 in participants with Alzheimer's Disease with and without neuropsychiatric symptoms. To most closely simulate the patient population for the indication evaluated, it is preferred that participants included in this study have symptoms of agitation-aggression or psychosis (defined as a severity of score ≥1 and frequency score of ≥2 on the NPI Agitation-Aggression and/or Delusions and/or Hallucinations domains).

Up to approximately 28 participants will be enrolled to ensure at least 16 participants complete the study. Note: Greater than 16 participants may be required to complete the study if additional study data are needed to further understand the safety and tolerability profile of MK-8189 in the AD population.

This is an outpatient study as participants will be dosing at home and will require visits to the CRU per the SoA. Therefore, participants must have a trial partner/caregiver as described in the inclusion/exclusion criteria.

The first 8 participants will be randomized to receive MK-8189 8 mg/placebo QD Days 1-3, 16 mg/placebo QD Days 4-28 (Titration 1). Participants may be down-titrated by the investigator at any time without consultation of the Sponsor in the case of safety or tolerability issues. Changes in the dosage regimen will be communicated to the Sponsor and the Sponsor will document changes in a Protocol Clarification Letter. After approximately 8 participants have completed approximately 3 weeks of dosing, AE data will be reviewed to determine whether to continue to enroll participants at the Titration 1 regimen or whether participants should receive an alternate dosing regimen (e.g., MK-8189 8 mg/placebo QD Days 1-3, 16 mg/placebo QD Days 4-6, 24 mg/placebo Days 7-28 (Titration 2) OR MK-8189 4 mg /placebo QD Days 1-3, 8 mg/placebo Days 4-6, 16 mg Days 7-9, 24 mg Days 10-28 (Titration 3)). Prior to initiation of an alternate regimen that includes escalation to a dose above 16 mg, the PK data from the initial cohort of participants will be required to be reviewed. The decision will be made jointly between the investigators and the Sponsor and any change to the dosing regimen will be documented in a Protocol Clarification Letter. See section 6.6 for allowed dose modifications.

As MK-8189 is not a treatment for Alzheimer's disease, participants may remain on their current Alzheimer's treatment as outlined in Section 6.5 Concomitant Therapy.

Outpatient visits are required per the SOA. Visits required for the first dose of study administration and any day when the dose is to be titrated-up, participants must be observed by site staff for at least 6 hours following the treatment of study intervention. The investigator will have discretion to domicile the participant or determine a longer duration of observation to ensure participant safety. Following administration of study intervention at the CRU, the participant should remain seated or semi-recumbent or ambulate with supervision.

If the investigator considers it appropriate for an individual participant to be domiciled (i.e., exacerbation of dementia or behavioral symptoms not expected), the participant may be domiciled through the titration period or for the entire intervention period (Day 1-28) (refer to Section 8.1.12). Any other duration of domiciling should be discussed with the Sponsor, except when considered necessary for participant safety.

Because this is a Phase 1 assessment of MK-8189 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 8.10.7 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

MK-8189 will be evaluated for the treatment of neuropsychiatric symptoms in dementia. Prior to the conduct of a larger POC study, this smaller study (n=28, randomized such that 21 are on MK-8189 and 7 on placebo) will be conducted as an initial assessment of safety and tolerability in a similar patient population.

This will be a randomized, placebo-controlled study to ensure an objective assessment of safety and tolerability. An outpatient trial is preferred as changing the environment in this patient population may adversely affect cognitive status. However, if deemed appropriate by the investigator, a participant may be domiciled as described in Section 8.1.12. An ongoing trial has evaluated MK-8189 doses titrated up to 24 mg over 10 to 13 days in 21 healthy elderly participants and preliminary blinded data suggest MK-8189 is generally well tolerated, supporting outpatient dosing (refer to Section 2.2). However, as the tolerability may differ in a population with AD, the study will first enroll only 8 participants to ensure tolerability of the selected treatment regimen. If tolerability issues are found, a more conservative regimen will be administered to the remaining participants. At any time during treatment, the investigator may choose to down-dose a participant. The assessment of MK-8189 safety and tolerability from this trial, in which participants with AD with or without agitation-aggression and/or psychosis will receive study treatment for one month, will be used to determine if longer term safety and efficacy trials can be supported. Daily telephone calls by study staff to the participant, weekly safety evaluations and the requirement for participants to have a trial partner/caregiver will help ensure participant safety and compliance with study intervention administration and protocol requirements throughout the study.

As efficacy will not be assessed in this study, participants without or with neuropsychiatric symptoms (agitation-aggression or psychosis) will be permitted in the study. Those who are currently taking antipsychotics to control neuropsychiatric symptoms may be enrolled if it is clinically appropriate to have participants wash off their medication (e.g., participant is not tolerating current treatment or is not likely receiving benefit from the treatment). This will

ensure the safety and tolerability profile of MK-8189 is understood without confounding antipsychotic treatment. However, if during the study, neuropsychiatric symptoms worsen, rescue therapy specified may be administered.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Not Applicable

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical AEs as well as through the conduct of physical and neurological examinations, 12-lead ECGs, VS, and laboratory safety tests.

The C-SSRS will be administered to monitor mood and suicidal ideation and behavior in all trial participants (see Section 4.2.3).

Exploratory Safety Endpoints

As EPS are associated with antipsychotics and have been observed in the MK-8189 clinical program, the BARS, AIMS and SAS will be used to evaluate EPS throughout the study per the SoA. The BARS, comprised of objective and subjective items, as well as a global rating, assesses drug-induced akathisia. The global rating score ranges from 0 to 5, where 0 represents no evidence for akathisia, a score of 3 is moderate akathisia and a score of 5 is severe akathisia. The AIMS includes 12 items and uses a 5-point scale to assess abnormal movement in 3 areas (orofacial, extremities, trunk). The SAS is comprised of 10 items and uses a 5-point scale to measure symptoms of parkinsonism or parkinsonian side effects (including rigidity, tremor, bradykinesia/akinesia, and salivation).

The Mini-Mental State Exam, Edition 2, Standard Form (MMSE-2) assesses orientation, attention, memory, language, and visual-spatial skills and has a score range of 0-30, where higher scores reflect better performance. A score between 21 to 26 typically indicates that a participant is experiencing mild cognitive dysfunction impairment, while scores in the range of 10-20 are indicative of participants with more moderate cognitive impairment. The MMSE-2 administered at screening will be used for inclusion to ensure that enrolled participants fall into the cognitive impairment categories of mild to moderate severity. In addition, the MMSE-2 will be repeated as specified in the SoA to explore any changes in cognitive impairment.

The Neuropsychiatric Inventory (NPI) assesses behavioral and psychological domains and symptoms, including delusions, hallucinations, agitation or aggression, dysphoria or depression, anxiety, euphoria or elation, apathy or indifference, disinhibition, irritability or lability, aberrant motor behavior, sleep/nighttime behavior-and appetite/eating disturbances. The NPI includes both symptom frequency (scored 1-4) and severity ratings (scored 1-3), as well as trial partner/caregiver distress ratings.

4.2.1.3 Pharmacokinetic Endpoints

An exploratory objective of this study is to characterize the trough exposures of MK-8189. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to derive the PK parameter value for C24hr.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

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

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

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

In addition to studying variation across the human genome, polymorphs of CYP2C9 will specifically be investigated for association with the PK and PD of MK-8189 since MK-8189 is partially metabolized by CYP2C9. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study.

4.2.1.5 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

As the safety and tolerability profile is under continued evaluation, a placebo-control will be included in this trial to ensure objective assessment of AEs.

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 (e.g., 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

Currently the efficacious dose of MK-8189 is unknown, however, based on data from in vivo preclinical assays (see Section 2.1 and the IB), enzyme occupancy of 30% is expected to be required for efficacy in neuropsychiatric symptoms associated with dementia. A dose of 8 mg is expected to result in a mean C24 (90% confidence interval) enzyme occupancy of approximately 40% (34, 47). Proof of concept has been established for 12 mg of MK-8189 in schizophrenia patients (P005), however, doses up to and including 24 mg are being evaluated in a Phase 2b study (P008) to understand if greater efficacy is observed with higher doses. Recent literature suggests that for antipsychotics to be effective in the treatment of behavioral symptoms associated with dementia, doses may need to be similar to those used for the treatment of schizophrenia [Grossberg, G. T., et al 2020]. Preliminary PK data from P011 suggest the median C24 value in healthy elderly following multiple doses of MK-8189 16 mg will be similar to that observed following multiple 24 mg doses of MK-8189 in non-elderly adults with schizophrenia. Therefore, the initial titration regimen in the current study will escalate MK-8189 doses up to 16 mg. If multiple doses of MK-8189 16 mg is generally well tolerated in the initial cohort of ~8 participants and, based on a PK analysis of these participants, MK-8189 exposure is less than anticipated and thus closer to exposures observed in younger (< 60 years of age) adult participants, an alternate titration regimen escalating to 24 mg of MK-8189 (Titration Regimen 2) may be explored.

As this is a Phase 1 assessment of MK-8189 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.7.

4.3.1 Starting Dose for This Study

The first 8 participants will receive the following treatment regimen: MK-8189 8 mg/placebo Days 1-3 and 16 mg/placebo Days 4-28. This regimen and initiating dosing at 16 mg of MK-

8189 has been found to be generally well-tolerated in healthy elderly participants and young participants. In young participants with schizophrenia, a starting dose as high as 24 mg has been evaluated and found to be well tolerated (see Section 2.2). The remaining participants will receive the same dose treatment regimen or an alternate treatment regimen. The starting dose for the selected regimen will not exceed 8 mg of MK-8189.

4.3.2 Maximum Dose/Exposure for This Study

Participants may be escalated to a maximum MK-8189 dose of 24 mg/placebo. A daily dose of MK-8189 24 mg has been found to be generally well tolerated in healthy young (P007) and elderly participants (P011) and doses of MK-8189 48 mg have been generally well tolerated in participants with schizophrenia (P007).

Based on a population PK model, the steady-state Cmax and AUC0-24hr at the 24-mg dose is predicted to be 0.975 μM and 19 μM.hr. Based on data from the chronic toxicology studies, the exposure multiple at the 24 mg dose for AUC0-24hr would be ~7-fold based on the 6-month rat study and ~9-fold based on the 9-month monkey study. Brief summaries of the chronic toxicology studies supporting dose escalation are provided below:

In the 6-month rat study, doses of 0, 25, 100 and 750 mg/kg/day were evaluated. Two high-dose (750 mg/kg/day) female rats were found dead (Week 13 and Week 24) with acute tubular necrosis (with and without tubular mineralization). Therefore, the 100 mg/kg/day dose was considered the no observed adverse effect level (NOAEL) for this study (AUC0-24hr = 130 μM·hr), providing an exposure margin of ~7-fold over the predicted exposure of 19 μM·hr at the 24 mg dose.

In the 9-month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK-8189 were administered. Renal tubular degeneration was observed in the high-dose group (600/300 mg/kg/day). The NOAEL for target organ toxicity is 150 mg/kg/day (AUC0-24hr = 170 μM·hr), providing ~9-fold over the predicted exposure of 19 μM·hr at the 24-mg dose. Therefore, clinical and preclinical data support dose escalation to 24 mg in this study.

4.3.3 Rationale for Dose Interval and Study Design

MK-8189 has been developed as a CR formulation to ensure adequate exposures are maintained throughout the dosing interval with once-daily dosing. Initiating dosing at 8 mg for 3 days allows for tolerability to be assessed at steady-state exposures before titrating up and may improve tolerability. Dosing for a total of 28 days is expected to provide sufficient safety and tolerability data to determine if a larger and longer term POC study should be conducted.

4.4 Beginning and End-of-Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Section 10.1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data is to follow all local laws and guidelines in keeping with the needs for participant confidentiality 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.

This study will enroll male/female participants between the ages of 65 and 85 years (inclusive), with diagnosis of Alzheimer disease for at least 1 year. In addition, it is preferred participants enrolled have symptoms of agitation-aggression and/or psychosis (defined as a severity of score ≥1 and frequency score of ≥2 on the NPI Agitation-Aggression and/or Delusions and/or Hallucinations domains) for at least 4 weeks prior to Screening.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has a documented diagnosis of probable Alzheimer disease based on National Institute on Aging-Alzheimer Association criteria for AD, with a history of cognitive and functional decline with gradual onset and slow progression for at least 1 year before screening, that is either corroborated by an informant who knows the participant well or is documented in medical records. Note: PIs should ensure that non-neurological medical comorbidities, including treatable causes of dementia, have been ruled out at the time of diagnosis, including, but not limited to, hypothyroidism, B12, and folate deficiency as well as increased levels of homocysteine.

2. Has an MMSE-2 score between 10 and 24, inclusive at Screening.

3. Lives in the community setting with a reliable trial partner/caregiver or lives alone in an assisted living facility, with supervision and has a reliable trial partner/caregiver.

4. Has a reliable and competent trial partner/caregiver who must have a close relationship with the participant and is knowledgeable of the participant's condition and progress and able to read, understand and speak the designated language at the study site. The trial partner/caregiver should understand the nature of the trial and adhere to trial requirements (e.g., dosing, visit schedules, and evaluations). The trial partner/caregiver must:

    - be willing to sign informed consent,
    - have face to face contact at least four days a week for a minimum of 8 waking hours a week (or more in accordance with local requirements),
    - be willing to accompany the participant to all trial visits, as required per protocol (and arrange for an alternative transportation means when, on occasion, the trial partner/caregiver may not be available) and
    - be willing to monitor compliance of study intervention administration and record study intervention administration.

5. Can read at the 6th grade level/equivalent as determined by the investigator.

6. Has an academic and/or employment history sufficient to exclude intellectual disability and is able, in the opinion of the investigator, to fully participate in the study (e.g., speak, read, hear, understand trial staff language) and be able to comply with protocol assessments.

7. Is in generally good physical health based on medical history, physical examination, VS measurements, and ECGs performed before randomization. Participants with chronic medical conditions such as hypothyroidism, diabetes, high BP, chronic respiratory conditions or other mild forms of these medical conditions could be considered as candidates for study enrollment if their condition is stable and the prescribed dose and regimen of medication is stable for at least 2 months prior to screening and there are no expected changes in co-medication during the study. Participants should have mean systolic blood pressure of ≤150 mmHg and mean diastolic blood pressure of ≤95 mmHg at screening. In addition, screening orthostatic vital sign changes should be asymptomatic with a standing systolic blood pressure of ≥90 mmHg.

8. Be in generally good health based on laboratory safety tests obtained at the screening visit and before administration of the initial dose of study intervention. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out-of-range laboratory values.

9. Participants receiving treatment with a cholinesterase inhibitor or other treatment for AD (i.e. memantine and aducanumab), must have been on a stable regimen for 3 months prior to screening and there are no expected changes in co-medication during the study.

10. Is able to discontinue any antipsychotic medication they are taking at the time of Screening. The antipsychotic must be discontinued 2 weeks or 5 half-lives (whichever was longer) prior to Baseline. Investigators should not withdraw a prohibited medication for the purpose of enrolling them into the study unless discontinuation of the medication was deemed to be clinically appropriate (e.g., symptoms are not well-controlled, or the subject can't tolerate the current medication).

11. Has a BMI > 18 and ≤ 35kg/m2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

Demographics

12. Is male or female, 65 years to 85 years of age, inclusive, at the time of signing the informed consent.

13. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

  - Has a negative highly sensitive pregnancy test (serum or urine as required by local regulations) within 120 hours before the first dose of study intervention. (If a urine test cannot be confirmed as negative [eg, an ambiguous result], a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.) Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

14. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has agitation/aggression or psychosis that is attributable to concomitant medications, environmental conditions, substance abuse, or an active medical or psychiatric condition.

2. Has a MHIS Score > 4 at Screening (i.e., evidence of vascular dementia).

3. Has a known history of stroke or evidence from prior MRI scan (if available) that is clinically important in the investigator's opinion.

4. Has evidence of a clinically relevant neurological disorder other than the disease being studied (i.e., probable AD) at Screening, including but not limited to: vascular dementia, parkinsonism, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, neurosyphilis, dementia with Lewy bodies, posterior cortical atrophy, logopenic primary progressive aphasia, other types of dementia, intellectual disability, hypoxic cerebral damage, cognitive impairment due to other disorders, or head trauma with loss of consciousness that led to persistent cognitive deficits.

5. Has a history of seizures or epilepsy within the last 5 years before Screening.

6. Has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-5 criteria, including schizophrenia, schizophrenia spectrum or other psychotic disorder, bipolar disorder, major depressive disorder, or delirium. Note: Major depressive disorder in remission is not exclusionary and mild, stable, treated depression is not exclusionary.

7. Is at imminent risk of self-harm, based on clinical interview or on the C-SSRS, 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 (i.e., suicidal ideation Item 4 or 5 on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.

8. Has a history of alcoholism or drug dependency/abuse within the last 5 years before screening.

9. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous 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 (e.g., malignancies that have been successfully treated ≥10 years prior to the prestudy [screening] visit).

10. Has a family history of prolonged QTc syndrome.

11. Has an estimated eGFR ≤ 50 mL/min/1.73 m^2 based on the MDRD.

    MDRD Equation:

    eGFR (mL/min/1.73 m^2) =
    175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if black or African American])

    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/1.73m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

12. Has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e., systemic allergic reaction) to prescription or nonprescription drugs or food.

13. Previously developed severe EPS following administration of any prescribed medication or study treatment. Severe EPS is defined as follows: Parkinsonism type symptoms persisting for ≥3 days, or induction of a tremor that interferes with daily living, dystonia persisting for > 24 hours, or objective restlessness consistent with akathisia.

14. Is positive for HBsAg, hepatitis C antibodies or HIV.

15. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

16. Has received treatment with monoamine oxidase inhibitors or unable to refrain from the use of co-medication with a moderate or strong inhibiting or inducing effect on CYP3A or moderate to strong inducing effect on CYP2C9 (CYP2C9 inhibitors are permitted) beginning approximately 2 weeks or 5 half-lives, whichever is longer, prior to administration of the initial dose of trial drug and throughout the trial.

Prior/Concurrent Clinical Study Experience

17. Has 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

18. Has a QTc interval >450 msec.

Other Exclusions

19. Does not agree to follow the smoking restrictions as defined by the CRU.

20. Consumes greater than 3 glasses of alcoholic beverages (1 glass 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 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

21. 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.

22. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 years. Participants must have a negative UDS (with the exception of cannabis and/or prescribed medications permitted at the discretion of the PI and Sponsor) prior to randomization.

23. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

24. 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

Fasting requirements for laboratory safety evaluations are specified in Appendix 2.

Participants should fast overnight prior to all visits to the CRU including the screening and poststudy visits. Otherwise, participants will consume their usual diet except for grapefruit products (section 5.3.1.2). At CRU visits, participants may be given a light breakfast following study treatment administration.

5.3.1.2 Fruit Juice Restrictions

Participants should refrain from the consumption of more than 1 grapefruit or 1 glass (8 ounces) of grapefruit juice a day, throughout the entire study period. Otherwise, participants can consume their usual diet throughout the study period.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

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 all CRU visits including the screening and poststudy visits. 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 during visits.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (i.e., weightlifting, running, bicycling, etc.) from the screening visit until administration of the initial dose of study intervention, throughout the study 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-8189/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 1.

Table 1 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/ NIMP	Sourcing
Active	Experimental	MK-8189	Drug	Tablet	4 mg 12 mg	All dosage levels	Oral	Titrations 1, 2 and 3	Experimental	IMP	Provided centrally
Placebo	Placebo Comparator	Placebo	Drug	Tablet	0 mg	All dosage levels	Oral	Titrations 1, 2 and 3	Experimental	IMP	Provided centrally

IMP=investigational medicinal product; NIMP=noninvestigational medicinal product.

The classification of IMP and NIMP 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/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 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 (e.g., not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

The sample allocation schedule is provided in Table 2.

Table 2 Sample Allocation Schedule

Titration 1					
		Days 1-3	Days 4-28		
MK-8189	N=21	8 mg QD	16 mg QD		
Placebo	N=7	PBO	PBO		
Titration 2					
		Days 1-3	Days 4-6	Days 7-28	
MK-8189	N=21	8 mg QD	16 mg QD	24 mg QD	
Placebo	N=7	PBO	PBO	PBO	
Titration 3					
		Days 1-3	Days 4-6	Days 7-9	Days 10-28
MK-8189	N=21	4 mg QD	8 mg QD	16 mg QD	24 mg QD
Placebo	N=7	PBO	PBO	PBO	PBO
Note: The allocation scheduled will be stratified to AD participants with and without agitation-aggression and/or psychosis symptoms. Participants without agitation-aggression and/or psychosis symptoms will be assigned starting at the low allocation range and participants with agitation-aggression and/or psychosis symptoms (defined as a severity score of ≥1 and frequency score ≥ 2 on the NPI Agitation-Aggression and/or Hallucination and/or Delusion domains) will be assigned starting at the upper allocation range.					

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

1. participants with and without agitation-aggression and/or psychosis symptoms

   For example, participants without agitation-aggression and/or psychosis symptoms will be assigned starting at the low allocation range and participants with agitation-aggression and/or psychosis symptoms will be assigned starting at the upper allocation range. For this protocol agitation-aggression and/or psychosis symptoms are defined as a severity score of ≥1 and frequency score of ≥2 on the NPI Agitation-Aggression and/or Delusions and/or Hallucinations domains.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-8189 will be packaged identically to the matching placebo so that blind is maintained. The participant, the trial partner/caregiver, the investigator, and Sponsor personnel or delegate(s) who are involved in

the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

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

- When participants self-administer study intervention(s) at home, daily phone calls will be made to check study intervention administration compliance. Compliance with study intervention will also be assessed at each subsequent visit by direct questioning and site review of the completed study intervention dosing diary as captured by the participant/trial partner/caregiver. In addition, compliance will be monitored via counting of returned tablets at selected CRU visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

- A record of the number of MK-8189/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

- When participants are dosed at the site, study intervention administration will be witnessed by the CRU staff. The staff will witness the participant/trial partner/caregiver record the dosing in the study intervention diary.

6.5 Concomitant Therapy

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination during the ongoing study (i.e., after randomization or intervention allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates 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.

Acetaminophen and antacids (e.g., magnesium hydroxide) may be used for minor ailments without prior consultation with the Sponsor.

Moderate to strong inhibitors or inducers of CYP3A and moderate to strong inducers of CYP2C9 are not allowed as MK-8189 is being metabolized by these CYP enzymes and co-administration of inhibitors or inducers may potentially alter the metabolism and PK of MK-8189. See also Section 6.5.1 on rescue medication.

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

- Non-live vaccines may only be administered in consultation with the Sponsor.
- COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

  Exception: Investigational COVID-19 vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

Continued Medication Use

Participants may continue treatment with their prescribed cholinesterase inhibitors, memantine and aducanumab for the treatment of AD during the trial. The prescribed dose and regimen of medication must be stable for at least 3 months prior to screening and there are no expected changes in co-medication during the study.

In addition, medications to treat mild chronic conditions such as hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other medical conditions are allowed during the study. For permitted medications, the prescribed dose and regimen of medication must be stable for at least 2 months prior to screening and there are no expected changes in co-medication during the study.

A participant's continued use of medications that may cause somnolence, including but not limited to benzodiazepines and sedating antihistamines, must be discussed between the investigator and the Sponsor prior to MK-8189 administration.

6.5.1 Rescue Medications and Supportive Care

If over the course of the study behavioral symptoms worsen, if medically appropriate, the participant may be administered quetiapine 50 mg.

6.6 Dose Modification (Escalation/Titration/Other)

The dose regimen for this trial is MK-8189 8mg/placebo Days 1-3 days followed by 16 mg/placebo Days 4-28 (Titration 1).

Following MK-8189/placebo treatment of approximately 8 participants for approximately 3 weeks, a decision will be made to continue dosing newly enrolled participants with the current regimen or modify to an alternate regimen. The following alternate treatment regimens may be explored during the study following a review of safety and tolerability data and a discussion with the investigators and the Sponsor. However, dose escalation above 16 mg will not occur without a review of PK data from the initial cohort of approximately 8 participants. Any change in the treatment regimen will be documented in a Protocol Clarification Letter.

- 8 mg/matched placebo Days 1-3, 16 mg/placebo Days 4-6 and 24 mg/placebo Days 7-28 (Titration 2)
- 4 mg/matched placebo Days 1-3, 8 mg/placebo Days 4-6, 16 mg/placebo Days 7-9 and 24 mg/placebo Days 10-28 (Titration 3)
- Other more conservative regimen

If medical care necessitates participants may:

- Skip a single dose and dosing may continue at the same dose level or adjusted downwards.
- Receive the same dose level to further explore safety and tolerability at that level.
- Receive a lower dose of the study intervention.
- Stop dosing.

Any change in dosing regimen will be documented in a Protocol Clarification Letter.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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 regimen

will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or per a PCL, if available.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, or through the emergency unblinding call center.
- The participant interrupts study intervention administration for more than 2 consecutive days or has 4 cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a positive UDS except for allowed concomitant medication administered during trial, at any time during the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.
- Any participant with EPS requiring treatment that is not or cannot be managed by down dosing.
- The participant no longer has a trial partner/caregiver or the trial partner/caregiver withdraws consent and a substitute cannot be identified.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 193.5 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

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

8.1.1.1 General Informed Consent

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.

Documented informed consent from each participant's trial partner/caregiver (referred to as trial partner informed consent) will also be obtained by the investigator or qualified designee.

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, including psychiatric history and substance usage, 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 and record medications taken by the participant within 3 months of the Screening visit.

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 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 8.10.2.

8.1.7 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 allocation/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.

Refer to the study operations manual for detailed procedures for requesting a treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention will occur in the CRU on Day 1 and at CRU visits or at home as described in Section 1.3 Schedule of Activities.

Participants will be supervised for at least 6 hours following the first administration of study intervention and following the first administration of each study intervention titration. Supervision will be done by the site staff.

Participants will receive bottle(s) of study intervention on Day 1 and at each CRU visit. Prior to dispensing a new bottle of study intervention, the previous bottle dispensed will be collected. Each bottle will contain enough study intervention to cover the duration between each CRU visit.

Participants and their trial partner/caregiver will be instructed on how to administer at home study intervention by the CRU staff.

8.1.8.1 Timing of Dose Administration

Study intervention should be administered orally in the morning at approximately the same time each day. Study intervention will be administered fasted (in CRU) or with/without food (at home) with approximately 240 mL of water.

Trial partners/caregivers will record time of dosing in a study intervention dosing diary. On days when study intervention is administered in the CRU, dose administration will be witnessed by the investigator and/or study staff.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.5 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, 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.

8.1.11 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.

8.1.12 Domiciling (optional)

For sites that have domiciling capability to keep participants overnight, the site may offer study participants the option to stay in the CRU for the duration of the titration period or the entire intervention period (Day 1-28). Any other domiciling period will need to be discussed with the Sponsor. The study partner/caregiver is not required to stay overnight but may do so if requested by the study participant and the site can accommodate.

At the discretion of the investigator, participants will report to the CRU the evening before Day 1 and remain in the CRU until after the completion of study procedures on Day 7 (Titration 1 and Titration 2)/Day 10 (Titration 3) or Day 28. Participants may be permitted to leave the unit, for emergency situations only, at the discretion of the investigator after discussion with the Sponsor.

Study staff will also witness the study medication and work with the participants/trial partners/caregivers in completing the dosing diary when the participants are in the CRU.

Study drug administration fasting requirements will be required on the same days indicated in the SoA.

8.2 Efficacy 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 below. The total amount of blood to be drawn over the course of the study (from screening to poststudy visits), including approximate blood volumes drawn 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.

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/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

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

8.3.2 Vital Signs

8.3.2.1 Resting Vital Signs

Pulse Rate, Blood Pressure, Respiratory Rate and Body Temperature

Participants should be resting in a quiet setting without distractions in a semi-recumbent position for at least 10 minutes before having VS measurements obtained. Semi-recumbent VS will include pulse rate, 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 participants' arm is essential to increase the accuracy of BP measurements.

The Screening and Day 1 predose (prior to dose) pulse rate and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart. The Day 1 predose triplicate

measurement will be taken within 3 hours prior to dosing MK-8189/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). All VS measurements after Day 1 dosing will be single measurements.

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

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (pulse rate and systolic and diastolic BP) will also be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

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, semi-recumbent, 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 CRU 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.

Day 1 predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MK-8189. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

If a participant demonstrates an increase in QTc interval ≥60 msec compared with mean 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 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.

8.3.4 Clinical Safety Laboratory Assessments

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

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

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

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

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

8.3.5 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3.6 Suicidal Ideation and Behavior Monitoring

8.3.6.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at 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 (i.e., 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.

8.3.7 Rater Expectations and Training for Clinical and Cognitive Assessments

For this study, potential raters of clinical and/or cognitive assessments (BARS [Section 8.3.11], SAS [Section 8.3.11], AIMS [Section 8.3.11], C-SSRS [8.3.6.1], MHIS [Section 8.3.8], MMSE-2 [Section 8.3.9], and NPI [Section 8.3.10]) will be identified based on review of their reported credentials against target minimum credentials for education, prior experience with AD, MCI or similar populations and direct, hands-on experience with study-specific or similar assessments. Persons whose credentials meet or exceed those targets will then be considered ‘qualified’ as raters in this trial. For the MMSE-2 and NPI, raters will subsequently complete overview, didactic, protocol-specific training before conducting

assessments in this trial. It is recommended that the same rater conducts the same assessments throughout the study for a given participant, where feasible.

All clinical and cognitive assessments will be administered after dosing and following an optional light breakfast provided by the CRU.

8.3.8 Rosen-Modified Hachinski Ischemia Scale

The MHIS will be completed by an experienced rater at timepoints specified in Section 1.3 Schedule of Activities.

8.3.9 Mini Mental State Examination Second Edition

The paper version of the MMSE-2 (Standard version, both Red and Blue forms) will be administered and scored by a qualified, trained rater at timepoints specified in Section 1.3 Schedule of Activities. Additional information concerning administration, scoring and documentation may also be provided in rater training and in the MOA.

8.3.10 Neuropsychiatric Inventory

The paper version of the NPI (12 items) will be administered by a qualified, trained rater at timepoints specified in Section 1.3 Schedule of Activities. Additional information concerning administration, scoring and documentation may also be provided in rater training and in the MOA.

8.3.11 Monitoring of Extrapyramidal Symptoms

The Barnes Akathisia Ratting Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) and Simpson Angus Scale (SAS) will be completed by a qualified rater at timepoints specified in Section 1.3 Schedule of Activities.

Refer to the MOA for additional information regarding the BARS, AIMS and SAS.

8.3.12 Neurological Exam

The General (Full) Neurological Exam will be performed at the Screening and Baseline visits. The Targeted Neurological Exam will be administered at times specified in the SoA.

The General and Targeted Neurological Exams are contained in Appendix 10.

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 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 allocation/randomization, must be reported by the investigator for randomized participants only if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

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

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

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

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

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

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

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Not applicable

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

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 an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

3. Severe EPS or EPS resulting in study intervention discontinuation

4. Suicidal ideation, suicidal behavior

5. Treatment-emergent adverse event of new or worsening tardive dyskinesia

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator

or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189 and/or Metabolites Assay

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

8.6.2 Blood Collection for Plasma Donepezil Assay

Sample collection, storage, and shipment instructions will be provided in the laboratory manual.

8.6.3 Blood Collection for Plasma Memantine Assay

Sample collection, storage, and shipment instructions will be provided in the laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis
- Blood for Exploratory Plasma Biomarkers for AD Diagnosis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C9 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9 genotyping. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the operations/laboratory manual.

8.8.2 Exploratory Plasma Biomarkers for Alzheimer's Disease Diagnosis Sample Collection

Sample collection, storage, and shipment instructions for exploratory plasma biomarker samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover main study plasma from MK-8189 and/or metabolites assay stored for future research.

8.10 Visit Requirements

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

8.10.1 Trial Partner/Caregiver Participation

The trial partner/caregiver is required to accompany the participant to the Screening Visit, to sign the trial partner informed consent. This trial partner/caregiver should be willing and make every effort to accompany the participant to all study visits. In the event the trial partner/caregiver in unable to attend a study visit, he/she should discuss alternative arrangements with the site (e.g., participant transportation, return of study intervention and dosing diary) and availability of the trial partner/caregiver to provide and receive input by phone as needed (e.g. questions/instructions related to dosing information captured on dosing diary).

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

8.10.2 Screening (Visit 1)

Approximately 6 weeks before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Any participants being treated with antipsychotics at Screening must wash off their medications if considered medically appropriate (see Inclusion Criterion No. 10). If a participant has washed-off antipsychotic therapy (minimum 2 week or 5 half-life washout, whichever is

longer) during Screening, the NPI for that participant should be repeated, and will be considered the baseline value.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention randomization if there are Baseline procedures planned per protocol.

Please see the operations manual for eCRF screening data entry requirements prior to randomization.

8.10.3 Baseline (Visit 2)

Within 3-5 days prior to study intervention administration, participants will have Baseline safety evaluations per Section 1.3 Schedule of Activities.

8.10.4 Intervention Period Visit (Visits 3-9)

Day 1 (Visit 3)

Participants will return to the CRU on Day 1 for a predose assessments per the SoA. Participants will be administered study treatment by the CRU staff per section 8.1.8. On Day 1, participants will remain at the CRU until the last study assessment is complete and for at least 6 hours following the first administration of study intervention (Day 1).

Outpatient CRU Visits (Visits 4-9)

Participants, not domiciled, will return for CRU visits on Day 4, Day 7, Day 10 (Titration 3 only), Day 14, Day 21 and Day 28. Participants should be fasted upon return to the CRU. Participants will be administered study intervention by CRU staff and safety and PK assessments will be performed per the SoA. Participants will remain at the CRU until the last study assessment is complete. If the dose is the first administration at the next titrated dose level, participants will be required to be supervised by CRU staff for at least 6 hours post dose.

Participant Daily Home & CRU Requirements

Participants will self-administer study intervention (Section 8.1.8) on days not required to be in the CRU. Participants or trial partners/caregivers will record dosing date, time and number of tablets taken in a study intervention diary.

CRU staff will call the participants daily to check study intervention compliance, review/record AEs and if necessary, remind participants of next scheduled visit.

8.10.5 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion

of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.6 Poststudy (Visit10)

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

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

See Section 6.6 for Dosing modifications permitted per protocol.

This is a Phase 1 assessment of MK-8189 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 and/or titration steps of the study intervention administered.
- Decrease in the duration of study intervention administration (e.g., number of days).
- Addition of PK pause.
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data.
- Modification of the PK sample processing and shipping details based on newly available data.

The PK sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (e.g., 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 an 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 (e.g., 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 brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2).

Safety:

For the primary objective, all AEs and AEs leading to discontinuation of study intervention will be summarized and tabulated.

Summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back transformed for reporting (percent change from baseline).

For exploratory objectives, summary statistics and plots will be generated for Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) and Simpson Angus Scale (SAS), as well as for change from baseline. Responses to the C-SSRS will be listed. Additionally, summary statistics for change from baseline will be provided for MMSE-2, and NPI.

Pharmacokinetics:

Descriptive summary statistics will also be provided for MK-8189 C24hr.

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 Pharmacology 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 Clinical Study Report.

9.3 Hypotheses/Estimation

Objectives:

Refer to Section 3 for primary and exploratory objectives.

9.4 Analysis Endpoints

Safety: Primary safety endpoints will include all types of AEs and AEs leading to discontinuation of study intervention.

Additionally, for exploratory purposes, laboratory safety tests, 12-lead ECGs, and VS will be summarized. For laboratory safety tests, baseline is defined as readings obtained prior to first dose (Note: Readings from screening (Visit 1) will not serve as baseline for these parameters). For 12-lead ECGs and VS, baseline is defined as Day 1 predose readings.

Exploratory:

BARS, AIMS, and SAS for all participants.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (i.e., ideation and behavior). Responses on the C-SSRS are classified according to 11 prespecified categories as described in procedure manual. The most severe treatment-emergent ideation and behavior event reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it newly emerged or is more severe compared to recent history (i.e., protocol-defined recent history prior to entering the trial as stated in the Inclusion/Exclusion criteria for suicidal ideation/behavior, up to and including the randomization visit). Readings from Day -5 to Day-3 in Visit 2 will serve as baseline.

MMSE-2, and NPI for all participants. Readings from screening (Visit 1) will serve as baseline. (Note: For NPI, if AP is washed off, the NPI readings obtained post washout will be used as baseline.)

9.5 Analysis Populations

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

All Participants as Treated (APasT): 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 (dose level) will be included in the Per-Protocol dataset. This population will be used for the PK analysis.

9.6 Statistical Methods

Safety:

For primary objective, all AEs and AEs leading to discontinuation of study intervention will be summarized and tabulated.

Summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back transformed for reporting (percent change from baseline).

For exploratory purposes, summary statistics and plots will be generated for BARS, AIMS, SAS, as well as for change from baseline. Responses to the C-SSRS will be listed. Additionally, summary statistics for change in MMSE-2 and NPI from baseline will be provided.

Pharmacokinetics:

Individual C24hr values will be listed, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

The exploratory objective pertaining to the assessment of relationship between CYP2C9 genetic polymorphs and the laboratory and PK of MK-8189, and the relationship between genetic variation and response to the treatment may be addressed in a separate report.

9.7 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (safety labs, VS, ECGs) will be prepared as needed to support decision-making meetings. No individual participant level results will be provided. There are no planned interim analyses to test any formal hypotheses.

9.8 Multiplicity

Since there are no pre-specified hypotheses, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

Since there are no hypotheses, no power calculations are provided

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

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

10.1.4 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.

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 4 will be performed by the central laboratory.
  Exception: Routine urinalysis and urine pregnancy tests will be done locally at the site. A urinalysis sample will only be sent to the central lab if microscopic examination is required, i.e. blood or protein is abnormal.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

- 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 4 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate or Total CO_2	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)
Other Screening Tests	• FSH (as needed in WONCBP only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • All study-required laboratory assessments will be performed by a central 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	

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 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 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.

10.3.3 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

10.3.4 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

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not Applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- 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 will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [If hormonal contraception efficacy for a female participant is potentially decreased due to interaction(s) with study intervention(s), add the following footnote. If hormonal contraception is prohibited, or if hormonal contraception efficacy is NOT decreased due to interaction with study intervention(s), delete the following footnote:] [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

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@merck.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

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

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

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

8. Data Security

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

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

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

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@merck.com.

13. References

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10.7 Appendix 7: Country-specific Requirements

Not Applicable

10.8 Appendix 8: Blood Volume Table

All Participants	Screening/ Baseline	Intervention	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	4	1	7	6	42
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Blood for Genetic Analysis		1		1	8.5	8.5
Blood for Exploratory Plasma Biomarkers for AD Diagnosis		1		1	18	18
Blood for MK-8189 and/or Metabolites Assay		10		10	4	40
Blood for Plasma Donepezil Assay		5		5	3	15
Blood for Plasma Memantine Assay		5		5	3	15
Total Blood Volume per Participant[a]						**143.5 mL**

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

10.9 Appendix 9: 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 of 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:

    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.

10.10 Appendix 10: General (Full) and Targeted Neurological Exam

The General (Full) and Targeted Neurological Examination will be performed at the time points specified in the Schedule of Activities (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 his or her medical judgment.

The General (Full) Neurological Examination

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

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 volunteer's use of language throughout the interview.

C. Orientation (time, place, person)

D. Attention/Concentration

   Ask the subject to count backwards from 100 by 7's ("Serial 7's") or ask to recite months backwards or spell a 5 unique letter word (e.g. "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 one error.**

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)

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

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 e.g. by rubbing fingers on each side of subject'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**

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

1. Ask the volunteer to relax.

2. Flex and extend the volunteer's elbows and at the knees (bilaterally).

3. There is a small, continuous resistance to passive movement.

4. Observe for involuntary movements (e.g., 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 subject to stand up from sitting without using hands

Grade: ***NORMAL, IMPAIRED*** **and describe abnormality**

2. Test proximal limb strength by having the volunteer 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

3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer'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

1. Ask the volunteer to hold both arms straight forward with, palms up and eyes closed for ~10-15 seconds as tolerated; watch for how well the arm position is maintained.

2. Instruct the volunteer to keep both arms still while you tap them briskly downward. The volunteer 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**

MODULE 4 - REFLEXES

A. Biceps

B. Knee

Note: *Other deep tendon reflexes may be tested at Investigator's discretion (e.g. 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**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer 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 subject will be asked to strike his 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 MN weakness.)

B. Point-to-Point Movements

1. Ask the volunteer 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 subject 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 volunteer to stand with both feet together and eyes closed for 20 to 30 seconds without support.

2. Be prepared to catch the volunteer if they are unstable.

Grade: **NORMAL or IMPAIRED**

D. Gait

1. Ask the volunteer 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**

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

Grade: **NORMAL or IMPAIRED and describe abnormality**

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, e.g., coin, key).

Score: ***left and right***

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

Targeted Neurological Exam

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

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)

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

MODULE 3 - MOTOR SYSTEM

B. Muscle Tone

1. Ask the volunteer to relax.

2. Flex and extend the volunteer's elbows (may also move wrists simultaneously) and at the knees (bilaterally). When testing the upper limbs, do this again while the subject makes large repetitive movements with the opposite arm (e.g. patting the palm of the hand on the knee).

3. There is a small, continuous resistance to passive movement.

Score: ***left and right***

Grade: ***NORMAL, IMPAIRED, or DECREASED*** **and describe abnormality**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer 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 subject will be asked to strike his 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 MN weakness.)

D. Gait

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

Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 6 - SENSORY

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
BDS	blood drug screen
BID	twice daily
BMI	body mass index
BP	blood pressure
CCU	Cardiac care unit
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
CL	clearance
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HR	heart rate
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
LAM	lactational amenorrhea method
MDRD	Modification of Diet in Renal Disease
MHIS	Modified Hachinski Ischemia Scale
MMSE-2	Mini Mental State Examination Second Edition
MOA	Manual of Assessments
MRI	magnetic resonance imaging
NCS	not clinically significant
NDA	New Drug Application
NPI	Neuropsychiatric Inventory
PCL	Protocol Clarification Letter
PK	pharmacokinetic
po	orally
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
QD	Once a day
QP2	Department of Quantitative Pharmacology and Pharmacometrics
QTc	Corrected QT interval
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures

Abbreviation	Expanded Term
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
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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