Official Protocol Title:	A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, PK and the Effect of MK-8189 on QTc in Participants with Schizophrenia
NCT number:	NCT05406440
Document Date:	18-Nov-2022

Title Page

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Protocol Title: A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, PK and the Effect of MK-8189 on QTc in Participants with Schizophrenia

Protocol Number: 014-05

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	118,986

Approval Date: 18 November 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 5	18-NOV-2022	Allow conduct of Panel C without review of Panel A-1 PK as it has been determined that even if PK is not predicted to achieve 2-fold the high clinical exposure scenario, lower exposures may support an integrated (non-clinical and clinical) concentration-QTc analysis that may negate the need for a TQT study (ICH E14 & S7B Q&A August 2022). In addition, as evaluation of an MK-8189 dose lower than 80 mg may also support an integrated concentration-QTc assessment, language has been removed indicating no further panels would be conducted if Panel A-1 is not well tolerated. To note, in Panel A of the current protocol, preliminary blinded data indicate doses up to and including MK-8189 60 mg are generally well tolerated.
Amendment 4	21-OCT-2022	Addition of a new panel with an alternate dose regimen and removal of unnecessary panels based on PK, safety and tolerability information from Panel A.
Amendment 3	14-SEP-2022	Updates to address FDA comments and other minor editorial updates
Amendment 2	29-JUN-2022	Updates to Schedule of Activities
Amendment 01	26-MAY-2022	Updates to exclusion criteria and ECG requirements
Original Protocol	11-MAY-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Conducting Panel C may support an integrated (non-clinical and clinical) concentration-QTc analysis negating the need for a TQT study per ICH E14 & S7B Q&A August 2022. It has been determined that even if PK is not predicted to achieve 2-fold the high clinical exposure scenario, a concentration-QTc analysis at lower exposures may still negate the need for a TQT study. Additionally, since lower doses of MK-8189 may also support an integrated concentration-QTc analysis, language has been removed that did not allow for Panel C if the dose regimen administered in Panel A-1 was not tolerated. If the Panel A-1 dose regimen is not tolerated, a lower dose in Panel C may be evaluated per Section 8.10.6 (Study Design/Dosing/Procedures Modifications Permitted withing Protocol Parameters) of the protocol. To note, in Panel A of the current protocol, preliminary blinded data indicate doses up to and including MK-8189 60 mg are generally well tolerated (Section 4.3.1).

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Removed language requiring the review of PK data from Panel A-1 prior to initiation of Panel C.	Confirmation of concentrations achieving 2-fold the high clinical exposure scenario are no longer critical for conduct of Panel C as lower exposures may be sufficient to support a concentration-QTc analysis.
	Updated Figure 2 Study Design -Decision Tree to remove Panel A-1 tolerability and PK requirement to conduct Panel C.	A lower dose may support an integrated concentration QTc analysis and Panel C may be conducted at a lower dose per Section 8.10.6 if Panel A-1 dose regimen is not tolerated.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Added language that a concentration QTc analysis at lower exposures may negate need for TQT study if supported by non-clinical data. Added reference to ICH E14 & S7B Q&A regulatory guidance.	Confirmation of exposures 2-fold the high clinical exposure scenario in Panel A-1 is not critical to dose regimen for Panel C.
4.3.1 Starting Dose for this Study	Updated language to say that preliminary blinded data from Panel A demonstrated good tolerability of MK-8189 48 mg/placebo administered on Day 1 and MK-8189 80 60 mg/placebo administered on Day 2, (instead of previous 80 mg/placebo on Day 2).	Minor edit to update erroneous text.
4.3.2 Maximum Dose/Exposure for This Study	Removed language requiring the review of PK data from Panel A-1 prior to initiation of Panel C. Added language that MK-8189 exposures at 80 mg or lower may be sufficient to support an integrated waiver assessment. Added reference to ICH guideline E14 & S7B Q&A August 2022.	Confirmation of exposures 2-fold the high clinical exposure scenario is no longer critical for conduct of Panel C.
4.3.3 Rationale for Dose Interval and Study Design	Removed language requiring the review of PK data from Panel A or Panel A-1 prior to initiation of Panel C.	Confirmation of exposures 2-fold the high clinical exposure scenario is no longer critical for conduct of Panel C.
Throughout	Minor grammatical and typographical errors were corrected.	These changes were non-substantial editorial corrections.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multiple Ascending Dose Clinical Study to Evaluate the Safety, Tolerability, PK and the Effect of MK-8189 on QTc in Participants with Schizophrenia

Short Title: MK-8189 Multiple Ascending Dose Clinical Study in Participants with Schizophrenia

Acronym: MAD

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in male and female participants with schizophrenia:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple ascending doses of MK-8189 in participants with schizophrenia	• Adverse events, discontinuation of study intervention due to adverse events

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Schizophrenia
Population	participants with schizophrenia or schizoaffective disorder
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind

Blinding Roles	Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9 weeks 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 12 participants with schizophrenia will be allocated/randomized for each of Panels A and A-1, such that approximately 8 participants are evaluable and complete the study in each of these panels. Up to 30 participants with schizophrenia will be allocated/randomized for Panel C such that up to 20 participants are evaluable and complete the study in each of these panels as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Active Panel A	MK-8189	12-mg	QD	Oral	4 tablets Day 1, 5 tablets Day 2	Test Product
Active Panel A-1	MK-8189	12-mg	QD	Oral	4 tablets Day 1, 6 tablets Day 2	Test Product
		4-mg	QD	Oral	2 tablets Day 2	Test Product
Active Panel C	MK-8189	12-mg	QD	Oral	4 tablets Days 1-2, 6 tablets Day 3	Test Product
		4-mg	QD	Oral	2 tablets Day 3	Test Product
Placebo Panel A, A-1, C	Placebo	0 mg	QD	Oral	Panel A 4 tablets Day 1, 5 tablets Day 2	Placebo Matched to Test Product
	Placebo	0 mg	QD	Oral	Panel A-1 4 tablets Day 1, 6 tablets Day 2	Placebo Matched to Test Product
	Placebo	0 mg	QD	Oral	Panel A-1 2 tablets Day 2	Placebo Matched to Test Product
	Placebo	0-mg	QD	Oral	Panel C 4 tablets Days 1-2, 6 tablets Day 3	Placebo Matched to Test Product
	Placebo	0-mg	QD	Oral	Panel C 2 tablets Day 3	Placebo Matched to Test Product

Total Number of Intervention Groups/ Arms	2 intervention groups
Duration of Participation	Panel A and A-1: Each participant will participate in the study for approximately 9 weeks from the time the participant provides documented informed consent through the final contact. After a screening, phase of 6 weeks, each participant will receive assigned intervention for approximately 2 days. After the end-of-treatment each participant will be followed for 2 weeks. Panel C: Each participant will participate in the study for approximately 9 weeks from the time the participant provides documented informed consent through the final contact. After a screening, phase of 6 weeks, each participant will receive assigned intervention for approximately 3 days. After the end-of-treatment each participant will be followed for 2 weeks.

Study Governance Committees:

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

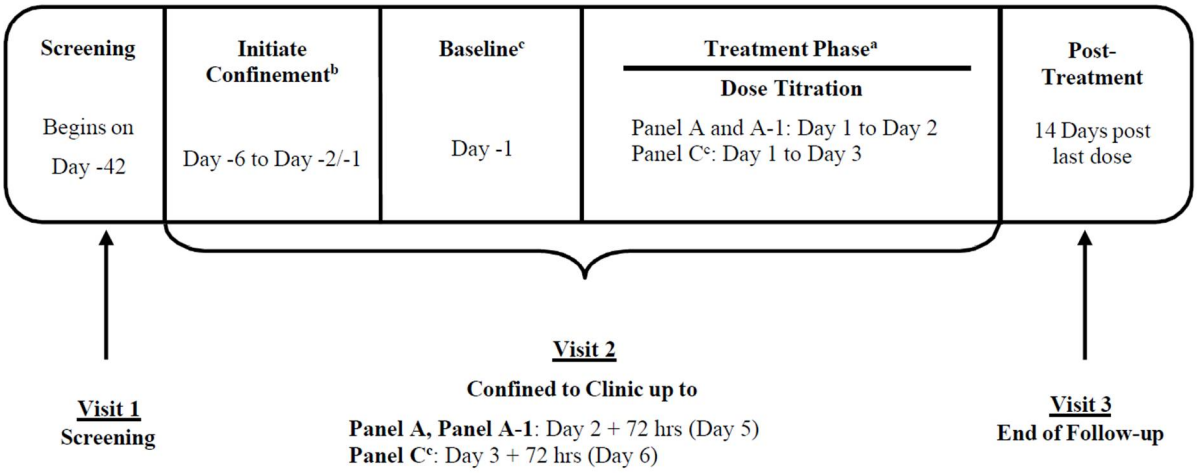
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 2.

1.2 Schema

The study design is depicted in Figure 1

Figure 1 Study Schema



a. Minimum 2 panels or maximum 3 panels to be conducted.
b. Participants on antipsychotic therapy will initiate confinement on Day -6. Participants not on antipsychotic therapy will initiate confinement on Day -2 (Panel C) or Day -1 (Panels A, A-1).
c. Panel C to include 24-hour Holter monitoring with prespecified time points for ECG waveform evaluation time-matched with PK

1.3 Schedule of Activities

Panel A												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Administrative Procedures												
Informed Consent	X											Sec. 8.1.1
Informed Consent for FBR	X											Sec. 8.1.1.2
Participant ID Card	X											Sec. 8.1.3
Inclusion/Exclusion Criteria	X			X								Sec. 5.1, Sec. 5.2 Specific criteria may be reviewed before randomization
Medical History (includes psychiatric history and substance usage)	X											Substances: Drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.1.5
Assignment of Screening Number	X											Sec. 8.1.6
Washout from current antipsychotic therapy		X	X									If on antipsychotic therapy, discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. For long half-life drugs washout may begin on outpatient basis (Sec. 4.1)
Assignment of Treatment Number					X							Sec. 8.1.7
MK-8189 or Placebo Administration						X	X					Day 1 48-mg, Day 2 60-mg
Standard Meals [a]				X	X	X	X	X	X			Sec. 5.3.1
Domiciling[b]				X ----------X								
Safety Procedures												
Full physical examination	X			X						X		Sec. 8.3.1
Height	X											
Weight	X			X						X	X	BMI to be taken only at Screening
Directed Physical Examination									X		X	Sec. 8.3.1

Panel A												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Full Neurological Examination	X			X						X		Day -1: within 24 hours of first dose. Upon discharge on Day 5. Sec. 8.3.7 and Appendix 11
Targeted Neurological Examination						X	X	X	X		X	Day 1-5: up to 3 hours pre-dose or equivalent. Poststudy visit. Sec. 8.3.7 and Appendix 11
Vital Signs (HR, BP) [c]	X			X		X	X	X	X	X	X	Sec. 8.3.2
Vital Signs (respiratory rate, temperature)	X			X		X[d]	X[d]	X[d]	X	X	X	Anytime during screening, Day -1 and poststudy visit. Predose on Day 1-2 and at 9 hours postdose (or equivalent) on Day 1-4. Upon discharge on Day 5. Sec. 8.3.2.
12-lead ECG [e]	X			X		X	X	X	X	X	X	Sec. 8.3.3
Serum (hCG; WOCBP only)	X										X	
Urine or Serum Pregnancy Test (WOCBP only)				X								Urine test will be collected. Serum test will be collected in the event that Urine test is positive or cannot be confirmed.
Serum FSH - (WONCBP)	X											
HIV, hepatitis B and C screen (per site SOP)	X											
UDS/BDS (per site SOP)	X			X								Screening UDS/BDS is mandatory, any additional UDS/BDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
Laboratory Safety Tests: (Hematology, Urinalysis, Chemistry)	X				X				X	X	X	Collected at predose (or equivalent) after ~8 hour fast
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	

Panel A												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Brief Psychiatric Rating Scale (BPRS)	X			X			X			X		up to 3 hours pre-dose or equivalent timepoint Sec. 8.3.7
C-SSRS Baseline	X											up to 3 hours pre-dose equivalent timepoint Sec. 8.3.6.1
C-SSRS Since Last Assessment							X	X	X	X		up to 3 hours pre-dose or equivalent Sec. 8.3.6.1
Barnes Akathisia Rating Scale (BARS)[f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec. 4.2.1.2
Abnormal Involuntary Movement Scale (AIMS) [f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec. 4.2.1.2
Simpson Angus Scale (SAS) [f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec. 4.2.1.2
Pharmacokinetics												
Blood for Plasma MK-8189 [g]					X	X	X	X	X	X		
Biomarkers												
Blood for Genetic Analysis					X							Collect predose from enrolled participants only. See section 8.8.1

Panel A												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1

ADA=antidrug antibody; 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. Meals should be given at approximately the same time starting on Day -1 (Day -6 if washing off antipsychotic therapy) time-matched to postdose meals, through 24 hours post last dose including; breakfast at ~1 hour postdose, lunch at ~4 hours postdose, snack at ~8 hours postdose and dinner at ~12 hours postdose. All subsequent meals will be unrestricted in timing. All meals will follow the completion of all specified procedures at that timepoint
b. Participants will be confined minimally from Day -1 until Day 5 procedures are complete. If participant is washing off antipsychotic therapy domiciling will begin on Day -6.
c. HR and BP, Day -1: Triplicate measurements time-matched to 9 hours post dose equivalent measurements
   • Single HR and BP measurements will be obtained at all postdose timepoints on the following days:
   • Days 1-2: at 9 hours post-dose
   • Days 3-4: 9 post-dose equivalent
   • Days 5: Upon discharge from the clinic
d. Respiratory rate only
e. 12-lead safety ECG measurements. On the following days, specific timepoints are noted:
   • Day -1: Triplicate measurements, Time-matched to 9 hours post dose equivalent measurements
   • Day 1-2: at 9 hours post-dose
   • Day 3-4: at 9 hours post-dose equivalent
   • Days 5: Upon discharge from the clinic
f. Additional BARS, AIMS and SAS assessments should be conducted if possible when there are observed or reported complaints of dystonia and/or akathisia
g. MK-8189 plasma PK sample collection:
   • Day 1: predose, 2, 6, 8, 10, 12, 14, 16 hours postdose
   • Day 2: predose, 2, 6, 8, 10, 12, 14, 16, 24, 48, 72 hours post-dose

• Leftover main study plasma will be stored for future biomedical research
All Panels/Periods

Panel A-1												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Administrative Procedures												
Informed Consent	X											Sec. 8.1.1
Informed Consent for FBR	X											Sec. 8.1.1.2
Participant ID Card	X											Sec. 8.1.3
Inclusion/Exclusion Criteria	X			X								Sec. 5.1, Sec. 5.2 Specific criteria may be reviewed before randomization
Medical History (includes psychiatric history and substance usage)	X											Substances: Drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.1.5
Assignment of Screening Number	X											Sec. 8.1.6
Washout from current antipsychotic therapy		X	X									If on antipsychotic therapy, discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. For long half-life drugs washout may begin on outpatient basis (Sec. 4.1)
Assignment of Treatment Number					X							Sec. 8.1.7
MK-8189 or Placebo Administration						X	X					Day 1 48 mg, Day 2 80 mg
Standard Meals [a]				X	X	X	X	X	X			Sec. 5.3.1
Domiciling[b]				X ----------X								
Safety Procedures												
Full physical examination	X			X						X		Sec. 8.3.1
Height	X											
Weight	X			X						X	X	BMI to be taken only at Screening
Directed Physical Examination									X		X	Sec. 8.3.1
Full Neurological Examination	X			X						X		Day -1: within 24 hours of first dose. Upon discharge on Day 5. Sec. 8.3.7 and Appendix 11

Panel A-1												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Targeted Neurological Examination						X	X	X	X		X	Day 1-5: up to 3 hours pre-dose or equivalent. Poststudy visit. Sec. 8.3.7 and Appendix 11
Vital Signs (HR, BP) [c]	X			X		X	X	X	X	X	X	Sec. 8.3.2
Orthostatic VS (HR, BP) [c]	X			X		X	X	X	X	X	X	Sec. 8.3.2.2
Vital Signs (respiratory rate, temperature)	X			X		X[d]	X[d]	X[d]	X	X	X	Anytime during screening, Day -1 and poststudy visit. Predose on Day 1-2 and at 9 hours postdose (or equivalent) on Day 1-4. Upon discharge on Day 5. Sec. 8.3.2.
12-lead ECG [e]	X			X		X	X	X	X	X	X	Sec. 8.3.3
Serum (hCG; WOCBP only)	X										X	
Urine or Serum Pregnancy Test (WOCBP only)				X								Urine test will be collected. Serum test will be collected in the event that Urine test is positive or cannot be confirmed.
Serum FSH - (WONCBP)	X											
HIV, hepatitis B and C screen (per site SOP)	X											
UDS/BDS (per site SOP)	X			X								Screening UDS/BDS is mandatory, any additional UDS/BDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
Laboratory Safety Tests: (Hematology, Urinalysis, Chemistry)	X				X				X	X	X	Collected at predose (or equivalent) after ~8 hour fast
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	
Brief Psychiatric Rating Scale (BPRS)	X			X			X			X		up to 3 hours pre-dose or equivalent timepoint Sec. 8.3.7

Panel A-1												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
C-SSRS Baseline	X											up to 3 hours pre-dose equivalent timepoint Sec. 8.3.6.1
C-SSRS Since Last Assessment							X	X	X	X		up to 3 hours pre-dose or equivalent Sec. 8.3.6.1
Barnes Akathisia Rating Scale (BARS)[f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Abnormal Involuntary Movement Scale (AIMS) [f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Simpson Angus Scale (SAS) [f]				X			X	X		X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Pharmacokinetics												
Blood for Plasma MK-8189 [g]					X	X	X	X	X	X		
Biomarkers												
Blood for Genetic Analysis					X							Collect predose from enrolled participants only. See section 8.8.1

Panel A-1												
Study Period:	**Screening**	**Washout**		**Intervention**							**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**Post-study**	Screening should occur within 6 weeks prior to Day 1

ADA=antidrug antibody; 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. Meals should be given at approximately the same time starting on Day -1 (Day -6 if washing off antipsychotic therapy) time-matched to postdose meals, through 24 hours post last dose including; breakfast at ~1 hour postdose, lunch at ~4 hours postdose, snack at ~8 hours postdose and dinner at ~12 hours postdose. All subsequent meals will be unrestricted in timing. All meals will follow the completion of all specified procedures at that timepoint
b. Participants will be confined minimally from Day -1 until Day 5 procedures are complete. If participant is washing off antipsychotic therapy domiciling will begin on Day -6.
c. HR and BP, Day -1: Triplicate measurements in the supine position, time-matched to 9 hours post dose equivalent measurements. A single orthostatic assessment will be conducted following the last supine vital sign measurement.
   • Single supine HR and BP measurements followed by orthostatic HR and BP measurements will be obtained at all postdose timepoints. On the following days, specific timepoints are noted
   • Days 1-2: at 9 hours post-dose
   • Days 3-4: 9 post-dose equivalent
   • Days 5: Upon discharge from the clinic
d. Respiratory rate only
e. 12-lead safety ECG measurements. On the following days, specific timepoints are noted:
   • Day -1: Triplicate measurements, Time-matched to 9 hours post dose equivalent measurements
   • Day 1-2: at 9 hours post-dose
   • Day 3-4: at 9 hours post-dose equivalent
   • Days 5: Upon discharge from the clinic
f. Additional BARS, AIMS and SAS assessments should be conducted if possible when there are observed or reported complaints of dystonia and/or akathisia
g. MK-8189 plasma PK sample collection:
   • Day 1: predose, 2, 6, 8, 10, 12, 14, 16 hours postdose
   • Day 2: predose, 2, 6, 8, 10, 12, 14, 16, 24, 48, 72 hours post-dose
   • Leftover main study plasma will be stored for future biomedical research

All Panels/Periods

Panel C													
Study Period:	**Screening**	**Washout**		**Intervention**								**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1[i]**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**6**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Administrative Procedures													
Informed Consent	X												Sec. 8.1.1
Informed Consent for FBR	X												Sec. 8.1.1.2
Participant ID Card	X												Sec. 8.1.3
Inclusion/Exclusion Criteria	X			X									Sec. 5.1, Sec. 5.2 Specific criteria may be reviewed before randomization
Medical History (includes psychiatric history and substance usage)	X												Substances: Drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.1.5
Assignment of Screening Number	X												Sec. 8.1.6
Washout from current antipsychotic therapy		X	X										If on antipsychotic therapy, discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. For long half-life drugs washout may begin on outpatient basis (Sec. 4.1)
Assignment of Treatment Number					X								Sec. 8.1.7
MK-8189 or Placebo Administration						X	X	X					Day 1-2 48-mg, Day 3 80-mg
Standard Meals [a]			X	X	X	X	X	X	X	X			Sec. 5.3.1
Domiciling[b]			X ----------								X		
Safety Procedures													
Full physical examination	X		X								X		Sec. 8.3.1
Height	X												
Weight	X		X								X	X	BMI to be taken only at Screening
Directed Physical Examination										X		X	Sec. 8.3.1
Full Neurological Examination	X			X							X		Day -1: within 24 hours of first dose. Upon discharge on Day 6. Sec. 8.3.7 and Appendix 11

Panel C													
Study Period:	**Screening**	**Washout**		**Intervention**								**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1[i]**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**6**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
Targeted Neurological Examination						X	X	X	X	X		X	Day 1-5: up to 3 hours pre-dose or equivalent. Poststudy visit. Sec. 8.3.7 and Appendix 11
Vital Signs (HR, BP) [c]	X			X		X	X	X	X	X	X	X	Sec. 8.3.2
Orthostatic VS (HR, BP) [c]	X			X		X	X	X	X	X	X	X	Sec. 8.3.2.2
Vital Signs (respiratory rate, temperature)	X			X		X[h]	X[h]	X[h]	X	X	X	X	Sec. 8.3.2, anytime during screening, Day -1, and poststudy visit. Predose on Days 1-3, and at 9 hours postdose (or equivalent) on Day 1-5. Upon discharge on Day 6.
24-hour Holter ECG & Extraction [d]				X	X	X	X	X	X	X	X		
12-lead ECG [e]	X			X		X	X	X	X	X	X	X	Sec. 8.3.3
Serum (hCG; WOCBP only)	X											X	
Urine or Serum Pregnancy Test (WOCBP only)			X										Urine test will be collected. Serum test will be collected in the event that Urine test is positive or cannot be confirmed.
Serum FSH - (WONCBP)	X												
HIV, hepatitis B and C screen (per site SOP)	X												
UDS/BDS (per site SOP)	X		X										Screening UDS/BDS is mandatory, any additional UDS/BDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
Laboratory Safety Tests: (Hematology, Urinalysis, Chemistry)	X				X					X	X	X	Collected at predose (or equivalent) after ~8 hour fast
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	
Brief Psychiatric Rating Scale (BPRS)	X		X				X			X	X		up to 3 hours pre-dose Sec. 8.3.7

Panel C													
Study Period:	**Screening**	**Washout**		**Intervention**								**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1**[i]	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**6**	**Post-study**	Screening should occur within 6 weeks prior to Day 1
C-SSRS Baseline	X												up to 3 hours pre-dose Sec. 8.3.6.1
C-SSRS Since Last Assessment							X	X	X	X	X		up to 3 hours pre-dose or equivalent Sec. 8.3.6.1
Barnes Akathisia Rating Scale (BARS) [f]			X				X	X			X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Abnormal Involuntary Movement Scale (AIMS) [f]			X				X	X			X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Simpson Angus Scale (SAS) [f]			X				X	X			X	X	Up to 3 hours pre-dose on dosing days. Any time on non-dosing days Sec.4.2.1.2
Pharmacokinetics													
Blood for Plasma MK-8189 [g]					X	X	X	X	X	X	X		Sample to be collected within 10 minutes of end of ECG extraction window
Biomarkers													
Blood for Genetic Analysis					X								Collect predose from enrolled participants only. See section 8.8.1

Panel C													
Study Period:	**Screening**	**Washout**		**Intervention**								**Post-study**	**Notes**
Scheduled Day	**Screening**	**-6**	**-2**	**-1[i]**	**Pre-Dose**	**1**	**2**	**3**	**4**	**5**	**6**	**Post-study**	Screening should occur within 6 weeks prior to Day 1

ADA=antidrug antibody; 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. Meals should be given at approximately the same time every day starting on Day -2 (Day -6 if washing off antipsychotic therapy) time-matched to postdose meals, through Day 5. Breakfast will be given at ~1 hour postdose, lunch given at ~4 hours postdose, a snack given at ~8 hours postdose and dinner at ~12 hours postdose. All meals will follow the completion of all specified procedures at that timepoint

b. Participants will be confined minimally from Day -2 until Day 6 procedures are complete. If participant is washing off antipsychotic therapy domiciling will begin on Day -6.

c. HR and BP, Day -1: Triplicate measurements in the supine position time-matched to 9 hours post dose equivalent measurements. A single orthostatic assessment will be conducted following the last supine vital sign measurement.
   • Single supine HR and BP measurements followed by orthostatic HR and BP measurements will be obtained at all postdose timepoints. On the following days, specific timepoints are noted;
   • Days 1-3: at 9 hours post-dose
   • Days 4-5: 9 post-dose equivalent
   • Days 6: Upon discharge from the clinic

d. (24-hour) Holter ECG measurements will be performed from approximately 30 minutes prior to dose administration and until 24 hours post-dose.
   ECG data will be extracted on:
   • Day -1 (baseline measurement): time matched to dosing days at the following timepoints: 0.5hr, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16
   • Day 1: predose, 0.5hr, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 hours postdose
   • Day 2: predose, 1, 2, 6, 8, 10, 12, 14, 16 postdose
   • Day 3: pre-dose, 1, 2, 6, 8, 10, 12, 14, 16, 24, 36 hours post-dose. In addition, Holter ECGs will be obtained 48 (Day 5) and 72 hours (Day 6) following the Day 3 dose.

e. 12-lead safety ECG measurements. On the following days, specific timepoints are noted:
   • Day -1: Triplicate measurements, Time-matched to 9 hours post dose equivalent measurements
   • Day 1-3: at 9 hours post-dose
   • Day 4-5: at 9 hours post-dose equivalent
   • Days 6: Upon discharge from the clinic

f. Additional BARS, AIMS and SAS assessments should be conducted if possible when there are observed or reported complaints of dystonia and/or akathisia

g. MK-8189 plasma PK sample collection:
   • Day 1: predose, 0.5hr, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 hours postdose
   • Day 2: predose, 1, 2, 6, 8, 10, 12, 14, 16 hours postdose
   • Day 3: predose, 1, 2, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72 hours post-dose
   • Leftover main study plasma will be stored for future biomedical research

h. Respiratory rate only

i. Participants should be encouraged to have periods of ambulation, outside of the rest periods required prior to and during Holter extraction

All Panels/Periods

2 INTRODUCTION

2.1 Study Rationale

This study is being conducted to support efforts to de-risk the potential for MK-8189 to prolong QT as required by ICH E14. Thus, this study will be conducted to 1) evaluate a supratherapeutic dose regimen in participants with schizophrenia to support, if required, a TQT in participants with schizophrenia and 2) perform a concentration-QTc analysis in participants with schizophrenia receiving supratherapeutic doses such that the need for a TQT study may be negated.

To appropriately interrogate the potential for a drug to prolong QT, a TQT study requires the administration of a supratherapeutic dose that is expected to cover the high clinical exposure scenario; this reflects the exposure of the drug when affected by the intrinsic or extrinsic factor that causes the greatest increase in plasma concentrations. Thus, this study will evaluate safety, tolerability, and PK of multiple oral doses of MK-8189 at doses that will result in concentrations that are greater to those expected when MK-8189 is co-administered with a strong CYP3A inhibitor (1.27-fold increase in Cmax), the factor which is expected to cause the greatest increase in MK-8189 concentrations. Doses up to 80 mg of MK-8189 will be evaluated to provide a clinical margin of 2-fold to the predicted steady-state Cmax following administration of MK-8189 24 mg, the highest clinical dose evaluated in Phase 2B. Conducting TQT studies in participants with schizophrenia is challenging; this patient population is expected to have several co-morbidities and concomitant therapy which could confound a QTc assessment. Thus, to avoid confounding the QTc assessment, patients would be required to wash off their stable regimen of antipsychotic therapy for several weeks as well as other treatments that may affect heart rate and therefore QTc evaluation. To ensure appropriate power and account for discontinuations, it is anticipated that approximately 100 participants with schizophrenia would need to be enrolled. Therefore this study will also evaluate whether a concentration-QTc analysis could be conducted in a smaller number of participants (n=30) in a study of shorter duration than a TQT study would require. Thus one panel of participants will be escalated over 3 days to 80 mg of MK-8189 which may provide exposures approximately 2-fold peak concentrations following MK-8189 coadministration with strong CYP3A inhibitor at steady-state (high clinical exposure scenario). Achieving these exposures and assessing ECG parameter values, would support a concentration-QTc assessment and de-risk the potential for MK-8189 to induce QT prolongation, even in the absence of a positive control, which is required in a TQT study.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

MK-8189 is a potent and selective inhibitor of PDE10A that is being developed as a novel therapeutic for the treatment of schizophrenia.

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 [Seeger, T. F., et al 2003].

Preclinical pharmacology studies demonstrate that PDE10A inhibition increases cAMP/cGMP signaling in pathways that have been associated with underlying pathology (glutamate) as well as clinically validated therapeutics (dopamine D2 receptor antagonists)for schizophrenia. Enhanced signaling in these pathways is hypothesized to restore behavioral inhibition that is impaired in schizophrenia [Grauer, S. M., et al 2009] [Schmidt, C. J., et al 2008]. PDE10A inhibitors may potentially be an alternative treatment as monotherapy and/or adjunct treatment in schizophrenia patients who have inadequate response to first line AAP treatment.

2.2.2 Preclinical and Clinical Studies

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

Completed Phase 1 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 Panel 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.

Overview of 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.

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. Preliminary data from an ongoing DDI study (P015, described in 2.2.3) demonstrated that 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. Preliminary

data from an ongoing hepatic impairment study (P012) demonstrated that MK-8189 AUC and Cmax were approximately 1.18-fold and 1.22-fold higher in participants with moderate hepatic impairment compared to healthy matched controls, respectively. Preliminary results from an ongoing study in adult and elderly (P011) suggest that PK exposures in elderly participants with and without schizophrenia are generally similar to one another and similar to those observed in adult participants < 60 years of age with schizophrenia.

Overview of Safety:

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 two SAEs. One participant experienced an SAE of gastroenteritis in P003 which was not considered treatment related. The other SAE of psychosis occurred in a participant with schizophrenia in P007. Both SAEs are detailed in the IB.

In a Phase 2 POC trial (P005), MK-8189 was generally well tolerated by the 90 participants who received at least one dose of the once daily MK-8189 (titrated every 3 days from 4 mg to 8 mg and 12 mg, as tolerated). Participants were dosed after they were able to taper off psychotropic medications. Adverse Events that occurred in ≥5% of participants in the MK-8189 intervention group and had greater incidence than placebo were diarrhea, nausea, vomiting, decreased appetite, akathisia, dystonia, headache, sedation, somnolence, anxiety, and insomnia. No deaths were reported in the P005 study. No SAEs were reported for participants on MK-8189. Eight participants [8.9%]) had an AE of dystonia and 2 participants (2.2%) had an AE of oromandibular dystonia.

Detailed PK and safety information from individual completed studies are summarized in the IB.

2.2.3 Ongoing Clinical Studies

As of 14-February-2022, 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, double-blind, placebo-controlled, multicenter, 2-part study. Part 1 (Panel A/B/C) evaluated the safety and tolerability of different titration regimens (including without titration) in participants ≤60 years of age with schizophrenia. Part 1 is clinically complete and all data are preliminary and blinded. Panel C was not conducted per protocol since the regimens in Panel A and B were generally well tolerated. Part 2 is evaluating the safety, tolerability, and PK of MK-8189 in elderly participants with schizophrenia and healthy elderly participants between 61 and 80 years of age (inclusive). All data presented are blinded.

In Part 1, Panel A, participants with schizophrenia initiated dosing with 16 mg of MK-8189/placebo for 3 days, then escalated to 24 mg/placebo for 4 days. In Panel A, all 8 participants enrolled completed treatment. Most AEs were mild, and no SAEs or deaths were reported. 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. The participant was also receiving hydroxyzine, a sedating antihistamine. 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, was treated with benztropine and resolved in 22 hours. The participant continued in the study 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, participants with schizophrenia were dosed with 24 mg of MK-8189/placebo (no titration) for 7 days. In Panel B, enrollment and dosing are complete. 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. 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). No AEs of akathisia or dystonia were reported.

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. Fifteen participants have been dosed and 10 completed the study. No deaths or SAEs have been reported. Most AEs were mild or moderate; 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. Five participants have discontinued the trial: Two participants withdrew consent. One participant reported an AE of severe somnolence which began following the 8 mg/placebo dose and resolved on Day 3. On Day 3 following treatment with 8 mg/placebo, the same participant had an AE of moderate dystonia which resolved in 2 days with a single dose of cyclobenzaprine. This participant also 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 rash and conjunctivitis.

One participant experienced dystonia of the throat after the Day 3 16 mg/placebo dose which was treated with benztropine. Tightness of the throat muscles which the investigator considered to be mild dystonia 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.

As of the cut-off date, this panel was 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), rash (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 with the same treatment regimen as Panel D. Five participants completed the trial and one participant discontinued due to an AE. Most AEs were mild in intensity and 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 ongoing 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. Most AEs were mild. Three AEs were severe (2 participants with severe somnolence and 1 participant with severe hypnagogic hallucination) and are described below; no deaths or SAEs were reported. All AEs resolved. Three participants discontinued due to treatment related AEs. Beginning on the evening of Day 7, following 2 days of dosing with MK-8189 24 mg/placebo, one participant reported mild akathisia (~20 hour), moderate tactile hallucinations (15 min), mild palpitations (2 min) and bilateral hand hyperhidrosis (5 hour) and severe hypnagogic hallucinations (5 min). The participant reported these AEs on the morning of Day 8, the dose was held, 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 benztropine. 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 a 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.

Two 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. As of the cut-off date, 7 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 4 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). 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. P015 was clinically complete as of the cut-off date. 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 pre-syncopal 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 013

P013 (non-IND study) is a multiple ascending dose, randomized, double-blind, placebo-controlled (3:1) parallel-group study being conducted in China to evaluate the safety, tolerability, and PK of MK-8189 titrated from 8 mg to 24 mg in healthy Chinese participants (n=16). P013 was clinically complete as of the cut-off date. All data presented are blinded.

There were no SAEs or deaths reported. One participant discontinued due to an AE of moderate delusion with a duration of 15.5 hours following their first dose of MK-8189 8 mg/placebo. This participant also had the following AEs (duration): mild somnolence on 2 occasions (6 hours and 18.5 hours), moderate depressed mood (3 days), mild dystonia (7.5 hours), and mild insomnia on two occasions (7.5 hours and 4 days).

One participant reported an AE of suicidal ideation without intent which lasted for 5 seconds following their second dose of 24 mg/placebo: It was reported that after a dream the participant had mood swings and was crying. The concept of transient suicide appeared. He was observed during the clinical course. The subject did not receive treatment for the event. The participants mood AE resolved in 20 minutes. On Study Day 12, the participant received their last dose of 24 mg of MK-8189/ placebo per protocol. The investigator considered suicidal ideation (mild) to be related to study intervention. This subject also reported AEs (duration) of mild headache (3 hours), mild somnolence (18.5 hours), mild cognitive disorder (16 hours), mild anxiety (14 hours), mild tremor (12 hours) following the first dose of 8 mg/placebo, mild ventricular tachycardia (1.3 weeks) with ventricular rate ranging from 62 to 78 bpm (Screening ventricular rate was 75 bpm), mild increased total bilirubin (also elevated at Screening) with direct bilirubin within the normal range (3 weeks) following their second 12 mg/placebo dose, mild unrelated pharyngeal swelling (9 hours) following their second 16 mg/placebo dose, mild insomnia (5 days) two days following their last 24 mg/placebo dose, mild hyperphosphatemia (1.7 weeks), mild hypercalcemia (also elevated at Screening) (1.7 weeks) three days following their last 24 mg MK-8189/placebo dose.

The most frequently reported treatment related AEs (N ≥2) were somnolence (N=12), insomnia (N=10), decreased appetite (N=5), dystonia (N=5), nausea (N=5), akathisia (N=3), anxiety (N=3), tremor (N=3), blood bilirubin increased (N=2), delusion (N=2), headache (N=2), hyperhidrosis (N=2) and vomiting (N=2). The majority of AEs reported were mild and no AEs were severe. The AEs of akathisia, dystonia, delusions, and most AEs of anxiety and somnolence resolved within a few hours. Most of these AEs resolved spontaneously and only one AE of dystonia, anxiety and akathisia were treated. One participant had moderate depressed mood beginning with the 8 mg/placebo dose which resolved within 3 days with continued dosing. Other mood AEs resolved within hours with continued dosing.

2.2.3.5 Protocol 016

P016 is a randomized, double-blind, placebo-controlled parallel-group, multiple ascending dose study conducted in Belgium to evaluate the safety, tolerability, and PK of MK-8189

titrated from 8 mg to 72 mg in 25 healthy participants. Participants were administered the following dose regimen; 8 mg/placebo Day 1, 16 mg/placebo Day 2, 24 mg/placebo Day 3, 48 mg/placebo Day 4 and Day 5, 72 mg Day 6. Data are preliminary and blinded. No SAEs or deaths occurred.

During dosing of the first 12 participants, 4 out of 12 did not dose escalate to the highest dose of 72 mg due to tolerability issues. Per protocol, if 4 participants randomized to MK-8189 did not dose escalate the stopping rules were met and the trial would be terminated. Though the trial remained blinded, conservatively it was decided to stop the trial and therefore no further participants were dosed. Two participants did not dose escalate from 48 mg/placebo to 72 mg/placebo and discontinued treatment due to mild and moderate adverse events of vomiting following their second dose of 48 mg. One of these participants also discontinued treatment due to moderate anxiety (9 hours) following their second dose of 48 mg/placebo. A third participant was down-titrated following their first dose of 48 mg to 24 mg due to moderate somnolence; the somnolence resolved prior to the 24 mg dose administration. A fourth participant discontinued treatment following their 24 mg/placebo dose due to severe akathisia (duration 22.5 hours) and moderate affect lability which began after the 16 mg/placebo dose (4 days). After the 72 mg dose, one participant reported mild dystonia on one occasion lasting 17 minutes. One other participant reported a mild AE of oral dyskinesia following the 16 mg dose which lasted for 3 hours. Another participant reported intermittent mild akathisia after administration of the 72mg dose. The majority of AEs were mild and only one severe AE (akathisia described above) was reported. AEs reported by more than one participant regardless of causality were as follows: nausea (n=7), decreased appetite (n=6), headache (n=5), nightmare (n=4), insomnia (n=4), restlessness (n=3), leukocyturia (n=3), dizziness (n=2), hematuria (n=2), palpitations (n=2), diarrhea (n=3), dyspepsia (n=2), eructation (n=2), pyuria (n=2), systolic blood pressure increased (n=2), muscle spasms (n=2), myalgia (n=2), akathisia (n=2), somnolence (n=2), vomiting (n=2) and affect lability (n=2). With the exception of a poststudy unrelated AE of leukocyturia in one participant, all other AEs resolved. Administration of MK-8189/placebo up to 24 mg was generally well tolerated. The aggressive titration regimen above 24 mg was not generally well tolerated in healthy participants.

2.2.3.6 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. Recruitment was initiated in December 2020. 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.

2.2.4 Information on Other Study-related Therapy

Not applicable.

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

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

The following objectives will be evaluated in male and female participants with schizophrenia:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple ascending doses of MK-8189 in participants with schizophrenia	• Adverse events, discontinuation of study intervention due to adverse events
Secondary	
• Not applicable	• Not applicable
Tertiary/Exploratory	
• To estimate the pharmacokinetics of MK-8189 following multiple ascending doses of MK-8189 in participants with schizophrenia	• AUC0-24, Cmax, C24, AUC0-inf, Tmax, CL/F, Vz/F and apparent t1/2
• To evaluate the effect of MK-8189 concentrations on QTc interval and ECG parameters in participants with schizophrenia	• QTc, PR and RR intervals, heart rate, QRS duration, T wave morphology, presence of U waves and outlier assessment

Objectives	Endpoints
• To investigate the relationship between the genetic polymorphisms of CYP2C9 and the pharmacokinetics of MK-8189. Variation in CYP2C9 alleles 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

4 STUDY DESIGN

4.1 Overall Design

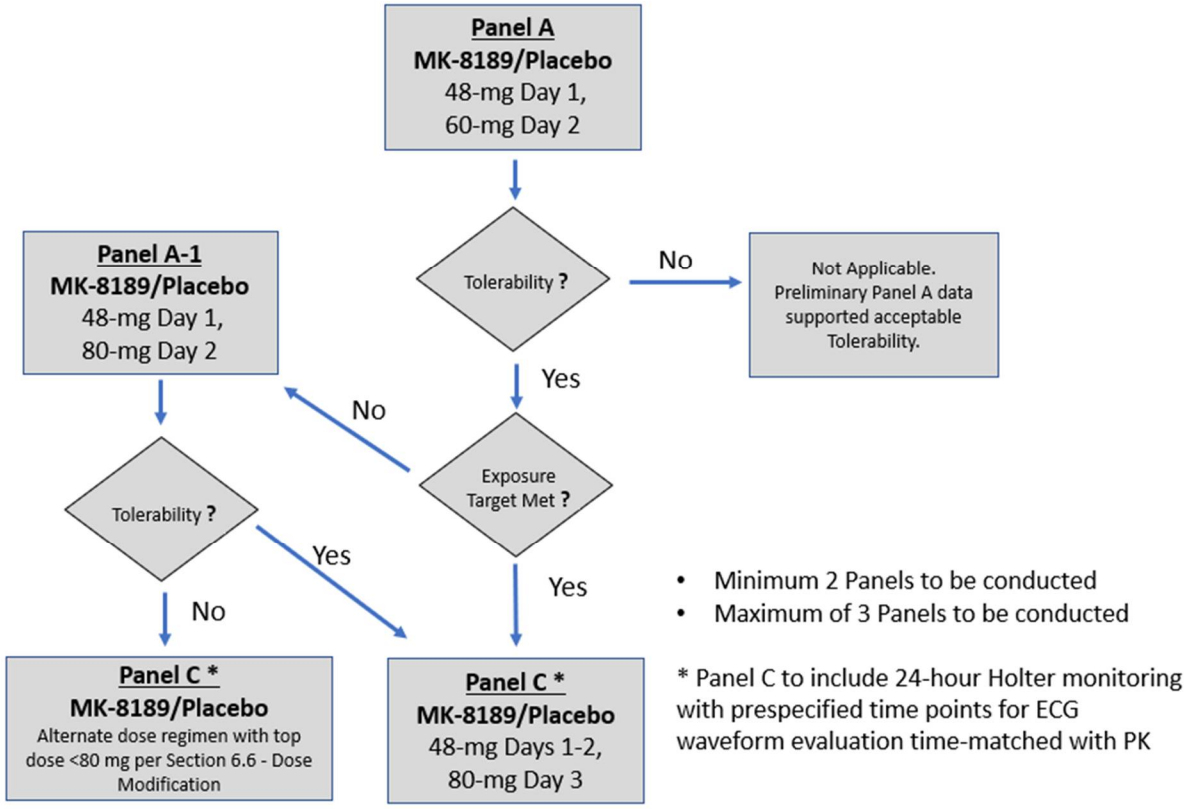
This is a randomized, placebo-controlled, parallel-group, multisite, double-blind, multiple-panel study of MK-8189 in participants with schizophrenia.

Panels A and A-1 will enroll up to 12 participants each with schizophrenia (9 on active and 3 on placebo). Participants will be randomized to receive orally administered rising-doses of MK-8189 or placebo. For Panel A, participants will receive MK-8189 48 mg/placebo Day 1, MK-8189 60 mg/placebo Day 2. For Panel A-1, participants will receive MK-8189 48 mg/placebo Day 1, MK-8189 80 mg/placebo Day 2.

Panel C will initiate if the dose regimen in Panel A and Panel A-1 are found to be generally well tolerated. Panel C will enroll up to 30 participants with schizophrenia (18 on active and 12 on placebo). Participants will be randomized to receive orally administered rising-doses of MK-8189 or placebo; MK-8189 48 mg/placebo Days 1-2, MK-8189 80 mg/placebo Day 3.

Following completion of dosing in each Panel A and Panel A-1, the decision on which dose regimen to evaluate next per Figure 2 will be made jointly by the investigator and sponsor following a review of the adverse event data. The dose regimen selected will be documented in a Protocol Clarification Letter.

Figure 2 Study Design – Decision Tree



If applicable, participants will be washed off their current antipsychotic therapy. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants should not receive antipsychotics for at least 5 days or 3 half-lives (whichever is longer) prior to Day -1. For longer half-life antipsychotics (eg, aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment (ie,cessation of atypical antipsychotic therapy) as an outpatient, but should be confined to the clinical research unit within a week of stopping treatment and minimally beginning on Day -6. If participants are not currently receiving antipsychotic therapy, they will be domiciled beginning on Day -1 through 72 hours post dose in Panels A and A-1, on Day -2 through 72 hours post dose in Panel C. All participants in Panel C will have 24-hour Holter recordings on Day -1, which will be considered baseline, as specified in the SoA. In addition, Holter monitoring recordings and blood sampling for PK will be conducted on days and timepoints specified in the SoA up to 72 hours following the last dose administration. Blood sampling for PK will be within 10 minutes of the end of the ECG extraction period. Participants in Panel C should be encouraged to have periods of ambulation, outside of the rest periods required prior to and during Holter extraction, to procure wide ranges of heart rates on Day -1 to support the concentration-QTc analysis.

Following 72- hour assessments, antipsychotic standard of care may be restarted. At the investigator's discretion, the participant may be domiciled for a longer duration if up titration is observation is required.

Titration will occur per the investigator's medical discretion based on the tolerability of MK-8189 within an individual participant. Anytime during the dose escalation, if the investigator deems it necessary, dose escalation within an individual may be paused temporarily for the duration of any tolerability issues involved and resumed immediately at the next dose level. Any changes to the dose regimen will not prolong an individual's participation in the trial and therefore it is acknowledged that failure to adhere to the protocol-defined titration regimen may result in some participants not reaching the escalation targets. Regardless of the state of the dose escalation of each participant it is important to keep participants in the study as the data collected at all doses could still be valuable for the purposes of defining a clinical tolerability margin. In Panel C, the 24-Holter extraction and PK sampling will not be repeated within an individual at the same dose level. Any changes to the protocol specified treatment regimen will be documented in a Protocol Clarification Letter.

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 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

The adaptive nature of this study design allows for the exploration of the safety and tolerability of multiple ascending dose regimens to support both a TQT study (Panels A, A-1) and concentration-QT analysis (Panel C). This study will allow for the selection of the optimal dose-regimen for a TQT study. To support a TQT study, the dose evaluated should achieve peak concentrations that are approximately 2-fold the steady-state Cmax following administration of the highest clinical dose of MK-8189. Titration within an individual per protocol will be based on the tolerability profile (AE data) and will be at the discretion of the investigator. Prior to this amendment, Panel A was completed. Eleven participants were enrolled and all completed treatment per protocol and the dose regimen was found to be well tolerated. Preliminary PK analysis from this panel showed exposures were not sufficient to support a TQT study; mean peak concentrations approximated only 1.7-fold the predicted steady-state Cmax following administration of 24 mg vs the required 2-fold multiple. As such, this amendment is including Panel A-1 to evaluate the safety, tolerability, and PK of MK-8189 48 mg administered on Day 1 and 80 mg administered on Day 2.

In order for concentration-QT analysis (Panel C) to negate the need for a TQT study, key elements must be included in the study design including 1) administration of a dose that provides concentrations that are at least 2-fold those observed at the highest clinical dose when administered under conditions where exposures are expected to maximally increase. In the case to MK-8189, this scenario would be co-administration of MK-8189 with a CYP3A inhibitor, which results in a 27% increase in peak concentrations. 2) a sufficient sample size

(evaluable data from 12 active and 8 placebo) and 3) robust ECG assessments time-matched to PK assessments. In addition, if an exposure of 2-fold the high clinical exposure scenario cannot be achieved, a lower exposure multiple may be acceptable if non-clinical data also support the lack of a QT effect at sufficient margins to the clinical dose (ICH E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential-Questions and Answer-Guidance for the Industry August 2022 (Final)) [European Medicines Agency 2022]. Thus, in Panel C, this study will collect Holter recordings for 24-hour periods at multiple dose levels, with additional recordings at 48 and 72 h following the last dose to assess the ECG parameter intervals across a wide range of concentrations. Replicate ECGs and central core lab assessments are incorporated in the design to assess ECG intervals with reduced variability. The PK assessments on the same days/timepoints will facilitate further exploration of temporal and concentration dependance on ECG parameters.

As all participants are domiciled throughout the trial, there is adequate monitoring for any safety concerns and participants will be continued to be domiciled for 72 hours following the last dose of study intervention. Thus, the sponsor feels the evaluation of a dose regimen to support a TQT study or concentration-QT analysis can be evaluated safely.

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 neurological exams, physical exams, 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.). In addition, scales will be included to evaluate EPS and general well-being.

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 quantify any EPS observed in the study. The BARS is an akathisia rating scale with objective and subjective measures and an overall rating from 0 to 5. A score of 0 presents no evidence for akathisia, a score of 3 is moderate akathisia and a score of 5 is severe akathisia. The AIMS evaluates 12 items and uses a 5-point scale to assess abnormal movement in 3 areas (orofacial, extremities, trunk). The SAS evaluates 10 items and uses a 5-point scale to measure symptoms of parkinsonism or parkinsonian side effects (including rigidity, tremor, akinesia, and salivation).

In case moderate EPS symptoms in an individual participant persist, the dose will not be further up titrated for this participant. Participants with severe EPS symptoms will be discontinued if not attenuated with dose reduction, dose titration and/or medical management.

The BPRS rating scale will be used to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behavior in a range of psychotic and affective symptoms in participants with schizophrenia. The BPRS has been used in clinical research as a tool to measure treatment effects and are effective scales to monitor the general well-being of the psychiatric patients. The BPRS consists of 18 symptom constructs and takes 20 to 30 minutes for the interview and scoring. The rater should enter a number ranging from 1 (not present) to 7 (extremely severe). Zero is entered if the item is not assessed. Participants who experience severe psychosis during the study will be discontinued and referred for additional treatment as indicated.

4.2.1.3 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK of MK-8189. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to derive the PK parameter values AUC0-24, Cmax, Tmax, C24, CL/F, Vz/F, and apparent t1/2.

4.2.1.4 Pharmacodynamic Endpoints

An exploratory objective of this trial is to evaluate effects of a supra-therapeutic dose of MK-8189 on QTc interval in participants with schizophrenia. The potential effect of a drug on cardiac repolarization can be measured as prolongation of the QT interval on ECG recordings. There is, in general, a qualitative relationship between substantial QT prolongation and the risk of TdP. The rationale for the endpoint is thus to demonstrate that MK-8189 does not meaningfully prolong (i.e. >10 msec) the QTc interval.

In Panel C, electrocardiogram data (eg, QT, QRS, RR and PR intervals) will be obtained with a digital Holter device on study days specified in the SoA. A 24-hour Holter will also be conducted on Day -1 such that ECG data can be extracted at timepoints time-matched to post-dose assessments as specified in the SoA.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

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

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

In addition to studying variation across the human genome CYP2C9 will specifically be investigated for association with the PK and PD endpoints 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.

4.2.1.6 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

As the safety and tolerability profile is under continued evaluation and limited data is available at higher doses of MK-8189, a placebo-control will be included in this trial to ensure objective assessment of AEs. A placebo arm is also required to support the concentration-QTc analysis and helps to avoid false positive and false negative results; in some instances study conditions have been found to prolong or shorten QT and placebo-correction is required to determine the true effect of the drug.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

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

4.3 Justification for Dose

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 8.11.6.

4.3.1 Starting Dose for This Study

In Panel A, A-1 and C, the starting dose will be MK-8189 48 mg/placebo. A starting dose of 24 mg/placebo was well tolerated in participants with schizophrenia in P011 (Section 2.2.3) Multiple doses of 48 mg (3 consecutive days) have been evaluated in participants with schizophrenia in P007, a multiple ascending dose study. In P007, participants were titrated from 8 mg to 48 mg. There were no clear trends for dose related increases in specific AEs and the 48 mg dose was found to be generally well tolerated. The majority of AEs were mild to moderate in severity. Adverse events (n, %) occurring in more than one participant were dizziness (3, 27%), nausea (2, 18%) and anxiety (2, 18%). One of the AEs of anxiety was considered severe and unrelated to study intervention. The AE began one day after the last dose of MK-8189 and resolved within the 3 days. Though this starting dose is 2-fold previously explored, enzyme occupancy of [redacted] These data support the exploration of a 48 mg starting dose in the current protocol. Panel C will only be conducted if the starting dose of 48 mg in Panel A is generally well tolerated.

Preliminary blinded data from Panel A demonstrated good tolerability of MK-8189 48 mg/placebo administered on Day 1 and MK-8189 60 mg/placebo administered on Day 2. There were no deaths or SAEs. Four of the 11 participants reported 5 AEs of mild severity. The following treatment-related AEs (duration) were reported; discomfort (3 days), leg tremor (2.5 weeks) and headache (2 days). There were no trends for clinical meaningful changes in safety laboratory values, VS, or ECGs.

4.3.2 Maximum Dose/Exposure for This Study

The highest dose evaluated in this study will be 80 mg which will be administered for one day. In the current protocol, a single dose of 60 mg was found to be well tolerated as described above in Section 4.3.1. Previously the highest dose evaluated in participants with schizophrenia was 48 mg which was found to be generally well tolerated as described in Section 4.3.1 above. In healthy participants the highest dose evaluated was 72 mg/placebo (n=8) in P016 (see section 2.2.3.6). Data from P016 are preliminary and blinded. In P016, poorer tolerability was observed in some participants at the 48 mg dose such that 4 of 12 participants on MK-8189/placebo did not dose escalate above 48 mg). The tolerability issues may have been due to the rapid titration above 24 mg/placebo in Protocol 016. Of the 8 participants that dose escalated to 72 mg/placebo, 5 reported AEs. The majority of AEs were mild in severity. Adverse events included: nausea (n=2), nightmare (n=1), insomnia (n=1), tremor in legs (n=1), muscle twitches (n=1), dystonia (n=1), staring (n=1), decreased appetite (n=1), headache (n=2), xerostomia (n=1), hot flashes (n=1), closed eye hallucination (n=1), pyrosis (n=1), muscle spasms (n=1), emotional instability (n=1), globus pharynges (n=1), hoarseness (n=1), akathisia (n=1). As all AEs are monitorable and reversible, escalating to 80 mg under domiciled conditions where participants are closely supervised is supported.

Moreover, across the multiple ascending dose studies (P003, P007 and P011), there was no dose relationship for specific AEs, including akathisia, somnolence, anxiety, nausea and vomiting.

The 80 mg dose was previously predicted to provide exposures 2-fold the high clinical exposure scenario (the highest possible clinical dose of MK-8189 coadministered with a strong CYP3A inhibitor) and support a concentration -QTc analysis that could negate the need for a much larger TQT study in patients. However, preliminary PK data from Panel A following a 60-mg dose of MK-8189 suggest that sufficient exposures may not be achieved following an 80-mg dose. However, exposures following an 80 mg, or lower dose if 80 mg is not generally well tolerated in Panel A-1, may be sufficient to support an integrated waiver assessment per ICH E14 &S7B Q&A [European Medicines Agency 2022].

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The predicted exposure at 80 mg is 71.5 µM·hr and the margin to the AUC_{0-24} for an 80 mg dose, as derived from the 6-Week and chronic toxicology studies, would be 5-12X and ~2 fold, respectively, further supporting evaluation of this supratherapeutic dose. Brief summaries of the 6-Week and chronic toxicology studies supporting dose escalation are provided below:

In the 6-Week rat study, doses of 25, 50 and 1000 mg/kg/day of MK-8189 were evaluated. There were no adverse findings in the study; therefore, the no observed adverse effect level (NOAEL) was 1000 mg/kg/day (12-fold in females (AUC_{0-24hr} = 822 µM·hour) and 9-fold in males (AUC_{0-24hr} = 653 µM·hour) over the predicted supratherapeutic exposure of 71.5 µM·hr at the 80 mg dose). The functional observational battery (FOB) evaluation conducted on Study Day 1 showed findings at all dose levels that consisted of non dose-dependent decreases in the mean number of line crosses and rears, and very slight, dose-dependent

decreases in mean body temperature. In addition, an absence of motor activity (akinesis) was noted in 1 of the 6 high-dose animals tested. Collectively, these observations are consistent with mild sedation. Importantly, these animals retained normal ability to respond to external stimuli as evidenced by normal responses to the noise, touch and approach stimuli. These findings were considered transient as they were not present before the subsequent dose on Study Day 2.

In the 6-Week monkey study, doses of 10, 30 and 300 mg/kg/day were administered. Pharmacologically-mediated physical signs were observed across all dose groups and consisted of somnolence, increased/decreased activity, unsteady gait, increased licking/chewing/chomping motion, vocalization, intermitted recumbency, intermitted whole body trembling, and/or salivation. These physical signs were considered transient, reversible and consistent with the expected pharmacology of PDE10A inhibition. The NOAEL in this study was 300 mg/kg/day ($AUC_{0\text{-}24hour}$ = 333 μM·hour) providing an exposure margin of 5 fold over the predicted supratherapeutic exposure of 71.5 μM·hr at the 80 mg dose.

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 (study week 13 and study 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 ($AUC_{0\text{-}24hr}$ = 130 μM·hr), providing an exposure margin of 2-fold over the predicted supratherapeutic exposure of 71.5 μM·hr at the 80 mg dose.

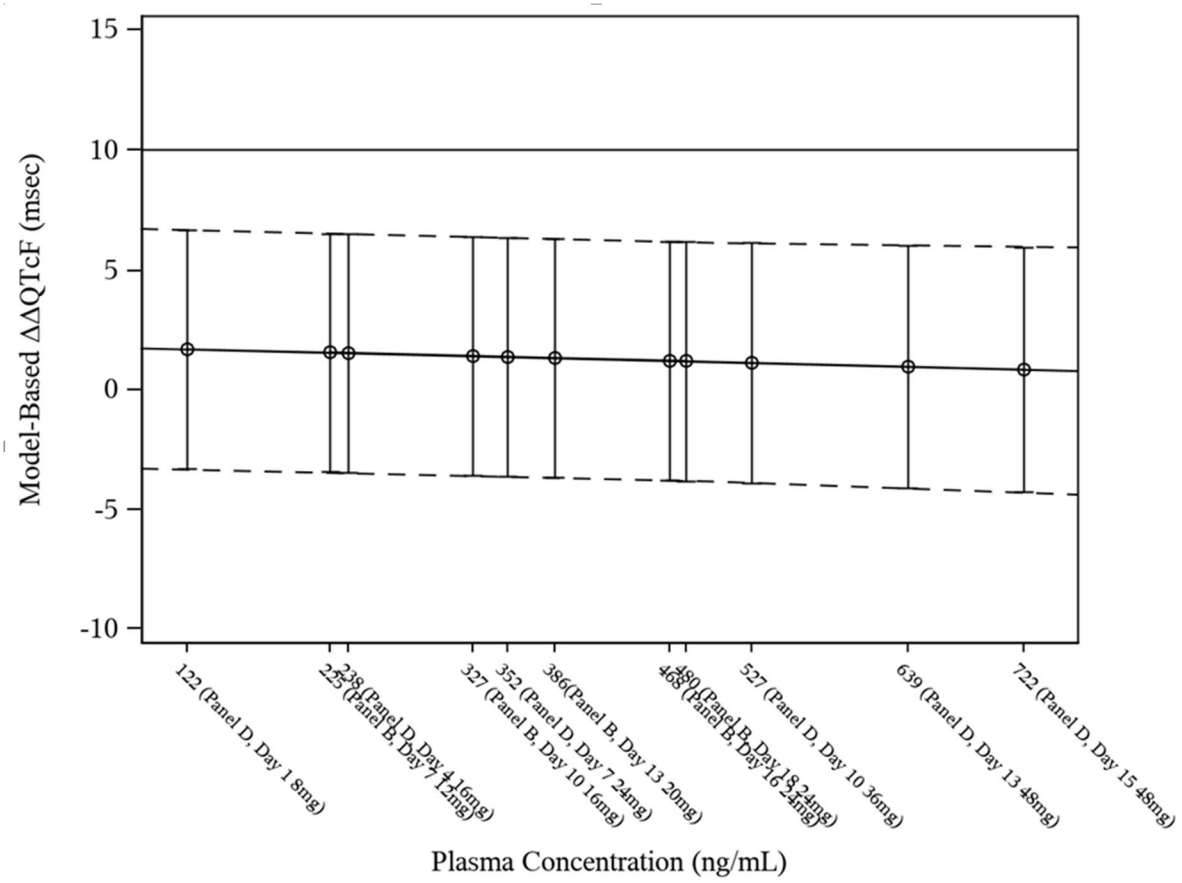
In the 9 month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK 8189 were administered. Similar to the 6-Week study, pharmacologically-mediated transient and reversible physical signs were observed in all dose groups in the study. In addition, beginning in Study Week 8 of this study, reversible physical signs of uncoordinated movements were observed down to the low-dose level. Due to the severity of the uncoordinated movements, the low-dose level had to be lowered (30 to 3 mg/kg/day) to increase tolerability of the test article. Based on these findings, the NOAEL for physical signs was <3 mg/kg/day. 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 ($AUC_{0\text{-}24hr}$ = 170 μM·hr), providing a 2-fold over the predicted supratherapeutic exposure of 71.5 μM·hr at the 80 mg dose.

The effects of MK-8189 on measures of cardiac conduction and repolarization were assessed in both in vitro (hERG current [IKr] evaluation) and in vivo (anesthetized guinea pigs and conscious telemetered monkey models). MK-8189 inhibited hERG current with an IC50 value of 81.9 μM, providing large margins (546-fold) to the projected median unbound Cmax at the supratherapeutic dose of 80 mg in humans (0.15 μM). In an anesthetized guinea pig study, MK-8189 had no effects on HR and ECG parameters. Average peak plasma concentrations of MK 8189 measured during the 20 min infusions of 10, 30 and 60 mg/kg were 56, 150 and 236 μM, respectively. Thus, the NOEL/NOAEL in this study was 236 μM, providing an exposure margin of ~63-fold relative to the projected clinical C_{max} at the 80 mg dose of 3.75 μM. In anesthetized rhesus monkeys, MK-8189 had no effect on CV parameters during rising IV doses up to a 27 μM plasma concentration (~7-fold above the projected clinical C_{max} at 80 mg of 3.75 μM).

In a telemetry study in monkeys, single oral doses of 2, 5, and 20 mg/kg were evaluated and test article-related dose-independent increases in HR, blood pressure (BP) and the rate-corrected QT interval were observed. In a second study at lower oral doses of 0.03, 0.1 and 0.3 mg/kg, there were no test article-related effects. Thus, the no-observed effect level was a single oral dose of 0.3 mg/kg (projected Cmax value of ~0.16 µM, estimated from a 6-week toxicity study [<1- fold of the projected clinical Cmax at 80 mg of 3.75 µM]). A number of studies were conducted to determine the underlying cause (see MK 8189 IB for additional details). The general conclusion from these studies was that increases in HR, BP and QT interval likely occur due to a stress induced release of epinephrine subsequent to PDE10A target engagement in conscious rhesus monkeys and therefore, these changes in QT, HR and BP are not relevant to humans.

Furthermore, a concentration-QTc analysis was conducted in P007 and as shown in Figure 4 there is no evidence for a relationship between concentration and QTc at MK 8189 exposures achieved with the 48 mg dose. Therefore, preclinical and clinical data support dose escalation to 80 mg in the current study. In addition, during the study safety and tolerability will be carefully assessed. Dose escalation may be stopped within an individual or the study based on tolerability.

Figure 4 Predicted Mean ΔΔQTcF Versus the Observed Geometric Mean Cmax for Each Dose Level Along With 90% Confidence Band



4.3.3 Rationale for Dose Interval and Study Design

MK-8189 is formulated as a controlled-release tablet intended for QD administration. To date most multiple ascending dose studies have been conducted as a within participant titration. The within participant titration was introduced based on results from the single-ascending dose trial (P001) in healthy participants, where following treatment with the 3-mg and 6-mg IR formulation, dystonia was observed around the time of peak MK-8189 concentration (See IB for details). One hypothesis for the observed acute dystonia is that the high MK-8189 IR formulation peak to trough ratio led to rapid-cycling of MK-8189 on and off the target enzyme, PDE10A. In addition to successfully reducing the peak-to-trough ratio through development of the CR formulation (4 with the IR vs 1.3 with the CR), a titration approach in the target patient population was implemented in the multiple ascending dose studies (P003 and P007) and the POC (P005) study, which significantly reduced the rate of observed EPS and dystonia and permitted evaluation of doses and exposures significantly greater than could be achieved tolerably with the IR formulation. Of note, in P007, where the highest likely clinical dose of 24 mg as well as supratherapeutic doses up to 48 mg have been evaluated, no MK-8189 -related dystonia has been reported in healthy participants or participants with schizophrenia. The peak concentration values at the 24-mg dose are ~1.7-fold those observed following 6 mg of the IR formulation, suggesting the absolute concentration is not a driver of dystonia. Across P003 and P007 the starting dose of the CR formulation has increased from 2 mg to 4 mg to 8 mg without an increase in the incidence in dystonia. Furthermore, Part 1 of P011 was conducted to evaluate the need for titration in participants with schizophrenia. As described in section 2.2.3 (preliminary and blinded data), initiating dosing at 24 mg/placebo was generally well tolerated in participants with schizophrenia. In this panel of participants, no AEs of EPS were reported.

As this study continues to explore safety and tolerability of supratherapeutic doses to support the evaluation of concentration-QT effect, a titration approach will be implemented, though it will be more aggressive than earlier studies.

In Panel A and Panel A-1 in participants with schizophrenia, participants will initiate dosing at MK-8189 48 mg mg/placebo (Day 1) and escalate to MK-8189 60 mg/placebo in Panel A (Day 2) and 80 mg in Panel A-1 (Day 2). If generally well tolerated, one of these regimens would allow for rapid attainment of the necessary exposures to satisfy a TQT study and minimize MK-8189 exposure and shorten the duration of the TQT study. Additionally, if well tolerated, Panel C will be conducted to support an integrated (non-clinical and clinical) concentration-QT analysis per ICH E14 & S7B Q&A [European Medicines Agency 2022] where doses will be escalated to MK-8189 80 mg/Placebo to potentially negate the need for a TQT study.

This study should define the highest tolerated dose that may be explored in a TQT study.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant

completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

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

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

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are 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.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Is in good health based on medical history, physical examination, VS measurements, and ECGs performed at the screening visit and/or prior to randomization. The assessment prior to randomization is based on the mean of triplicate measures. Note: TheQTcF-duration must be ≤450 msec, the QRS duration <120 msec and the PR interval <200 msec. Repeat 12-lead safety ECGs may be performed in participants whose parameters are, per investigator discretion, minimally outside the designated range.

2. Have a normal resting blood pressure (systolic blood pressure is ≥90 mm Hg and ≤140 mmHg; diastolic blood pressure is ≥60 mmHg and ≤90 mmHg) and normal resting heart rate (≥45 beats per minute [bpm] and ≤100 bpm) in the supine position at the pre-trial (screening) visit and/or prior to randomization. Repeat evaluations may be done if the values for a participant are, per investigator discretion, minimally outside the designated range. The assessment prior to randomization is based on the mean of the triplicate measures. Participants may be included if values are outside the normal range but considered not clinically significant per investigator discretion.

3. Is in good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

4. Have a Body Mass Index (BMI) $\geq$ 18.5 and $\leq$ 40 kg/m^2, inclusive, and total body weight of $\geq$ 50 kg (110 lbs) at the screening visit. See Section 8.3.2 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

5. Participants with hypothyroidism, diabetes, high blood pressure, 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 3 months prior to screening and there are no expected changes in co-medication during the study.

6. Has regular bowel movements and, in the opinion of the investigator, no clinically significant diarrhea or constipation.

7. Meets diagnostic criteria for schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria with the onset of the first episode being no less than 2 years prior to screening and monotherapy with antipsychotics for treatment should be indicated.

8. Has a total Brief Psychiatric Rating Scale (BPRS) score of < 48 with a BPRS score < 4 for #10 (hostility) and #14 (uncooperativeness) at the screening visit.

9. Is in the non-acute phase of their illness and clinically stable for 3 months prior to screening as demonstrated by:

    a. no clinically significant change in dose of prescribed antipsychotic medication, or clinically significant change in antipsychotic medication to treat symptoms of schizophrenia for two months prior to screening;

    b. no increase in level of psychiatric care due to worsening of symptoms of schizophrenia for three months prior to screening.

    Note: participants that are stable but not currently taking antipsychotic medications are eligible.

10. Has a history of receiving and tolerating antipsychotic medication within the usual dose range employed for schizophrenia.

11. Participant is able to discontinue the use of all antipsychotic medication at least 5 days or 3 half-lives (whichever is longer) prior to Day -1 and during the study period

Demographics

12. Is male or female, from 18 years to 55 years of age inclusive, at the time of providing informed consent. An attempt will be made to enroll approximately 40% of female participants.

Female Participants

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 (urine or serum as required by local regulations) within 72 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 and Appendix 2.

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 has provided documented informed consent for the study. The participant may also provide consent for future biomedical research (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 meets any of the following criteria:

Medical Conditions

1. Has an untreated or uncompensated clinically significant renal, endocrine, hepatic, respiratory, gastrointestinal, psychiatric, neurologic, cardiovascular, hematological, immunological or cerebrovascular disease, malignance, allergic disease or other chronic and/or degenerative process at screening.

2. Has any clinically significant abnormal laboratory, VS, physical examination, or 12-lead safety ECG findings at screening or changes from baseline that may interfere with the interpretation of PK or safety parameters or, in the opinion of the investigator, would make the participant inappropriate for entry into this study.

3. Is at imminent risk of self-harm, based on clinical interview and responses 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 or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.

4. Is a WOCBP who has a positive serum pregnancy test at the screening visit or a urine pregnancy test within 72 hours before the first dose of study intervention. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5. Has a history of cancer (malignancy).

   Exceptions: (1) Participants with adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the study; (2) Participants with other malignancies which have been successfully treated ≥10 years prior to the prestudy (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the prestudy (screening) visit (except those cancers identified at the beginning of this exclusion criteria); or (3) Participants, who, in the

opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study

6. Has evidence or history of a primary DSM-5 axis I psychiatric diagnosis other than schizophrenia or schizoaffective disorder per the allowed DSM-5 criteria within one month of screening.

7. Has evidence or history of mental retardation, borderline personality disorder, or organic brain syndrome.

8. Has a history of neuroleptic malignant syndrome or moderate to severe tardive dyskinesia.

9. Has a substance-induced psychotic disorder or behavioral disturbance thought to be due to substance abuse.

10. Has a DSM-5 defined substance use disorder (excluding nicotine and caffeine) within 3 months of screening.

11. Has a history of seizure disorder beyond childhood or is receiving treatment with any anticonvulsant to prevent seizures.

12. Has a clinically significant history or presence of sick sinus syndrome, first, second, or third degree AV block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QTc interval, or conduction abnormalities.

13. The participant meets any of the following cardiac parameters: a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), uncorrected hypokalemia or hypomagnesemia, or is taking concomitant medications that prolong the QT/QTc interval. Abnormal serum calcium at Screening or prior to dosing.

14. Has history of repeated or frequent syncope, vasovagal episodes, or epileptic seizures.

15. Has a family history of cardiac sudden death

16. Has a history of any illness that, in the opinion of the study investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

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

18. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

19. 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

20. Has received or is currently receiving treatment with clozapine (eg, for treatment of schizophrenia) for any length of time. Has received treatment with monoamine oxidase inhibitors within 3 months of screening or cariprazine within 2 months of screening.

21. Is unable to be washed off their parenteral depot antipsychotic medication prior to screening or requires a dose of a parenteral depot antipsychotic medication during the study.

22. Is unable to refrain from the use of co-medication that is a moderate or strong inhibitor or inducer of CYP3A or moderate or strong inducer of CYP2C9 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. (see Section 6.5).

23. Has received any nonlive vaccine starting from 14 days prior to study intervention or is scheduled to receive any nonlive vaccine through 30 days following study intervention.

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

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

Not applicable.

Other Exclusions

25. Under the age of legal consent.

26. Is a smoker that does not agree to follow the smoking restrictions as defined by the CRU.

27. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

28. 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.

29. 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 concomitant medications permitted at the discretion of the PI and Sponsor) prior to randomization.

30. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

31. 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 study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

During the study participants will fast from all food and drinks, except water, for at least 8 hours before study and during intervention administration. Participants will fast from all food and drinks, except water, between study intervention administration until 1 hour post dose. Meals and snack(s) will be provided by the investigator at time points indicated in the SoA. Participants will fast from all food and drinks, except water, between meals and snacks. For multicenter studies the meal content should be consistent within a given clinical site. Meals and snacks will be served after any coinciding Holter and/or PK procedure.

The caloric content and composition of meals will be the same. After the 24-hour postdose procedures have been completed in Panels A and A-1, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during study intervention administration. Water will be restricted 1 hour before and 1 hour after study intervention administration.

Meal and water restrictions on Day -1 will be time-matched to those timepoints on 24-hour Holter/PK days when treatment is administered. Similarly, during intermediate days and the days following the last scheduled dose, meal and water restrictions will be time-matched to 24-hour Holter/PK days when treatment is administered.

Each study intervention administration will need to be taken with water. Water will be restricted 1 hour before and 1 hour after study intervention administration.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention, throughout the study and until the poststudy visit.

On full PK sampling days (ie, Panels A and A-1 Days 1-2, Panel C Days 1-3), participants will refrain from the consumption of all fruit juices 24 hours before study intervention administration and during the entire day.

On all other days during the study, the consumption of all fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the prestudy and poststudy visits. On full PK sampling days (ie, Panel A and A-1 Days 1-2) and 24-hour Holter monitoring days (ie, Panel C Days 1-3), participants will be permitted to consume approximately 2 units of caffeinated beverages or xanthine-containing products only between 1 hour and 2 hours post dose. Otherwise, participants will refrain from consumption of such products 8 hours prior to study drug administration until the 24- hour postdose ECG/PK assessment is complete.

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits. During the in-house period, consumption of alcohol is not allowed. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU will be followed during the study.

5.3.3 Activity Restrictions

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

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

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

6 STUDY INTERVENTION

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

Clinical supplies [study intervention(s) provided by the Sponsor] will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel A Active	Experimental	MK-8189	Drug	Tablet	12 mg	48 mg 60 mg	Oral	Panel A	Test Product	IMP	Provided centrally
Panel A-1 Active	Experimental	MK-8189	Drug	Tablet	12 mg 4 mg	48 mg 80 mg	Oral	Panel A-1	Test Product	IMP	Provided centrally
Panel C Active	Experimental	MK-8189	Drug	Tablet	12 mg 4 mg	48 mg 80 mg	Oral	Panel C	Test Product	IMP	Provided centrally
Placebo	Placebo Comparator	MK-8189	Drug	Tablet	0 mg	All dosage levels	Oral	All Panels	Placebo	IMP	Provided centrally

IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.

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

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

The sample allocation schedules are provided in Table 2 (Panel A), Table 3 (Panel A-1), Table 4 (Panel C).

Table 2 Panel A Schizophrenic Sample Allocation Schedule

n[a]	Day 1	Day 2
9	48 mg	60 mg
3	PBO	PBO

[a] An attempt will be made to enroll approximately 40% female participants

Note: The allocation scheduled will be stratified to females and males. Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range.

Table 3 Panel A-1 Schizophrenic Sample Allocation Schedule

n[a]	Day 1	Day 2
9	48 mg	80 mg
3	PBO	PBO

[a] An attempt will be made to enroll approximately 40% female participants

Note: The allocation scheduled will be stratified to females and males. Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range.

Table 4 Panel C Schizophrenic Sample Allocation Schedule

n[a]	Day 1	Day 2	Day 3
18	48 mg	48 mg	80 mg
12	PBO	PBO	PBO

a An attempt will be made to enroll approximately 40% female participants

Note: The allocation scheduled will be stratified to females and males. Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range.

6.3.2 Stratification

The allocation schedules will be stratified to females and males. Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range to attempt to ensure approximately 40% of females.

6.3.3 Blinding

A double-blinding technique will be used. MK-8189 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant and the investigator who is involved in the study intervention administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

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

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

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

6.5 Concomitant Therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Paracetamol/acetaminophen (up to 4 g per day) and ibuprofen (up to 1.2g per day) and antacids (eg, magnesium hydroxide) may be used for minor ailments without prior consultation with the Sponsor.

For participants with schizophrenia, medications to treat mild chronic conditions such as hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other mild medical conditions are allowed during the study if the prescribed dose and regimen of medication is stable for at least three months prior to screening and there are no expected changes in co-medication during the study. Moderate to strong inhibitors or inducers of CYP3A and moderate or strong inducers of CYP2C9 are not allowed.

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

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

Exception: COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

Investigational COVID-19 vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed. The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

For the treatment of EPS, such as acute dystonia, all participants may be treated with an anticholinergic. If the symptoms are unresponsive to anticholinergic treatment or not recommended based on a participant's medical history/concomitant medication, a benzodiazepine can be used.

In case the participant presents with signs of akathisia without signs of dystonia, the participant can be treated with a β-adrenergic blocker. If symptoms do not disappear with the β-adrenergic blocker, treatment with an anticholinergic may be used. An anticholinergic may be used as first-line treatment in the case that a β-adrenergic blocker is not a preferred treatment based on a participant's medical history and/or concomitant medication.

Anticholinergics benzodiazepines and β-adrenergic blockers are often used in the treatment of EPS and are considered standard practice. Oral anticholinergic treatment is also used as concomitant medication to prevent EPS symptom with antipsychotic medication.

Participants with schizophrenia will be washed off from their antipsychotic treatment. The duration of washout period should be at least 5 days or cover at least 3 half-lives of the drug (whichever is longer) prior to Day -1 assessments (this includes any rescue medication given during the washout period). During the washout and treatment period, a benzodiazepine and zolpidem may be used to treat withdrawal symptoms. The drugs indicated above should not be moderate or strong inhibitors or inducers of CYP3A or moderate or strong inducers of CYP2C9 (see Section 6.5 for further details), thus no effect on the PK of MK-8189 would be expected during co-administration.

6.6 Dose Modification (Escalation/Titration/Other)

If, as judged by the Sponsor and/or investigator, the safety and tolerability data do not justify dose titration, the dose will not be increased as planned. Instead, 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
- Dosing may be stopped

If appropriate medical care necessitates dosing to be stopped or a lower dose given, the investigator may do so without consultation with the Sponsor.

Participant discontinuation criteria are outlined in Section 7.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

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

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant 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.
- Participants with severe EPS symptoms will be discontinued if not attenuated with dose reduction, titration, or medical management.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive UDS at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

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 225 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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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 allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 3 months of starting the study. Use of any prescription or nonprescription medication during the washout period should first be discussed between the investigator and Sponsor, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. Note: medications permitted under Section 6.5 of the protocol do not need to be discussed prior to use.

Washout from Antipsychotics:

All participants will be washed out from their antipsychotic medication prior to Day -1 Holter assessment. The washout may start with a down titration of the antipsychotic treatment during the screening phase.

Participants may restart their antipsychotic therapy following completion of the 72 hour post last dose study procedures.

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 8.10.1.

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.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff. Participants will fast from all food and drinks, except water, for at least 8 hours prior to all doses of MK-8189. Approximately 240 mL of water will be provided during study drug administration, but will be restricted 1 hour prior to and 1 hour post dose. Site staff will ensure that participants have swallowed study treatment.

8.1.8.1 Timing of Dose Administration

Participants will be dosed according to the SoA (Section 1.3). MK-8189 Treatment administration will be in the AM at approximately the same time each day (within a 30 minute window) and will occur after an 8-hour overnight fast. Participants will fast from all food and drinks, except water, between study intervention administration and the first scheduled meal. Participants will receive each oral dose of MK-8189/placebo with ~240mL of water.

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 8.11.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal

information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, 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 intensityof the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

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

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

8.1.11 Domiciling

Participants in Panel A and Panel A-1 will be domiciled in the study unit minimally from Day -1 until Day 5 procedures are complete. Participants in Panel C will be domiciled in the study unit minimally from Day -2 until Day 6 procedures are complete.

For any participant who is required to wash off antipsychotic therapy, domiciling will begin on Day -6. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably

calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

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

8.3.1 Physical Examinations

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

Brief directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at prespecified timepoints noted in the SoA (Section 1.3).

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

- Body temperature, heart rate, respiratory rate, and blood pressure will be assessed at prespecified timepoints noted in the SoA (Section 1.3).

- BP and heart rate measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart at the 9 hour post dose equivalent timepoint on Day -1. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

During Panels A-1 and C, orthostatic VS (HR and systolic and diastolic BP) will also be obtained following resting HR and BP measurements. Participants should be supine for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic VS.

8.3.3 Electrocardiograms

Triplicate 12-lead ECG on Day -1 will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals. Refer to Inclusion/Exclusion criteria and Appendix 9 for eligibility assessment and potentially significant findings.

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

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

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the

electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained per the schedule of activities on Day -1. These measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During each treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline (Day -1) 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.

During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

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

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

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

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

24-Hour Holter Assessment

For the entire 24-hour Holter recording duration, participants should not wear metal jewelry such as watches, necklaces, and/or bracelets from the waist up. Participants must also not use electronic devices such as cell phones, computers/laptops, MP3 players, etc. during Holter recording. Holter recording will be turned on approximately 30 minutes prior to trial drug administration. Participants will not be allowed to shower/bath for the duration of the 24-hour Holter assessment.

Holter data will be extracted (in triplicate) and analyzed using automated and semi-automated methods by a blinded core ECG laboratory according to a pre-specified algorithm. To minimize artifacts, participants must rest quietly in a supine position for ~10 minutes prior to the time points specified for extraction. The extraction window will be 10 minutes. No other study assessments or procedures should occur during the resting period.

Holters may be removed and reapplied (same Holter used by the same participant) per the instructions in the Acquisition Guide for Holter-recordings provided by the ECG vendor. Lead placement must be marked anytime electrodes are removed.

See the Acquisition Guide provided by the ECG vendor for specific instructions.

Procedures for transfer, archiving, and review of ECGs will be specified by the ECG vendor.

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.

8.3.6.2 Monitoring for Extrapyramidal Symptoms

The investigator or qualified designee will complete the BARS, AIMS and SAS at times specified in the SoA. Additional assessments at unscheduled times outside of the SoA will be conducted by study staff, as soon as reasonably possible, if it is observed or a participant reports complaints of dystonia and/or akathisia.

8.3.7 Assessment of Neuropsychological Effects

A general (full) Neurological Exam will be performed at the Screening visit, Baseline and prior to discharge. A targeted Neurological Exam will be administered at times specified in the SoA.

A BPRS evaluation will be performed at Screening, Baseline and will also be completed at times specified in the SoA.

The General and Targeted Neurological Exams are contained in Appendix 11.

8.3.8 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

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

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

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

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

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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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)
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

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

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

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

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

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

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

Disease-related Events and/or Disease-related Outcomes not qualifying as AEs or SAEs are not applicable to this study.

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 leading to study discontinuation

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

5. Suicidal ideation, suicidal behavior

6. Moderate or severe depression

7. Moderate or severe mood swings

8. Dystonia

8.4.8 Medical Device and Drug-device Combination Products - PQCs/Malfunctions

Not applicable

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.

Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189

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

8.7 Pharmacodynamics

ECG parameter values are extracted from 24-hour Holter monitoring per the SoA.

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

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. 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.

8.9 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 Screening

Within approximately 6 weeks before intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

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 allocation/randomization since there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Participants with schizophrenia that meet selection criteria for enrollment will participate, up to 12 participants in each of Panels A, and A-1, and up to 30 participants in Panel C. Participants must be washed out from any antipsychotic therapy for at least 5 days or cover at least 3 half-lives of the drug (whichever is longer) prior to Day -1. Participants will report to the CRU on Day -6 to start their washout period. However, if participants are not currently being treated with antipsychotic medications and therefore do not require a washout, they may be domiciled on Day -2 in Panel C, or Day -1 in Panels A and A-1.

On treatment days participants will be dosed once daily with MK-8189/placebo and have procedures completed per the SoA. Participants will remain in the unit through 72 hours post last dose and completion of all procedures and will be discharged at the discretion of the investigator.

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

At any point if a participant discontinues from treatment but continues to be monitored in the study, 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.

8.10.4 Poststudy

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.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the ECG parameter values extracted from the 24-hour Holter collection and time-matched blood samples for MK-8189 are the critical procedures for Panel C.

At any time point, these assessments need to be collected as close to the exact time point as possible. The PK sample should follow immediately after the Holter extraction window is complete. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

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

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

1. Holter ECG assessment (extraction period)
2. 12-Lead Safety ECG
3. Resting Blood Pressure and Heart Rate
4. Blood for MK-8189
5. Neurological exams, C-CSSRS, BPRS, BARS, AIMS, SAS

The following variance in procedure collection times will be permitted.

- PK Collection of samples which are not time-matched to Holter ECG assessments as outlined in Table 6.

Table 6 Pharmacokinetic (Blood) Collection Windows for samples not time-matched to Holter ECG assessments

PK Collection	PK Collection Window
0 to <1 h	5 min
1 to <24 h	15 min
24 to <48 h	1 h
48 to 168 h	2 h
>168 h	24 h

- Predose standard safety evaluations: VS and ECG triplicate measurements on Day -1 time matched to the 9 hour post-dose equivalent timepoint within 1 hour; physical exam within 24 hours and laboratory safety tests within 48 hours prior to dosing.
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam:
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to 168-hours postdose may be obtained within 2 hours of the theoretical sampling time
- Study intervention administration (multiple dose studies only): at 30 minutes.

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

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 panel
- Repeat of a panel at the same dose regimen or more conservative dose regimen.
- Entire period(s) or panel(s) may be omitted
- Decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, divided doses [bid to qd, qd to bid, tid, or vice versa])
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

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

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

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain

additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

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

9 STATISTICAL ANALYSIS PLAN

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).

9.1 Statistical Analysis Plan Summary

Safety: Adverse experiences and discontinuation of study intervention due to adverse events will be tabulated. Separately for each panel, 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). Day -1 or Day -2 readings will serve as baseline for laboratory parameters. Day -1 9-hour reading will serve as time-matched baseline for the corresponding post-dose 12-lead ECG and vital sign readings.

Summary statistics and plots will be generated for BPRS, BARS, AIMS, SAS, as well as for change from baseline. The difference from baseline will be computed on the original scale (raw change from baseline). Responses to the C-SSRS will be listed. 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).

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

The objectives are listed in section 3.0**.**

9.4 Analysis Endpoints

Primary Endpoints

Safety endpoints will include adverse experiences and discontinuation of study intervention due to adverse events.

Exploratory Endpoints

Safety: Laboratory safety tests, 12-lead ECGs, and VS. Baseline is defined as Day -1 or Day -2 readings for laboratory safety tests. Day-1 9-hour reading will serve as time-matched baseline for the corresponding postdose 12-lead ECG and vital sign readings.

BPRS, BARS, AIMS, 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).

PK variables: AUC0-24, Cmax, C24, AUC0-inf, Tmax, CL/F, Vz/F, and apparent t1/2.

Cardiodynamics (Panel C only): QTc change from baseline (Holter ECGs), HR, RR interval, PR interval, and QRS duration. U and T wave morphology.

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 major protocol deviations. Major 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 and Concentration-QTc analyses.

9.6 Statistical Methods

Safety

Adverse experiences and discontinuation of study intervention due to adverse events will be tabulated.

Separately for each panel, summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and 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). Day -1 or Day -2 readings will serve as baseline for laboratory parameters. Day -1 9-hour reading will serve as time-matched baseline for the corresponding post-dose ECG and vital sign readings.

Summary statistics and plots will be generated for BPRS, BARS, AIMS, SAS as well as for change from baseline. The difference from baseline will be computed on the original scale (raw change from baseline). Responses to the C-SSRS will be listed. 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. The most severe treatment-emergent event within each of three broad categories (suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior) reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it is either newly emerged or is more severe than the most severe event reported to have occurred in the trial-defined pre-treatment reference period. Individual C-SSRS listings will be provided.

Pharmacokinetics

Model-Based PK Summary

Separately for each panel and separately for each PK parameter, individual values of AUC0-24, Cmax, and C24 at each dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose, day (where applicable), and a random effect for subject. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent confidence intervals (CIs) for the least squares means for each dose will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means, and lower and upper limits of these CIs will yield estimates for the population GMs and 95% CIs about the GMs on the original scale.

Descriptive Statistics

For each panel individual values will be listed for each PK parameter by dose and day (where applicable), and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, 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).

Cardiodynamics:

The exploratory objective pertaining to QTc will be evaluated through development of a model describing the relationship between MK-8189 plasma concentrations and QTc change from baseline in participants with schizophrenia (Panel C). Details of the concentration-QTc analysis will be specified in a separate modeling analysis plan (MAP). This MAP will be completed prior to unblinding and database lock. Results of this analysis will be reported separately from the CSR.

9.7 Interim Analyses

No interim analysis is planned.

9.8 Multiplicity

No multiplicity adjustments are needed, as there are no hypotheses.

9.9 Sample Size and Power Calculations

Since there are no hypotheses, no power calculations are provided. For evaluation of the relationship between QTc and plasma concentrations, the number of dose levels being evaluated and the number of participants on each treatment is consistent with those deemed to be adequate in the white paper [Mehrotra, D. V., et al 2017].

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 and 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 7 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- 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.

Table 7 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 CO2	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose [fasting]	Calcium	Alkaline phosphatase	Magnesium
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• FSH (as needed in WONCBP only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable] • Serology [(HIV antibody, HBsAg, and hepatitis C virus antibody			

Laboratory Assessments	Parameters
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.

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity /toxicity

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of 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

Contraceptives allowed during the study include[a]:
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). [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[3, 4]

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

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

7. Retention of Specimens[3, 4]

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a

particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

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

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

Panels A, A-1, and C	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests including serum β-hCG (WOCBP) or serum FSH (WONCBP) and BDS	3	2	1	6	12	72
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	4.5	4.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-8189 Panel A		19		19	4	76
Blood for MK-8189 Panel A-1		19		19	4	76
Blood for MK-8189 Panel C		34		34	4	136
Total Blood Volume per Participant for Panel A[a]						**161 mL**
Total Blood Volume per Participant for Panel A-1[a]						**161 mL**
Total Blood Volume per Participant for Panel C[a]						**221 mL**

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

If criteria diverges from inclusion/exclusion criteria, more conservative criteria should be used.

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave. Baseline is defined as Predose Day 1		

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

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside 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.

10.11 Appendix 11: Neurological Exam

The following assessments are provided as an example of what will be collected at the appropriate time points in the SoA, Section 1.3.

The general (full) neurological exam and targeted neurological exam may be used for patient/subject assessment.

10.11.1 General (Full) Neurological Exam

See SoA, Section 1.3 for specific timepoints.

The **General 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 (eg, "WORLD") backwards.

Note: to avoid learning effects, switch between tests throughout the study

E. Memory: Test registration of 3 objects; then test immediate recall 5 minutes later.

Grade: **NORMAL or IMPAIRED and describe abnormality (for each, A to E, above). Normal performance on Serial 7's is getting to 65 with no more than 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)**

10.11.2 Targeted Neurological Exam

See SoA, Section 1.3 for specific timepoints.

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.

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
ADA	anti drug antibodies
ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIMS	abnormal involuntary movement scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti retroviral therapy
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
BICR	blinded independent central review
bid	twice daily
BMI	body mass index
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
CAC	Clinical Adjudication Committee
CCU	Cardiac care unit
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CF	compact flash
CG	Cockcroft-Gault
CHS	cough hypersensitivity syndrome
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale

Abbreviation	Expanded Term
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
E-R	exposure response
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin

Abbreviation	Expanded Term
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSSB	Hepatic-specific Safety Board
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
iCRO	imaging CRO
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWG	International Working Group
IWRS	integrated web response system
JAPIC-CTI	Japan Pharmaceutical Information Center Clinical Trials Information
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LCQ	Leicester Cough Questionnaire
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Expanded Term
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NCS	not clinically significant
NEAB	noneosinophilic bronchitis
NSCLC	non–small cell lung cancer
NDA	New Drug Application
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PBPK	physiologically-based PK
PCL	Protocol Clarification Letter
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RCC	refractory chronic cough
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale

Abbreviation	Expanded Term
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
siDMC	Standing Internal Data Monitoring Committee
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
SVR12	sustained viral response
TEA	Treatment Eligibility Assessment (form)
Tmax	Time to maximum plasma concentration
TMDD	target-mediated drug disposition
t1/2	half life
UACS	upper airway cough syndrome
UCC	unexplained chronic cough
UDS	urine drug screen
ULN	upper limit of normal
URTI	upper respiratory tract infection
UTN	Universal Trial Number
Vd	volume of distribution
VS	vital signs
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

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