Official Protocol Title:	A Multiple-Dose Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and QTc Effect of MK-8189 in Participants With Schizophrenia and Healthy Participants
NCT number:	NCT03565068
Document Date:	09-SEP-2019

Title Page

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Protocol Title: A multiple-dose clinical study to evaluate the safety, tolerability, pharmacokinetics and QTc effect of MK-8189 in participants with schizophrenia and healthy participants.

Protocol Number: 007-06

Compound Number: MK-8189

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	118,986

Approval Date: 09 September 2019

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Amendment 06	09-Sep-2019	Outdated protocol template language needed to be deleted from the contraception inclusion criteria to fix discrepancies and redundancies with the new language added in Amendment 05.
Amendment 05	15-Aug-2019	Updated Panel D to include 20 participants with schizophrenia, ECG Holter monitoring and an increase to a maximum dose of 48 mg.
Amendment 04	27-Sep-2018	Addition of Panel D to evaluate the safety, tolerability and pharmacokinetics (PK) of MK-8189 as monotherapy at doses up to 36 mg in healthy participants.
Amendment 03	06-Aug-2018	Addition of Panel C to evaluate the safety, tolerability and pharmacokinetics (PK) of MK-8189 as add-on therapy.
Amendment 02	19-Jul-2018	The additional assessments included in Protocol 007 Amendment 02 are to enhance safety monitoring based on consultation with a health authority. Medications permitted during the antipsychotic washout period and trial were added and additional protocol clarifications were made throughout.
Amendment 01	28-Jun-2018	The protocol was amended to allow subjects to begin their washout as an outpatient if the investigator deems it appropriate for a participant, the caffeine consumption restriction was updated on PK/ECG Holter days as it is not considered to impact the QTc/PK analysis or the PK of MK-8189 and Panel B eligibility was updated to include evaluation of the screening laboratory values. Additional changes were included to improve study logistics, clarify protocol language and correct typographical errors.
Original Protocol	17-May-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

Outdated contraception protocol template language needed to be deleted from the inclusion criteria to fix discrepancies and redundancies with the new language added in Amendment 05.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1.2 Panel B, Panel C and Panel D (Participants with Schizophrenia) Inclusion Criteria	The following language was removed from inclusion #24: a. If the participant is a female with reproductive potential, she must demonstrate a serum β-human chorionic gonadotropin (β-hCG) level consistent with the nongravid state at the prestudy (screening) visit and agree to use (and/or have their partner use) 2 acceptable methods of birth control beginning at the prestudy (screening) visit, throughout the study (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of study drug in the last treatment period. Acceptable methods of birth control are defined in Appendix 5. b. If the participant is a postmenopausal female: she is without menses for at least 1 year and has a FSH value in the postmenopausal range upon prestudy (screening) evaluation. c. If the participant is a surgically sterile female: she is status post hysterectomy, oophorectomy or tubal ligation. Note: Information regarding the procedure may be based on the participant's recall of her medical history, and details of the recall must be captured appropriately within the site's source documents.	This section contained language that was discrepant and redundant to the updated contraception language presented in Appendix 5. The contraception language in Appendix 5 is based upon Clinical Trial Facilitation Group (CTFG) recommendations and aligns with TransCelerate Common Protocol Template (CPT) guidelines for contraception which takes into account feedback from health authorities and regulators regarding acceptable contraception requirements.

Section # and Name	Description of Change	Brief Rationale
2.2.2. Preclinical and Clinical Studies	In the Clinical Study summary, the number of discontinuations due to AE in the Phase 1 studies was updated from 8 to 9.	The change reflects the true number of discontinuations throughout the Phase 1 program.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A multiple-dose clinical study to evaluate the safety, tolerability, pharmacokinetics and QTc effect of MK-8189 in participants with schizophrenia and healthy participants.

Short Title: MK-8189 multiple-dose clinical study in participants with schizophrenia and healthy participants.

Acronym: MDCS

Hypotheses, Objectives, and Endpoints:

The following objectives will be evaluated in participants with schizophrenia and healthy participants.

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of rising multiple once-daily oral doses of MK-8189 in participants with schizophrenia, as monotherapy and as add-on therapy, and healthy Japanese and non-Japanese participants	- Adverse experiences, laboratory safety tests, ECGs, and vital signs
Secondary Objectives	Secondary Endpoints
- To estimate the pharmacokinetics for MK-8189 following multiple once-daily oral doses in participants with schizophrenia, as monotherapy and as add-on therapy, and in healthy Japanese and non-Japanese participants	- AUC0-24, Cmax, C24hr, Tmax, CL, Vd and apparent t1/2
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To evaluate the effect of MK-8189 concentrations on QTc interval and other ECG parameters	- QTc, PR and RR intervals, heart rate, QRS duration, T wave morphology, presence of U waves and outlier assessment

- To investigate the relationship between [redacted] genetic polymorphs and the PK and pharmacodynamics of MK-8189. Genetic variation in [redacted] may be analyzed for association with any laboratory or clinical data collected in this study.	- Germline genetic variation in [redacted]
- To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	- Germline genetic variation

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of Schizophrenia
Population	Healthy participants and participants with schizophrenia or schizoaffective disorder
Study Type	Interventional
Intervention Model	Parallel This is a single-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 18 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 64 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use
Active Panel A, Panel B Panel C and Panel D	MK-8189	4 mg	QD	Oral	Panels A, B and C: 1 tablet Days 1-3, 2 tablets Days 4-6, 3 tablets Days 7-9, 4 tablets Days 10-12, 5 tablets Days 13-15, 6 tablets Days 16-18 Panel D: 2 tablets Days 1-3, 4 tablets Day 4-6, 6 tablets Days 7-9, 9 tablets Days 10-12, 12 tablets Days 13-15	Experimental Treatment
Placebo Panel A, Panel B Panel C and Panel D	Placebo	0 mg	QD	Oral	Panels A, B and C: 1 tablet Days 1-3, 2 tablets Days 4-6, 3 tablets Days 7-9, 4 tablets Days 10-12, 5 tablets Days 13-15, 6 tablets Days 16-18 Panel D: 2 tablets Days 1-3, 4 tablets Day 4-6, 6 tablets Days 7-9, 9 tablets Days 10-12, 12 tablets Days 13-15	Placebo Matched to Experimental Treatment

Total Number	2 intervention groups
Duration of Participation	Panel A (healthy Japanese and non-Japanese participants): Each participant will participate in the study for approximately 8 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 4 weeks, each participant will receive assigned intervention for approximately 18 days. After the end of treatment, each participant will be followed for 2 weeks. Panel B and Panel C (participants with schizophrenia; monotherapy and add-on therapy, respectively): Each participant will participate in the study for approximately 8 weeks from the time the participant signs the ICF through the final contact. After a screening phase of approximately 4 weeks (which may include a washout phase (Panel B only) of at least 5 days from the participant's standard of care medication) each participant will receive assigned intervention for approximately 18 days. After the end of treatment, each participant will be followed for 2 weeks. Panel D (participants with schizophrenia; monotherapy): Each participant will participate in the study for approximately 7.5 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 4 weeks (which may include a washout phase of at least 5 days from the participant's standard of care medication), each participant will receive assigned intervention for 15 days. After the end of treatment, each participant will be followed for 2 weeks.

Study Governance Committees:

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

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 13.

1.2 Schema

The study design is depicted in Figure 1, Figure 2, Figure 3 and Figure 4.

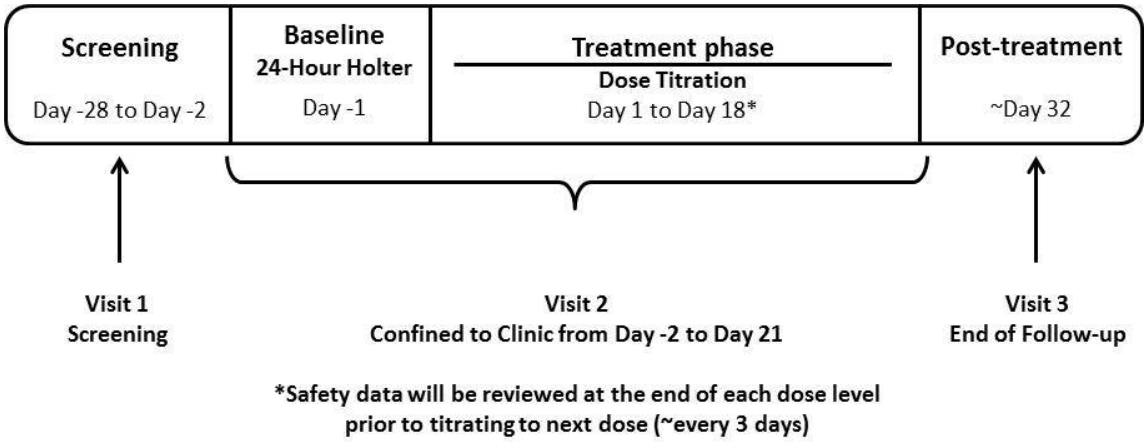


Figure 1 Study Schema Panel A: Healthy Participants (Japanese and non-Japanese)

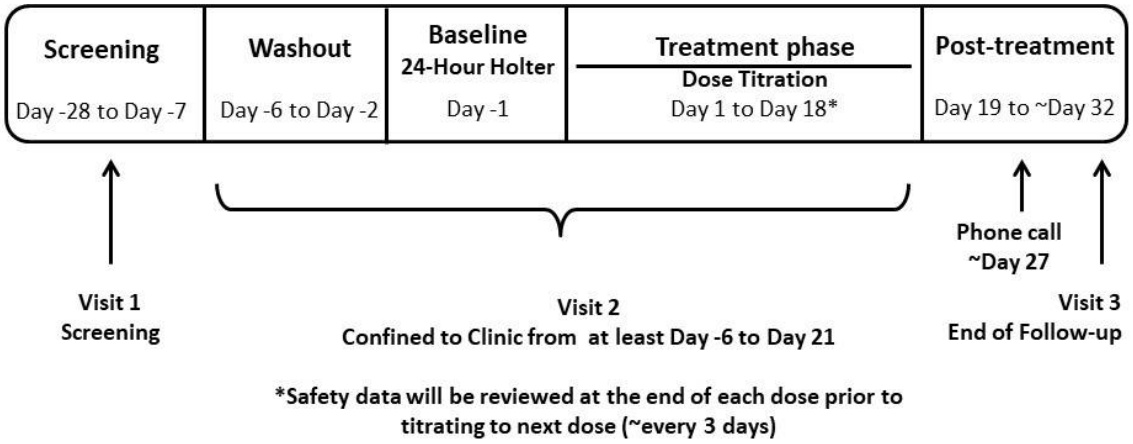


Figure 2 Study Schema Panel B: Participants with Schizophrenia (monotherapy)

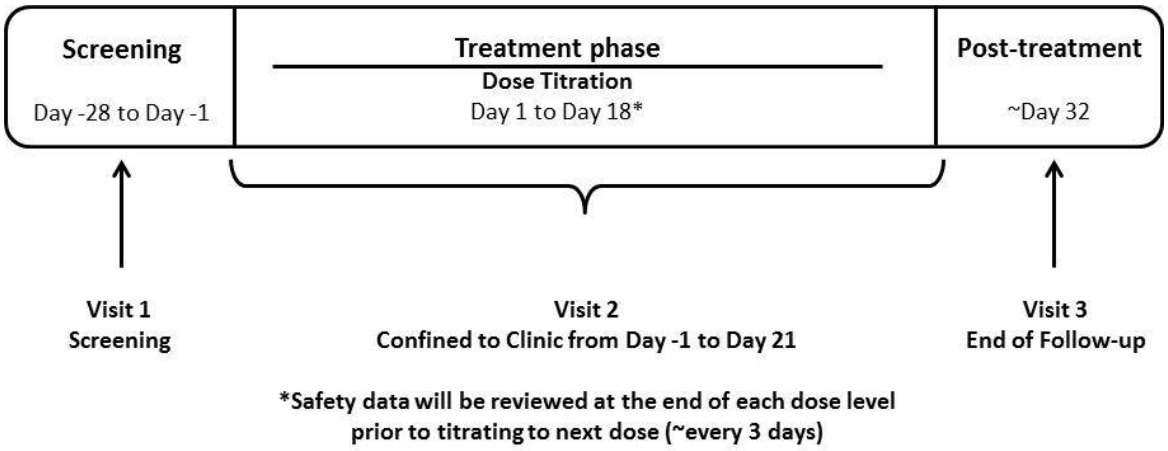


Figure 3 Study Schema Panel C: Participants with Schizophrenia (add-on therapy)

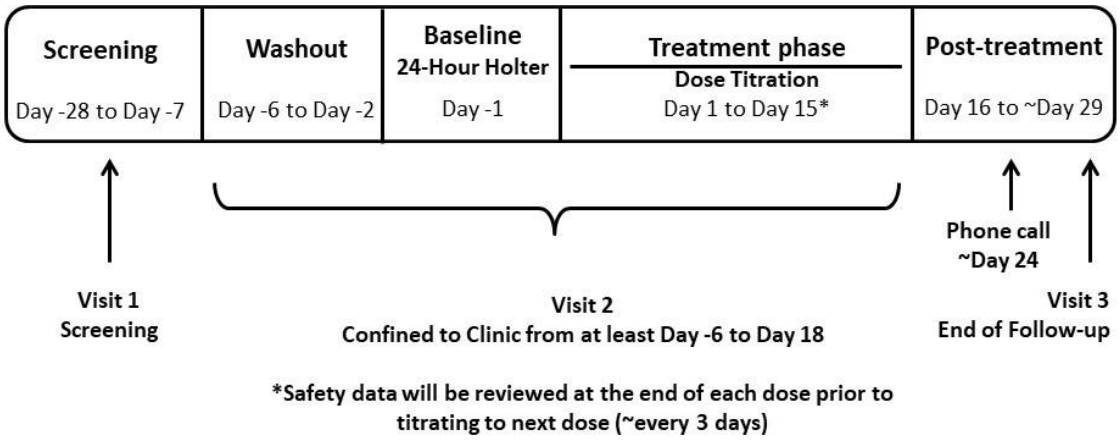


Figure 4 Study Schema Panel D: Participants with Schizophrenia (monotherapy)

1.3 Schedule of Activities (SoA)

Panels A, B and C																													
Study Period	Screening	Wash-out																										Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	~27		
Administrative Procedures																													
Informed Consent	X																												
Informed Consent for Future Biomedical Research	X																												
Inclusion/Exclusion Criteria	X																												Recheck clinical status before 1st dose of study intervention
Participant Identification Card	X																												
Medical History (includes psychiatric history and substance usage)	X																												Substances: drugs, alcohol, tobacco (Panel A only), and caffeine
Prior/Concomitant Medication Review	X----------X																												
Assignment of Screening Number	X																												
Washout from Antipsychotics – Panel B only		X	X																										Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1

Panels A, B and C																												
Study Period	Screening	Wash-out																									Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	~27		
Assignment of Allocation Number (Randomization)					X																							May occur on Day -1 if required for Holter
MK-8189/Placebo Administration					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						See Sections 8.1.9 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Confinement in Clinic[b]		X----------																							X			
Follow-up Phone Call – Panel B only																										X		May occur 5-7 days after discharge.
Safety Procedures																												
Full Physical Exam	X		X^m																						X		X	
Height	X																											
Weight	X		X^m																						X		X	
Full Neurological Exam	X		X^m																									
Targeted Neurological Exam						X			X			X			X			X			X				X		X	Complete predose on dosing days or anytime on non-dosing days; Days 2, 5, 11: Panel A only
Vital Signs (heart rate, blood pressure)[c]	X			X		X			X			X		X	X	X	X	X	X	X	X	X			X		X	Days 2, 5: Panel A only
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X		X			X			X		X	X	X	X	X	X	X	X	X			X		X	Days 2, 5: Panel A only

Panels A, B and C																													
Study Period	Screening	Wash-out																										Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	~27		
Vital Signs (respiratory rate, temperature)	X			X					X						X						X						X	Complete predose; Day 5: Panel A only
12-lead Safety ECG (Panels A and B only)[e]	X				X	X			X			X			X			X			X				X		X	Days 2, 5: Panel A only
24-hour Holter ECG & Extraction (Panels A and B only)[f]				X							X			X			X			X		X	X				
12-lead Safety ECG (Panel C only)[g]	X				X								X			X	X		X	X		X			X		X	
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X																										X	
Urine Pregnancy test (WOCBP only)[h]			X[m]																									
Serum Follicle Stimulating Hormone (FSH; WONCBP only)	X																											
HIV, hepatitis B and C Screen (per site SOP)	X																											
Urine Drug Screen (per site SOP)[i]	X		X																									
Laboratory Safety Tests (hematology, urinalysis, chemistry)	X		X[m]						X						X						X						X	Collected predose after ~8 hour fast
Columbia Suicide Severity Rating Scale (C-SSRS)-Baseline Version	X																											

Panels A, B and C																												
Study Period	Screening	Wash-out																									Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	~27		
Columbia Suicide Severity Rating Scale (C-SSRS)- Since Last Assessment Version[j]			X[m]						X						X				X					X		X	Complete predose
Barnes Akathisia Rating Scale (BARS)[j, k]			X[m]								X						X			X				X			Complete predose
Abnormal Involuntary Movement Scale (AIMS)[j, k]			X[m]								X						X			X				X			Complete predose
Simpson Angus Scale (SAS)[j, k]			X[m]								X						X			X				X			Complete predose
Bond and Lader Visual Analog Scale (VAS)[j]			X[m]		X			X			X			X			X			X				X			Days 2, 5, 11: Panel A only. Complete predose
Brief Psychiatric Rating Scale (BPRS; Panels B and C only)[j]	X		X[m]								X						X			X				X			Complete predose
AE/SAE review	X----------X																											
Biomarkers																												
Blood for Genetic Analysis[n]					X																						Collect predose from enrolled participants only; See Section 8.8	
Pharmacokinetics																												
Blood for Plasma MK-8189 and/or Metabolites assay[l]					X			X			X		X	X		X	X		X	X		X						

a. Meals should be given at approximately the same time every day starting on Day -1 (time-matched to postdose meals) through Day 20. 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. Panel A will be confined minimally from Day -2 through Day 21. Panel B will be confined within a week of starting their antipsychotic washout period through Day 21; minimally subjects will be confined from Day -6 through Day 21. Panel C will be confined minimally from Day -1 through Day 21.
c. Single HR and BP measurements will be obtained at all postdose timepoints. On the following days, specific timepoints are noted:
   - Day -1: Triplicate measurements time- matched to 8 hour post dose vital sign
   - Day 2 and Day 5: 8 hours post-dose (Panel A only)
   - Day 8, Day 11, Day 14 and Day 17: 8 hours post-dose
   - Day 10, Day 12, Day 13, Day 15, Day 16 and Day 18: 10 and 16 hours postdose
d. Orthostatic assessments in HR and BP will follow semi recumbent vital sign assessments. Subjects should be standing for approximately 3 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:
   - Day -1: Time- matched to 8 hour post dose orthostatic vital sign.
   - Day 2 and Day 5: 8 hours post-dose (Panel A only).
   - Day 8, Day 11, Day 14 and Day 17: 8 hours post-dose
   - Day 10, Day 12, Day 13, Day 15, Day 16 and Day 18: 10 and 16 hours postdose
e. For Panels A and B, single12-lead safety ECG measurements will be at all postdose timepoints. On the following days, specific timepoints are noted:
   - Day 1: Triplicate measurements within 2 hours prior to dosing.
   - Day 2 and Day 5: 8 hours post-dose (Panel A only).
   - Day 8, Day 11, Day 14 and Day 17: 8, 10 and 16 hours post-dose
f. For Panels A and B, continuous (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: 2, 6, 8, 10, 12, 16 and 24 hours
   - Day 7, Day 10, Day 13 and Day 16: predose, 2, 6, 8, 10, 12, 16 and 24 hours post-dose.
   - Day 18: 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.
   - If a subject discontinues study treatment at a dose of 12 mg or higher, an attempt should be made to collect 24-hour Holter data through 48 hours following their last dose.
g. For Panel C, triplicate 12-lead safety ECG measurements will be taken 1-2 minutes apart at all timepoints. On the following days, specific timepoints are noted:
   - Day 1: within 2 hours prior to dosing
   - Day 9, Day 12, Day 13, Day 15, Day 16 and Day 18: 8, 10, 16 and 24 hours post-dose
h. In the event the urine pregnancy test is positive or cannot be confirmed negative, a serum pregnancy test will be required.
i. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
j. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.
k. Additional BARS, AIMS and SAS assessments will be conducted when observed or reported complaints of dystonia and/or akathisia occur.
l. MK-8189 plasma PK sample collection (note: when time point coincides with Holter extraction, the PK sample will be collected as soon as possible after Holter extraction but must collected after any vital sign assessments):
   - Panel A and B and C: Day 1 and Day 4: pre-dose.
   - Panel A and B: Day 7, Day 10, Day 13 and Day 16: predose, 2, 6, 8, 10, 12, 16 and 24 hours post-dose
   - Panel C: Day 9, Day 12, Day 15; predose, 2, 6, 8, 10, 12, 16 and 24 hours post-dose.
   - Panel A and B and C: Day 18: 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose
   - Optional sample when signs of dystonia and/or akathisia occur
   - If a subject discontinues study treatment at a dose of 12 mg or higher, an attempt should be made to collect PK samples through 48 hours following their last dose.
   - Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.
m. In Panels A and B, assessments will be done on Day -2. In Panel C, assessments will be done on Day -1.
n. This sample will be drawn for CYP2C9 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 future biomedical research if the participant signs the future biomedical research consent.

Panel D																								
Study Period	Screening	Wash-out																					Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	~24		
Administrative Procedures																									
Informed Consent	X																								
Informed Consent for Future Biomedical Research	X																								
Inclusion/Exclusion Criteria	X																								Recheck clinical status before 1st dose of study intervention
Participant Identification Card	X																								
Medical History (includes psychiatric history and substance usage)	X																								Substances: drugs, alcohol, and caffeine
Prior/Concomitant Medication Review	X----------X																								
Assignment of Screening Number	X																								
Washout from Antipsychotics		X	X																						Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1
Assignment of Allocation Number (Randomization)					X																				May occur on Day -1 if required for Holter
MK-8189/Placebo Administration					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						See Sections 8.1.9 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Confinement in Clinic[b]		X----------X																							
Follow-up Phone Call																							X		

Panel D																								
Study Period	Screening	Wash-out																					Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	~24		
Safety Procedures																									
Full Physical Exam	X		X																			X		X	
Height	X																								
Weight	X		X																			X		X	
Full Neurological Exam	X		X																						
Targeted Neurological Exam[c]						X			X			X			X				X			X		X	
Vital Signs (heart rate, blood pressure)[d]	X			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X		X	
Orthostatic Vital Signs (heart rate, blood pressure)[e]	X			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X		X	
Vital Signs (respiratory rate, temperature)[c]	X			X		X						X			X			X				X		X	
12-lead Safety ECG[f]	X				X	X			X			X			X			X				X		X	
24-hour Holter ECG & Extraction[g]				X	X			X			X			X			X		X	X					
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X																							X	
Urine Pregnancy test (WOCBP only)[h]			X																						
Serum Follicle Stimulating Hormone (FSH; WONCBP only)	X																								
HIV, hepatitis B and C Screen (per site SOP)	X																								

Panel D																									
Study Period	Screening	Wash-out																						Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	~24		
Urine Drug Screen (per site SOP)[i]	X	X																							
Laboratory Safety Tests (hematology, urinalysis, chemistry)[c]	X		X						X				X						X			X		X	Collected after ~8 hour fast
Columbia Suicide Severity Rating Scale (C-SSRS)- Baseline Version	X																								
Columbia Suicide Severity Rating Scale (C-SSRS)- Since Last Assessment Version[c]			X							X						X			X			X		X	
Barnes Akathisia Rating Scale (BARS)[c,]			X						X			X			X				X			X			
Abnormal Involuntary Movement Scale (AIMS) [c, j]			X						X			X			X				X			X			
Simpson Angus Scale (SAS) [c, j]			X						X			X			X				X			X			
Bond and Lader Visual Analog Scale (VAS)[c]			X			X			X			X			X				X			X			
Brief Psychiatric Rating Scale (BPRS)	X		X						X			X			X				X			X			
AE/SAE review	X----------X																								

Panel D																								
Study Period	Screening	Wash-out																					Post-study	Notes
Scheduled Day	Screening	-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	~24		
Biomarkers																									
Blood for Genetic Analysis[m]					X																			Collect predose from enrolled participants only; See Section 8.8
Pharmacokinetics																									
Blood for Plasma MK-8189 and/or Metabolites assay[k]					X			X			X			X			X		X					
Urine for potential MK-8189 and metabolite profiling[l]																			X					

a. Meals should be given at approximately the same time every day starting on Day -1 (time-matched to postdose meals) through Day 17. 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 -1 until Day 18 procedures are complete.
c. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.
d. Single HR and BP measurements will be obtained at all postdose timepoints. On the following days, specific timepoints are noted:
- Day -1: Triplicate measurements time- matched to 8, 10, 16 hours post dose vital sign
- Day 1, Day 2, Day 5, Day 8, Day 11, Day 14: 8 hours post-dose
- Day 3, Day 6, Day 7, Day 9, Day 10, Day 12, Day 13, Day 15 and Day 17: 8, 10 and 16 hours postdose

e. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Subjects should be standing for approximately 3 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:
- Day -1: Time- matched to 8, 10, 16 hours post dose orthostatic vital sign.
- Day 1, Day 2, Day 5, Day 8, Day 11, Day 14: 8 hours post-dose
- Day 3, Day 6, Day 7, Day 9, Day 10, Day 12, Day 13, Day 15 and Day 17: 8, 10 and 16 hours postdose

f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:
- Day 1: Triplicate measurements within 2 hours of dosing
- Day 2, Day 5, Day 8, Day 11, and Day 14: 8, 10, 16 and 24 hours post-dose

g. Continuous (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: 2, 6, 8, 10, 12, 16 and 24 hours
- Day 1, Day 4, Day 7, Day 10 and Day 13: predose, 2, 6, 8, 10, 12, 16 and 24 hours post-dose.
- Day 15: 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.
- If a subject discontinues study treatment at a dose of 16 mg or higher, an attempt should be made to collect 24-hour Holter data through 48 hours following their last dose.

h. In the event the urine pregnancy test is positive or cannot be confirmed negative, a serum pregnancy test will be required.
i. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
j. Additional BARS, AIMS and SAS assessments will be conducted when observed or reported complaints of dystonia and/or akathisia occur.
k. MK-8189 plasma PK sample collection:
- Day 1, Day 4, Day 7, Day 10 and Day 13: predose, 2, 6, 8, 10, 12, 16 and 24 hours post-dose.
- Day 15: 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose
- Optional sample when signs of dystonia and/or akathisia occur.
- If a subject discontinues study treatment at a dose of 16 mg or higher, an attempt should be made to collect PK samples through 48 hours following their last dose.
- Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.

l. Spot collection between 8-12 hr postdose at the 48 mg dose only. Participants should void prior to dose administration.
m. This sample will be drawn for CYP2C9 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 future biomedical research if the participant signs the future biomedical research consent.

2 INTRODUCTION

2.1 Study Rationale

This study will evaluate safety, tolerability and pharmacokinetics (PK) of multiple oral doses of MK-8189, an inhibitor of phosphodiesterase 10A (PDE10A), in healthy participants and participants with schizophrenia at doses that are higher than those explored in the previous multiple-ascending dose study (MK-8189 PN003-06). Initially this protocol was intended to evaluate doses up to and including doses of 24 mg. However, doses up to 24 mg have been generally well tolerated in Panel A and B, and thus this amendment will allow the safety and tolerability assessment of doses up to and including 48 mg. This study will also evaluate the effect of MK-8189 on QTc.

The clinical dose of MK-8189 is currently unknown; however, 12 mg has demonstrated antipsychotic activity in acute exacerbation of schizophrenia and was generally well tolerated. Based on data from the current protocol as well as the potential for increased efficacy at higher doses of MK-8189, doses of MK-8189 as high as 24 mg are being considered for evaluation in Phase 2. Therefore, the current study, which will evaluate doses up to 48 mg of MK-8189 as monotherapy and up to 24 mg of MK-8189 as add-on therapy, would support safety and tolerability margins for doses as high as 24 mg or 16 mg, when given as monotherapy or as adjunct therapy, respectively. Therefore, these data would potentially support dosing in the presence of intrinsic and extrinsic factors which may increase MK-8189 exposure (e.g. CYP3A inhibition). In addition, if titration to supratherapeutic doses is achievable, this trial could support robust characterization of the effect of MK-8189 on QTc, which would depend on determination of the final clinical dose. Inclusion of healthy Japanese subjects will support the global clinical development in Japan.

It is recognized that an undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization leading to increased risk of development of life-threatening cardiac arrhythmias such as Torsade de Pointes (TdP) and possibly other ventricular tachyarrhythmias. 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 current trial will evaluate in a rigorous manner the impact of administration of MK-8189 on the QTc interval, to determine the risk of cardiac repolarization prolongation. While MK-8189 data to date do not suggest a QT prolongation risk, in fact, many antipsychotics are known to prolong QT. As MK-8189 is expected to be used as adjunct therapy, the QTc effect of MK-8189 will be an important assessment in the present study.

2.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-8189.

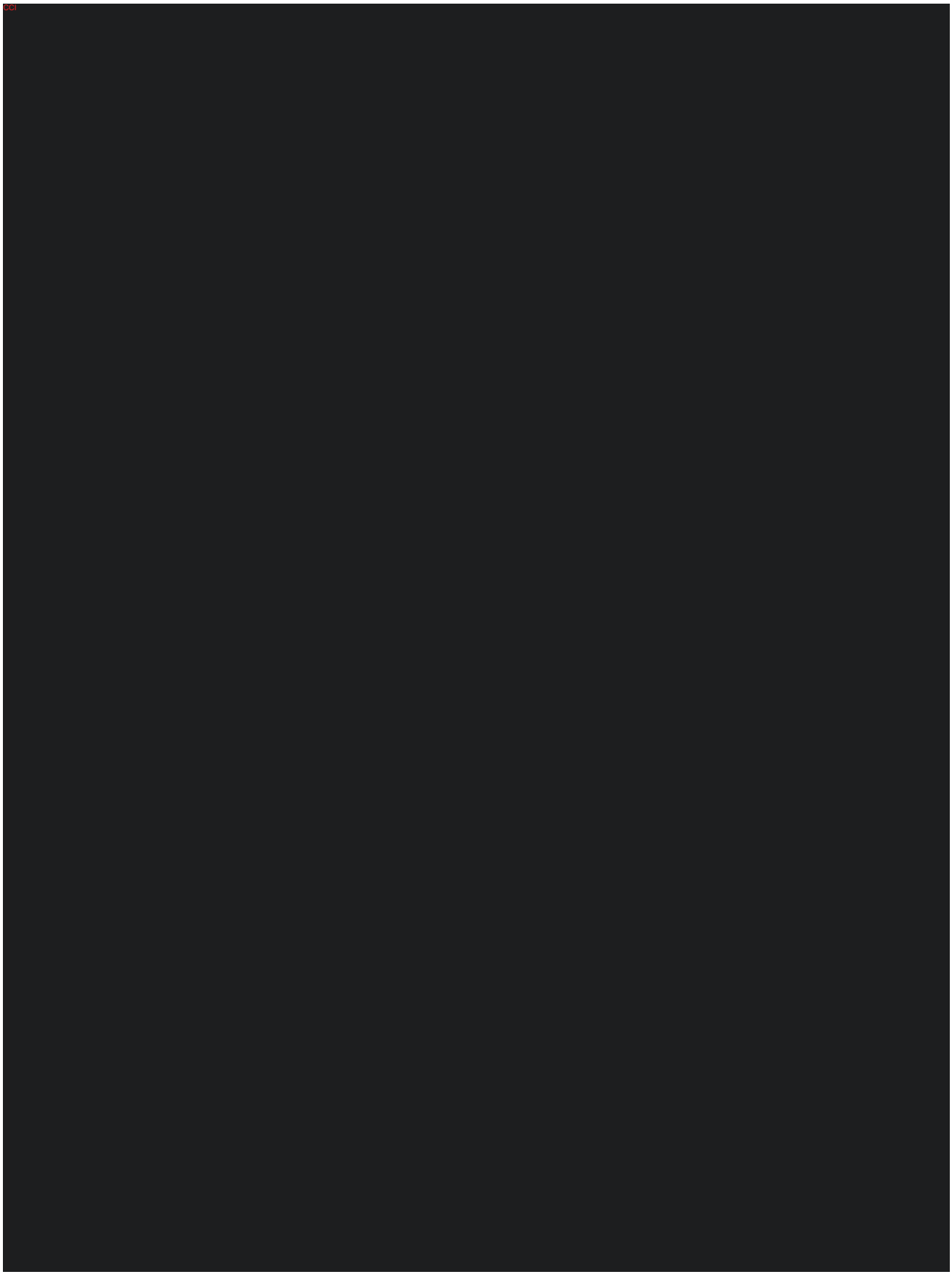
2.2.1 Pharmaceutical and Therapeutic Background

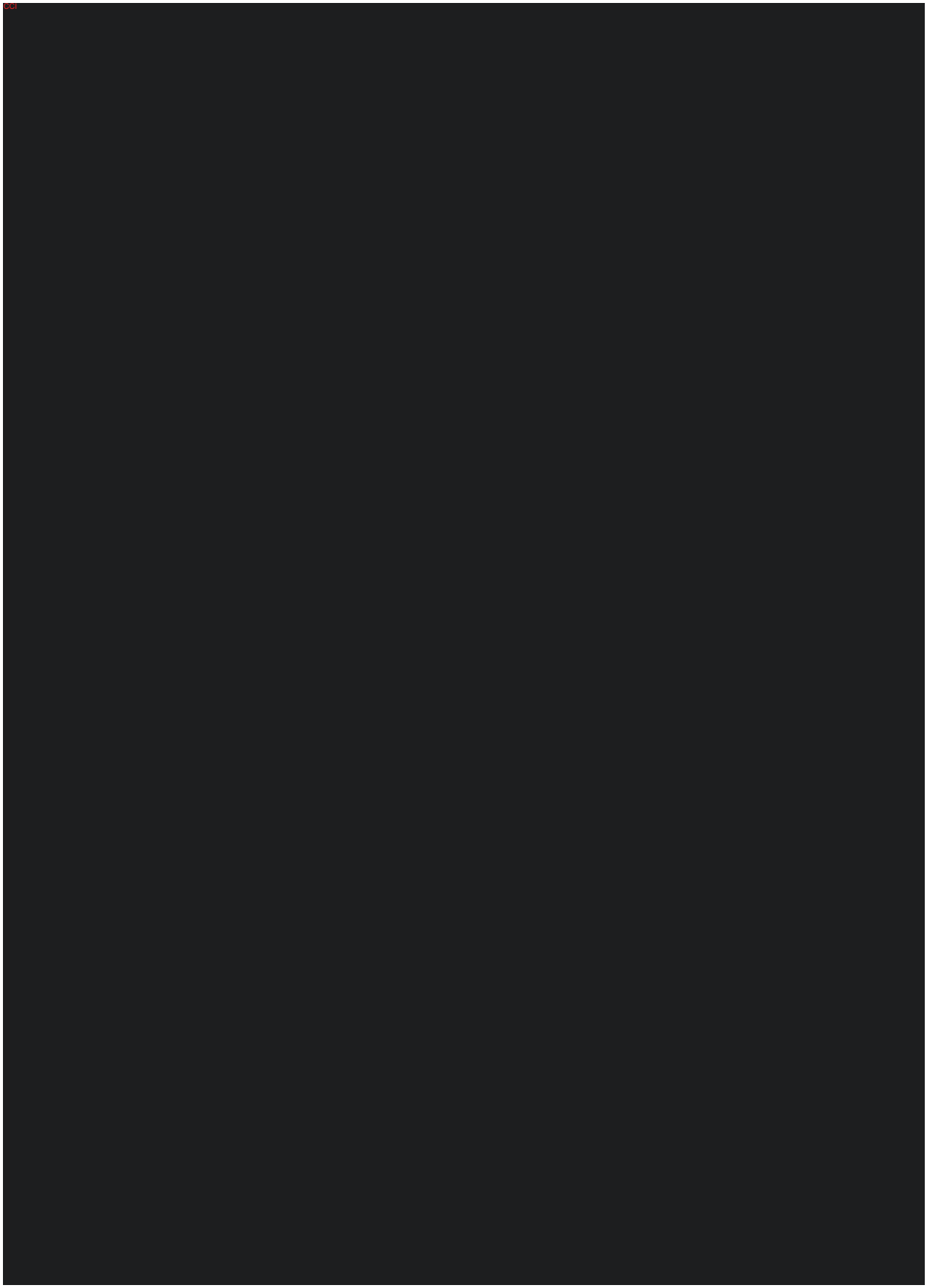
MK-8189 is a potent and selective inhibitor of PDE10A that is being developed as a novel therapeutic for the treatment of schizophrenia. The PDE10A enzyme metabolically inactivates the ubiquitous second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [Bender, 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 atypical antipsychotic (AAP) treatment.

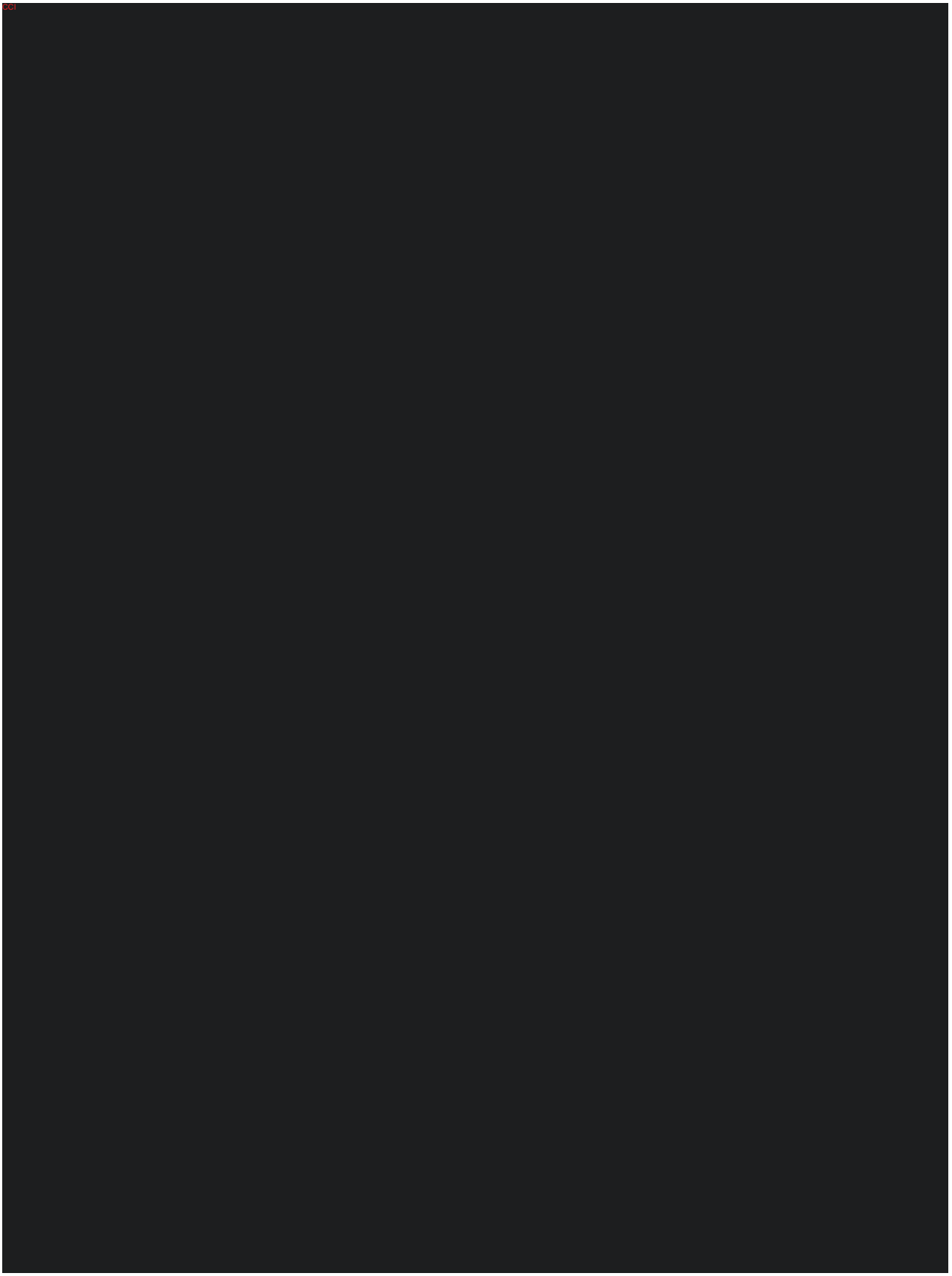
2.2.2 Preclinical and Clinical Studies

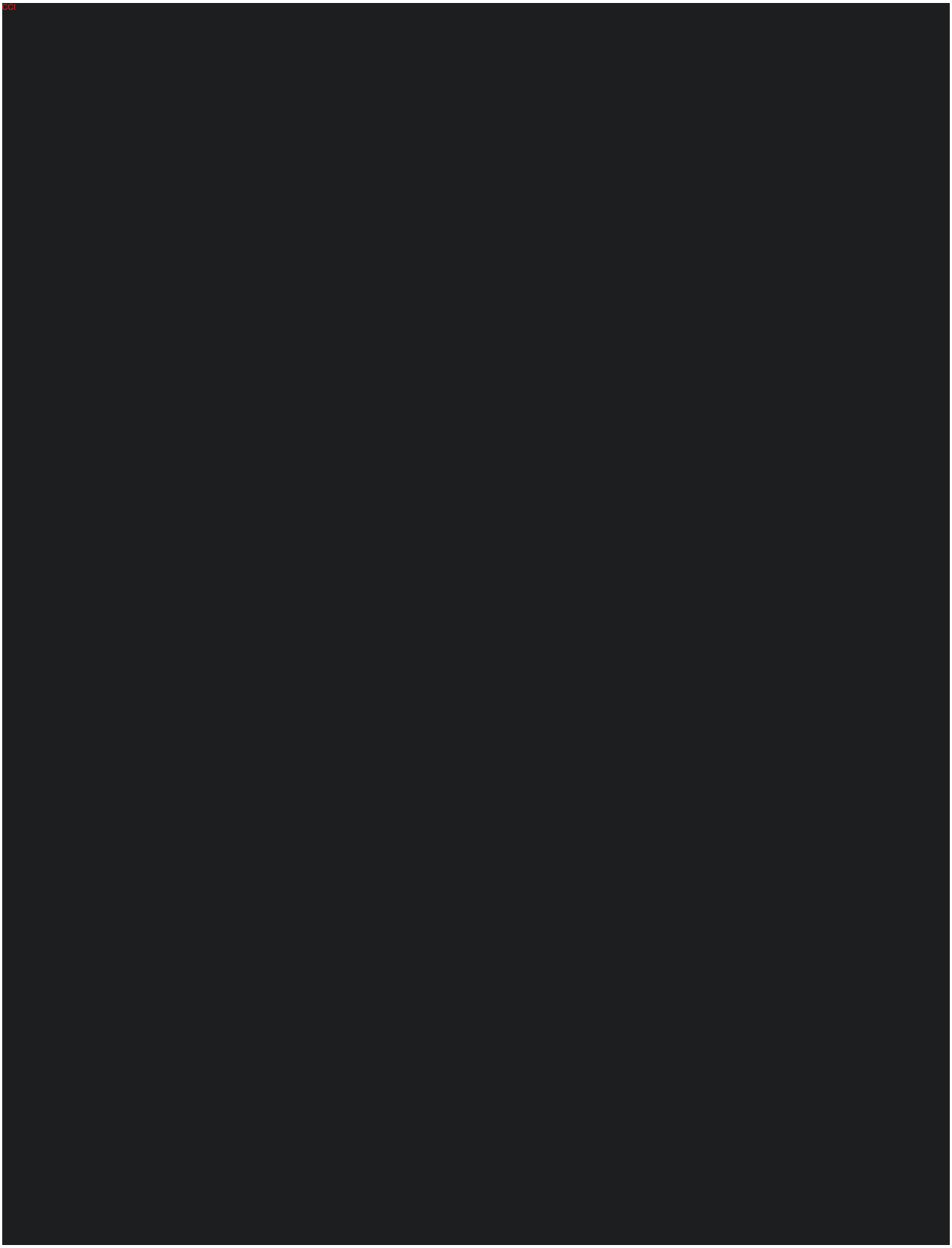
Preclinical Trials

[redacted]



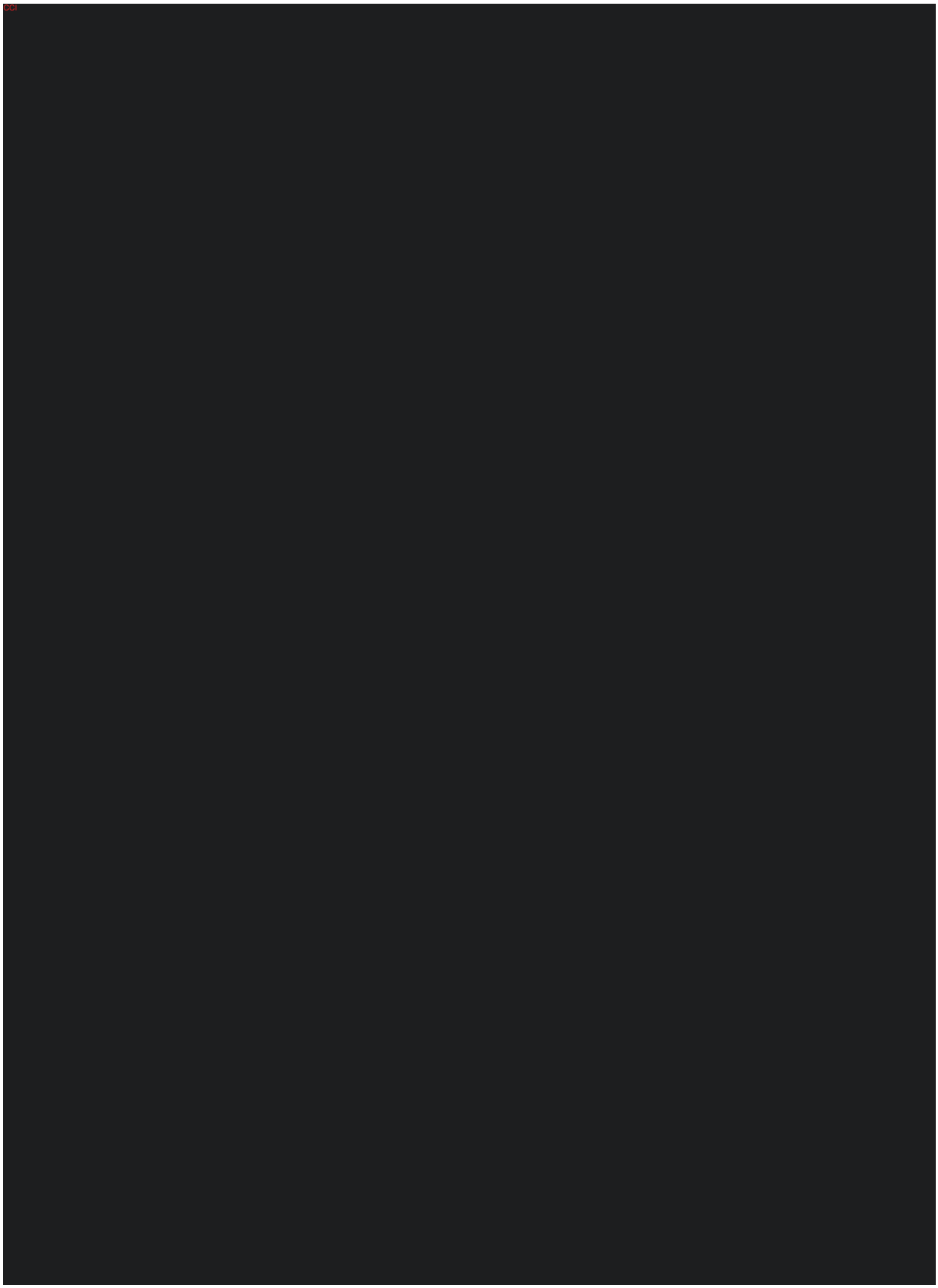






Additional data for P005 can be found in the MK-8189 IB.

2.2.3 Ongoing Clinical



2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

The following objectives will be evaluated in participants with schizophrenia and healthy participants.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of rising multiple once-daily oral doses of MK-8189 in participants with schizophrenia, as monotherapy and as add-on therapy, and healthy Japanese and non-Japanese participants	• Adverse experiences, laboratory safety tests, ECGs, and vital signs
Secondary	
• To estimate the pharmacokinetics for MK-8189 following multiple once-daily oral doses in participants with schizophrenia, as monotherapy and as add-on therapy, and in healthy Japanese and non-Japanese participants	• AUC0-24, Cmax, C24hr, Tmax, CL, Vd and apparent t1/2
Tertiary/Exploratory	
• To evaluate the effect of MK-8189 concentrations on QTc interval and other ECG parameters	• QTc, PR and RR intervals, heart rate, QRS duration, T wave morphology, presence of U waves and outlier assessment
• To investigate the relationship between [redacted] genetic polymorphs and the PK and pharmacodynamics of MK-8189. Genetic variation in [redacted] may be analyzed for association with any laboratory or clinical data collected in this study.	• Germline genetic variation in [redacted]
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

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

This is a four-panel, randomized, placebo-controlled, parallel-group, multiple-dose, double-blinded, safety, tolerability, PK and QTc study of MK-8189 in participants with schizophrenia and healthy participants.

Panel A will enroll up to 16 healthy participants (8 Japanese and 8 non-Japanese) and Panel B will enroll up to 16 participants with schizophrenia or schizoaffective disorder to ensure at least 12 completers per group. Panel C will enroll up to 12 participants with schizophrenia/schizoaffective disorder and Panel D will enroll up to 20 participants with schizophrenia; participants may be replaced at the discretion of the Sponsor in consultation with the principal investigator. Participants will be randomized to MK-8189 or matched-placebo in a ratio of 3:1 (Panels A, B and C) and 3:2 (Panel D) according to a computer generated allocation schedule; within Panel A, 6 Japanese and 6 non-Japanese will be randomized to MK-8189 and 2 Japanese and 2 non-Japanese will be randomized to receive placebo according to the computer generated allocation schedule.

Participants with schizophrenia in Panel B and Panel D will be washed off their antipsychotic medication. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants in Panel B and Panel D should not receive antipsychotics for at least 5 days or 3 half-lives (whichever is longer) prior to Day -1 Holter assessments. If deemed appropriate by the investigator, a participant may begin their washout as an outpatient, but should be confined within a week of starting the washout and minimally beginning on Day -6. In Panel C, participants with schizophrenia will remain on their study permitted atypical antipsychotic (AAP).

Panels A, B and C: Beginning on Day 1, participants randomized to MK-8189 will begin to receive MK-8189 QD and will be titrated from 4 mg to 24 mg over the course of an 18 day treatment period as follows: 1 x 4 mg tablet Days 1-3, 2 x 4 mg tablets Days 4-6, 3 x 4 mg tablets Days 7-9, 4 x 4 mg tablets Days 10-12, 5 x 4 mg tablets Days 13-15 and 6 x 4 tablets Days 16-18. Participants randomized to placebo will receive the same number of tablets matching the 4 mg tablet of MK-8189 as the active group. Dose titration decisions for each participant will occur, after 3 days of dosing per dose level, jointly between the investigator and Sponsor.

Panel D: Beginning on Day 1, participants randomized to MK-8189 will begin to receive MK-8189 QD and will be titrated from 8 mg to 48 mg over the course of a 15 day treatment period as follows: 2 x 4 mg tablets Days 1-3, 4 x 4 mg tablets Days 4-6, 6 x 4 mg tablets Days 7-9, 9 x 4 mg tablets Days 10-12 and 12 x 4 mg tablets Days 13-15. Participants randomized to placebo will receive the same number of tablets matching the 4 mg tablet of

MK-8189 as the active group. Dose titration decisions for each participant will occur, after 3 days of dosing per dose level, jointly between the investigator and Sponsor.

In Panel D, a small cohort (n=4) will initially be dosed with 8 mg to confirm tolerability prior to dosing the remainder of the cohort. Tolerability will be assessed following the second dose of 8 mg before the remainder of the panel is dosed; depending on tolerability, the remainder of the panel may i) be dosed starting with 8 mg, ii) a small cohort of the remainder of the panel may be dosed starting with 8 mg, or iii) the starting dose may be adjusted downward to 4 mg. The decision on how to proceed will be made by the principal investigator jointly with the Sponsor and documented in a protocol clarification letter. If any of the panel begins dosing at 4 mg, the following titration schedule may be followed: 1 x 4 mg tablets Days 1-3, 2 x 4 mg tablets Days 4-6, 4 x 4 mg tablets Days 7-9, 6 x 4 mg tablets Days 10-12 and 12 x 4 mg tablets Day 13-15.

If a participant does not tolerate escalation to the next dose, the participant may be titrated down to the previous dose (Panel A, B, C or D) or intermediate dose (Panel D). In addition, as discussed above, if the initial dosing cohort of Panel D or subsequent dosing cohort(s) does not tolerate the starting dose of 8 mg, subjects may be down-titrated to 4 mg. If appropriate medical care necessitates a down-dose, the investigator may do so independent of consultation with the Sponsor. If the participant tolerates continued dosing following down-titration, the participant may continue in the trial at that dose until study completion or may be re-challenged at a higher dose. Re-challenges are only to occur on regularly scheduled dose titration days, i.e. Day 4, Day 7, Day 10, etc. and will not extend the participant's time in the study. Participants will be followed for approximately 2 weeks after the last study treatment dose.

Panel A, healthy participants, will be confined to the clinical research unit (CRU) beginning on Day -2 through Day 21.

Participants with schizophrenia in Panel B and Panel D have a risk to experience exacerbations in psychotic symptoms both during the washout period as well as during the MK-8189 treatment period. To mitigate this risk, only participants with schizophrenia in the non-acute phase of their illness, with the onset of the first episode being no less than 2 years prior to study entry, will be recruited for study.

Panel B and Panel D, participants with schizophrenia, will be confined to the CRU within a week of beginning their antipsychotic medication washout and for at least the last 5 days of their washout (i.e. confinement will begin on Day -6 or earlier) and during the MK-8189 treatment to provide an enhanced level of participant supervision. If needed, rescue medication will be provided to treat withdrawal symptoms (see Section 6.5.1). Participants showing exacerbations in psychotic symptoms during the washout period will be re-evaluated for participation and referred for additional treatment as indicated.

Panel C, participants with schizophrenia, will be confined to the CRU beginning on Day -1 through Day 21.

The safety and tolerability of MK-8189 will be monitored by clinical assessment of AE, repeated measurements of ECGs and VS, physical and neurological examinations, and standard laboratory tests (hematology, chemistry, urinalysis). In addition, extrapyramidal symptoms (EPS) of dystonia and akathisia will be monitored along with psychological effects using rating scales.

All participants in Panels A, B and D will have 24-hour Holter recordings on Day -1, which will be considered baseline, and throughout the dosing period as specified in the SoA. Blood sampling for PK will follow each ECG extraction time. In addition, 24-hour Holter recordings and blood sampling for PK will be conducted for 2 additional days following the participant's last dose. In the case a participant has down-dosed or does not dose escalate and continues in the study, the participant will not repeat the 24-hour Holter monitoring and PK sampling at the given dose level. In the case of participant discontinuation at a dose of 12 mg or higher, an attempt should be made to collect 24-Holter and matched PK measurements for 48 hours following the participant's last dose. Panel C will not have Holter assessments but will have 12-lead ECG evaluations with coinciding PK samples at specified timepoints as per the SoA.

After completion of the MK-8189 treatment, participants with schizophrenia in Panel B and Panel D will resume the use of their own antipsychotic medication following collection of the last PK sample; Panel B: Day 18, 48- hour postdose PK sample (Day 20) and Panel D: the Day 15, 48- hour postdose PK sample (Day 17). Participants in Panels B and D will remain domiciled through Day 21 (Panel B) and Day 18 (Panel D) All participants will be followed for approximately 2 weeks after the last study treatment dose.

Because this is a Phase 1 assessment of MK-8189 in humans, the pharmacokinetic (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 8.12 for examples of modifications permitted within the protocol parameters.

4.2 Scientific Rationale for Study Design

Initially a 3-Panel design was selected such that MK-8189 could be evaluated in both healthy Japanese and non-Japanese participants (Panel A) and participants with schizophrenia as monotherapy (Panel B) and as add-on therapy (Panel C). At the time of study initiation, 12 mg was considered the likely clinical dose and characterization of higher dose (>12 mg) safety, tolerability and PK of MK-8189 in healthy participants could enable a determination of the safety/tolerability margin in this population, which is needed to understand the potential for healthy participants to participate in future Phase 1 clinical studies that require supratherapeutic doses or exposure. However, if dose escalation above 12 mg in healthy participants was poorly tolerated, high dose safety data in participants with schizophrenia would be used to understand the safety/tolerability margin in the target population, including evaluation of the effect of higher doses of MK-8189 on QTc. Panel C of this study will provide safety data in a small number of participants to support the evaluation of doses higher than 12 mg of MK-8189 in the setting of add-on therapy in a planned Phase 2 study.

A 4th panel is being added (Panel D) to the current protocol as preliminary data from Panel A and B of the ongoing study suggest that MK-8189 is generally well tolerated in healthy participants and participants with schizophrenia up to and including doses of 24 mg. Since the clinical dose may be as high as 24 mg, Panel D will evaluate the safety and tolerability of MK-8189 at doses up to including 48 mg in participants with schizophrenia to provide a clinical margin to the 24 mg dose. This margin may be needed to cover exposure increases resulting from potential effects of intrinsic and extrinsic factors on MK-8189 PK in future trials. While MK-8189 was generally well tolerated in both healthy participants and participants with schizophrenia, the schizophrenia population was selected for evaluation in Panel D as preliminary data suggest that exposures may be greater in the patient population.

Doses will be titrated up to 24 mg (Panels A, B and C) and 48 mg (Panel D) of MK-8189 to improve tolerability and minimize EPS (see Section 4.3) and a matched placebo-control will be included to reduce bias with regards to the patient reporting and investigator assessment of AEs. In addition, inclusion of a placebo cohort will also control for potential bias introduced by study procedures and to increase the power to exclude modest QTc effects in a study with a relatively small sample size.

In Panel A, Panel B and Panel D, Holter monitoring for 24 hour periods and ECG interval extraction at pre-specified timepoints for review by a blinded central reader will be included to support the rigorous evaluation of QT effect in accordance with the QT white paper [Garnett, C., et al 2017]. Replicate ECGs (triplicate) extracted from 24-hour Holter tracings and a centralized core laboratory to assess QTc interval will reduce variability. Pharmacokinetics will also be evaluated on Holter days to support a concentration-QTc analysis allowing for characterization of the exposure-QTc relationship at a multiple above expected therapeutic concentrations. In Panel C, 12-lead triplicate ECGs and PK will be evaluated at timepoints expected to coincide with peak concentrations at doses ≥12 mg to monitor safety and to explore the QTc-concentration relationship in the setting of add-on therapy (Panel C).

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical AEs as well as through the conduct of physical and neurological examinations, 12-lead ECGs, VS, and laboratory safety tests. In addition, scales will be included to evaluate EPS and general well-being.

A preliminary exposure-response model based on data from the MAD study (P003), which evaluated doses [redacted] found no relationship between MK-8189 concentrations and QTcF intervals or heart rate (HR). In addition, preclinical data do not suggest a risk of prolonged cardiac repolarization. As QTc is a pharmacodynamic (PD) endpoint of this study, this endpoint is further discussed under Section 4.2.1.3. However, as doses are being escalated in this trial above doses previously evaluated, the safety ECGs will be conducted around the time of peak plasma concentrations.

As EPS are associated with antipsychotics and have been observed in the MK-8189 clinical program, the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) and Simpson Angus Scale (SAS) will be used to quantify any EPS observed in the trial. 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.

To monitor the psychological well-being, the Bond and Lader Visual Analogue Scale (VAS) will be used in all participants. In participants with schizophrenia, the Brief Psychiatric Rating Scale (BPRS) will be used. The BPRS is rating scale to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behavior in a range of psychotic and affective symptoms. 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 20-30 minutes for the interview and scoring. The rater should enter a number ranging from 1 (not present) to 7 (extremely severe). 0 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.

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

All dose titration decisions will be made jointly by the investigator and the Sponsor. Each dose titration decision for each individual participant will occur after 3 days of dosing per dose level. However, if a participant needs to be discontinued or have a dose reduction based on safety/tolerability, the principal investigator may do so independent of consultation with the Sponsor.

4.2.1.2 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK of MK-8189, particularly at higher doses which have not been previously evaluated. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to drive the PK parameter values AUC0-24, Cmax, Tmax, C24hr, CL, Vd and apparent t1/2.

4.2.1.3 Pharmacodynamic Endpoints

An exploratory objective of this trial is to evaluate effects of a supra-therapeutic dose of MK-8189 on QTc interval. 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 Panels A, B and D, electrocardiogram data (e.g. QT, QRS, RR and PR intervals) will be obtained with a digital Holter device at each dose level, beginning with the 12 mg dose in Panels A and B and the 8 mg dose in Panel D. 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.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; 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 will be used for research related to the study intervention(s), the disease under study, and 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 or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

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

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

4.2.1.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

A matched placebo-control will be included to reduce bias with regards to the participant reporting and investigator assessment of AEs. In addition, inclusion of a placebo cohort will also control for potential bias introduced by study procedures and to increase the power to exclude modest QTc effects in a study with a relatively small sample size.

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 trials conducted under Investigational New Drug (IND) applications and trials that are intended for submission in a New Drug Application to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in trials that fall within the guidance for other reasons (e.g., central nervous system active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

4.3 Justification for Dose

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

4.3.1 Starting Dose for This Study

A 4 mg starting dose with the CR tablet formulation has been shown to be well tolerated in previous clinical trials in schizophrenia including the MAD study (P003) as well as the POC study (P005). Since the safety and tolerability profile in healthy participants and participants with schizophrenia is similar, a 4 mg dose has been selected for the current protocol in Panels A, B and C. As higher doses are being proposed for Phase 2, it is important to explore optimized titration schedules, therefore Panel D will explore a starting dose of 8 mg. Initiating the dose at 8 mg is supported by the tolerability observed in Panel A, Panel B and Panel C. In addition, the average receptor occupancy increase from 4 to 8 mg is approximately [redacted] with a large degree of overlap between doses (see figure below in section 4.3.3), thus the tolerability is expected to be similar between the two starting doses. As described in the study design (Section 4.1), a small cohort (n=4) will initially be dosed with 8 mg to confirm tolerability prior to dosing the remainder of the cohort.

4.3.2 Maximum Dose/Exposure for This Study

As described in Section 2.2.2, previous trials have demonstrated that MK-8189 has been generally well tolerated up to doses of 12 mg in healthy participants and up to 16 mg in participants with schizophrenia; doses up to 12 mg have been evaluated as monotherapy and doses up to 16 mg have been evaluated as add-on therapy. Data from the present trial indicate doses up to 24 mg are generally well tolerated as monotherapy in healthy participants and participants with schizophrenia.

Following a titration schedule from 2 mg to 12 mg over 14 days, the AUC0-24 was found to be approximately [redacted]. If PK remains dose proportional up to 48 mg, the predicted exposure margin to the AUC0-24 for a 48 mg dose, as derived from the chronic toxicology studies, would be [redacted]. The PK profile for MK-8189 is similar when administered as monotherapy or as add-on therapy. Brief summaries of the chronic toxicology studies supporting dose escalation are provided below:

In the 6 month rat study, doses of 0, 25, 100 and 750 mg/kg/day were evaluated. Two high-dose (750 mg/kg/day) female rats were found dead (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 (AUC0-24hr = [redacted] providing an exposure margin of [redacted] over the predicted supratherapeutic exposure of [redacted] at the 48 mg dose.

In the 9 month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK-8189 were administered. Renal tubular degeneration was observed in the high-dose group (600/300 mg/kg/day). The NOAEL for target organ toxicity is 150 mg/kg/day (AUC0-24hr = [redacted]), providing a [redacted] over the predicted supratherapeutic exposure of [redacted] at the 48 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 [redacted] providing large margins [redacted] to the projected median unbound Cmax for efficacy (12 mg dose) in humans. 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 [redacted] respectively. Thus, the NOEL/NOAEL in this study was [redacted] providing an exposure margin of [redacted] relative to the projected clinical Cmax at the 48 mg dose of [redacted]

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 providing exposure margins of [redacted] of the projected clinical Cmax of [redacted] 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.

Therefore, preclinical data support dose escalation to 48 mg in the current study. In addition, during the study safety and tolerability will be carefully assessed including scales to assess dystonia. Dose escalation may be stopped based on tolerability.

4.3.3 Rationale for Dose Interval and Study Design

To mitigate the risk of EPS, antipsychotic treatment is generally initiated using dose titration schedules in which the dose is gradually increased while monitoring for frequency and severity of EPS symptoms. The dose titration steps in Panel A, B and C of the current study are based on dose titration paradigms used in prior MK-8189 studies, which have been generally well tolerated. As doses as high as 24 mg are planned to be evaluated in Phase 2, Panel D will explore an optimized titration scheme to shorten the time to reach the intended therapeutic dose while minimizing the potential for AEs. The MK-8189 program initially based its titration strategy on current practice of titration schedules for antipsychotics and on information available on dose titration schedules with other investigational PDE10A inhibitors. Dose titration of antipsychotics is usually done every 1 or 2 days [Janssen Pharmaceutical Ltd 1993] [Novartis Pharmaceuticals 1989] [U.S. Prescribing Information 2017] [Pfizer 2010] [Eli Lilly 1996] [U.S. Prescribing Information 2017]. However, for compounds with a longer half-life such as olanzapine (t1/2=30 hours) and aripiprazole (t1/2=75 hours) a slower dose titration is recommended [Department of Public Health 2006]. Following administration of MK-8189 as an immediate- release dose form, MK-8189 has a half-life of [redacted] comparable to quetiapine and ziprasidone, and dose titration once every 3 days is anticipated to be adequate to prevent EPS AEs (i. e. dystonia and akathisia) or to allow EPS to attenuate before the next titration step. The dose titration schedules for all Panels are described in Section 1.1 and Section 4.1. As described in Section 4.1, an alternate dose titration schedule regimen is provided for Panel D if it is found that a starting dose of 8 mg (as compared to 4 mg) is not well tolerated. In this alternate titration schedule, a larger final titration step of 2-fold (24 mg to 48 mg) as compared to the previous

titration step of 1.5-fold (16 mg to 24 mg) will occur. This is supported since at the higher end of the dose escalation, the flat portion of the dose-enzyme receptor occupancy is approached, and therefore only small changes in pharmacodynamic response would be anticipated (see figure below).

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Prior to a final decision on continuation or termination of the study , a study may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, 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 Institutional Review Board(s)/Independent Ethics Committee(s) [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

Healthy Japanese and non-Japanese and schizophrenic male and female participants, with an attempt to enroll approximately 40% of female participants (in each panel), between the ages of 18 and 60 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

5.1.1 Panel A (Healthy Participants) Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Is in good health based on medical history, physical examination, vital sign (VS) measurements and 12-lead safety ECGs performed prior to randomization. Appendix 8 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

2. 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 9 provides an algorithm for the assessment of out of range laboratory values.

3. Have a Body Mass Index (BMI) $\geq$ 18.5 and $\leq$ 35 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.

4. Have no clinically significant abnormality on the 12-lead safety ECG performed at the pre-trial (screening) visit and/or prior to randomization. The assessment prior to randomization is based on the mean of the triplicate measures. Note: The QTcF duration must be <450 msec for males and <470 msec for females, 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. Appendix 8 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

5. 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 semi-recumbent position at the pre-trial (screening) visit and/or prior to randomization (up to the time-matched 8 hour assessment). 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.

Demographics

6. Participant is Male or Female.

7. Participant is from 18 years to 60 years of age inclusive, at the time of signing the informed consent.

Female Participants

d. If the participant is a female with reproductive potential, she must demonstrate a serum β-human chorionic gonadotropin (β-hCG) level consistent with the nongravid state at the prestudy (screening) visit and agree to use (and/or have their partner use) 2 acceptable methods of birth control beginning at the prestudy (screening) visit, throughout the study (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of study drug in the last treatment period. Acceptable methods of birth control are defined in Section 5.3.1.

e. If the participant is a postmenopausal female: she is without menses for at least 1 year and have a follicle stimulating hormone (FSH) value in the postmenopausal range upon prestudy (screening) evaluation.

f. If the participant is a surgically sterile female: she is status post hysterectomy, oophorectomy or tubal ligation. Note: Information regarding the procedure may be based on the participant's recall of her medical history, and details of the recall must be captured appropriately within the site's source documents.

Japanese Participants

a. If the participant is of Japanese descent, both biological parents and all biological grandparents must be born in Japan. Adequate documentation to verify the descent should be obtained and kept with source documents. While 2nd and 3rd generation Japanese are acceptable for enrollment, preference should be given to enrollment of subjects who were born in Japan.

Informed Consent

8. The participant provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

9. Is willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.1.2 Panel B, Panel C and Panel D (Participants with Schizophrenia) Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

10. 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 9 provides an algorithm for the assessment of out of range laboratory values.

11. 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.

12. Have no clinically significant abnormality on 12-lead safety ECG performed at the pre-trial (screening) visit and/or prior to randomization. The assessment prior to randomization is based on the mean of the triplicate measures. Note: The QTcF duration must be <450 msec for males and <470 msec for females, 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. Appendix 8 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

13. 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 semi-recumbent 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. For Panel C and Panel D, participants may be included if values are outside the normal range but considered not clinically significant per investigator discretion.

14. 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.

15. 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.

16. 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.

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

18. Has a stable living situation in which the patient or a contact person can be reached by the investigator if there is a need for follow up.

19. 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.

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

21. Panels B and D: Participant is able to discontinue the use of all antipsychotic medication at least 5 days prior to the start of the treatment period and during the study period.

Demographics

22. Participant is Male or Female.

23. Participant is from 18 years to 60 years of age inclusive, at the time of signing the informed consent.

Female Participants

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

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, 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.

- A WOCBP must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 24 hours before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

25. The participant provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

26. Is willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.2 Exclusion Criteria

5.2.1 Panel A (Healthy Participants) Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has a history of clinically diagnosed depression, anxiety disorder, or any history of psychiatric disorders having required drug treatment or hospitalization. Participants who have had situational depression more than 5 years before the start of the study may be enrolled in the study at the discretion of the investigator.

2. Has a history of stroke, chronic seizures, or major neurological disorder.

3. Has a history of dystonic reaction to antipsychotic, anti-emetic or related medication

4. 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 (e.g., positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 5 years or suicidal behavior in their lifetime.

5. Is a woman of childbearing potential (WOCBP) who has a positive serum pregnancy test at the screening visit or a positive urine pregnancy test within 48 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.

6. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (e.g., uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

7. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

8. 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.

9. 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.

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

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

12. Has a family history of sudden death.

13. 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.

14. Participant has an estimated creatinine clearance (CrCl) ≤ 80 mL/min based on the Cockcroft-Gault (CG) Equation.

    Cockcroft-Gault Equation:

    $$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

When creatinine is measured in micromole/litre, use this formula:

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L]} \times 0.0113)}$$

For females, multiple the result by 0.85.

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

Participants who have a measured creatinine clearance of up to 10% below 80 mL/min may be enrolled in the study at the discretion of the investigator.

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

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

17. 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

18. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies, beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

20. Has history or presence of risk factors for TdP (e.g., cardiac disease, heart failure, hypokalaemia or hypomagnesaemia, hypertrophy, cardiomyopathy, or family history of long QT syndrome). For Panel A, plasma calcium must be within normal limits at screening and serum calcium must be within normal limits prior to dosing.

Other Exclusions

21. Is a smoker and/or has used nicotine or nicotine-containing products (e.g., nicotine patch and electronic cigarette) within 3 months of screening.

22. Is under the age of legal consent.

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

24. 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.

25. 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 urine drug screen (UDS) prior to randomization.

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

27. 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.

5.2.2 Panel B, Panel C, and Panel D (Participants with Schizophrenia) Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

28. 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.

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

30. Has a history of neuroleptic malignant syndrome or moderate to severe tardive dyskinesia (TD).

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

32. Has a DSM-5 defined substance abuse or dependence disorder (excluding nicotine and caffeine) within three months of screening.

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

34. 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.

35. 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.

36. 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 (e.g., 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.

37. Is a WOCBP who has a positive serum pregnancy test at the screening visit or a urine pregnancy test within 48 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.

38. 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.

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

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

41. Has a family history of sudden death.

42. 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.

43. Participant has an estimated creatinine clearance (CrCl) ≤ 80 mL/min based on the Cockcroft-Gault (CG) Equation.

    Cockcroft-Gault Equation:

    $Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$

    When creatinine is measured in micromole/litre, use this formula:

    $Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L]} \times 0.0113)}$

    For females, multiple the result by 0.85.

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

    Participants who have a measured creatinine clearance of up to 10% below 80 mL/min may be enrolled in the study at the discretion of the investigator.

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

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

46. 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

47. Has received treatment with clozapine for schizophrenia or treatment with monoamine oxidase inhibitors within 3 months of screening. Participant in Panel C has received a total daily dose of risperidone > 6 mg.

48. Has received a parenteral depot antipsychotic medication within 3 months of pre-trial (screening).

49. Is unable to refrain from the use of co-medication with a moderate or strong inhibiting or inducing effect on [redacted] and/or [redacted] 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 or is unable to refrain from the use of sensitive substrates of [redacted] Unable to refrain from cyclic hormone replacement therapy. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

51. Has history or presence of risk factors for TdP (e.g., cardiac disease, heart failure, hypokalaemia or hypomagnesaemia, hypertrophy, cardiomyopathy, or family history of long QT syndrome). Plasma calcium must be in within normal limits at screening and serum calcium must be within normal limits prior to dosing.

Other Exclusions

52. Is under the age of legal consent.

53. Has been in incarceration or imprisonment within three months prior to screening.

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

55. 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.

56. 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 prior to randomization.

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

58. 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 Section 8.0.

Each study drug administration will need to be taken with 240 mL of water after an 8 hour fast. Water will be restricted 1 hour prior to and 1 hour after study drug administration. Subjects will remain fasting until 1 hour post dose.

On full PK sampling days and/or 24-hour Holter monitoring days, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration until 1 hour post-dose. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the SoA. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each full PK sampling and/or Holter evaluation day in each panel. Meals and snacks will be served after any coinciding Holter and/or PK procedure. After the Day 15 (Panel D) or Day 18 (Panel A, Panel B and Panel C) 48-hour post-dose procedures have been completed (Day 17 or Day 20, respectively for Panel D or Panel A, Panel B, Panel C), subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Meal and water restrictions on Day -1 (Panels A, B and D only) will be time-matched to those timepoints on 24-hour Holter/PK days when treatment is administered. Similarly, meal and water restrictions will be time-matched on Day 19 and Day 20 (Panel A and B) and Day 16 and Day 17 (Panel D) to 24-hour Holter/PK days when treatment is administered.

On intermediate days, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will remain fasted until 1 hour post-dose. Meals and snacks should be standardized for caloric content, composition and timing. Meals and snacks should be served after any scheduled ECG procedure.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study until 48 hours following last dose administration.

On full PK sampling and/or Holter days, participants will refrain from the consumption of all fruit juices 24 hours prior to study drug administration.

On intermediate days, 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 prior to the prestudy and poststudy visits.

On full PK sampling and/or Holter days (Panels A and B: Day -1, Day 7, Day 10, Day 13, Day 16, Day 18 and Day 19; Panel C: Day 9, Day 12, Day 15 and Day 18; Panel D: Day -1, Day 1, Day 4, Day 7, Day 10, Day 13, Day 15 and Day 16), 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.

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

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to 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 (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

For Panel A (healthy participants), smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

For Panel B, Panel C and Panel D (participants with schizophrenia), 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 (i.e., weight lifting, running, bicycling, etc.) from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (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

A participant who discontinues from study intervention or withdraws from the study in Panel A or Panel B will not be replaced.

If a participant discontinues from study intervention or withdraws from the study in Panel C or Panel D, 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 study site should contact the Sponsor for the replacement participant's 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 , MK-8189 and matching placebo, will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Type	Dose Form	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen	Use	IMP/ NIMP	Sourcing
Active	Experimental	MK-8189	Drug	Tablet	4 mg	All dosage levels	Oral	Panels A, B and C: Titration period, days 1-18 Panel D: Titration period, days 1-15	Experimental	IMP	Provided centrally
Placebo	Placebo Comparator	MK-8189	Drug	Tablet	0 mg	All dosage levels	Oral	Panels A, B and C: Titration period, days 1-18 Panel D: Titration period, days 1-15	Experimental	IMP	Provided centrally

All supplies indicated in Table 1 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

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 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 in a 3:1 ratio within each Panel. The sample allocation schedules are provided in Table 2, Table 3 and Table 4.

Table 2 Panel A (healthy participants) and Panel B (participants with schizophrenia: monotherapy) Sample Allocation Schedule

Panel	n	Days 1-3	Days 4-6	Days 7-9	Days 10-12	Days 13-15	Days 16-18
A[a]	12	4 mg	8 mg	12 mg	16 mg	20 mg	24 mg
	4	PBO	PBO	PBO	PBO	PBO	PBO
B[b]	12	4 mg	8 mg	12 mg	16 mg	20 mg	24 mg
	4	PBO	PBO	PBO	PBO	PBO	PBO

a. Panel A allocation schedule will be stratified to Japanese and non-Japanese participants. Japanese participants will be assigned the lower allocation range (first 8 numbers) and non-Japanese will be assigned the upper allocation range (last 8 numbers). This will allow an equal number of active and placebo within the Japanese and non-Japanese participants.
b. Panel B allocation schedule will not be stratified

Table 3 Panel C (participants with schizophrenia; add-on therapy) Sample Allocation Schedule

Panel	n	Days 1-3	Days 4-6	Days 7-9	Days 10-12	Days 13-15	Days 16-18
C	9	4 mg	8 mg	12 mg	16 mg	20 mg	24 mg
C	3	PBO	PBO	PBO	PBO	PBO	PBO

Table 4 Panel D (participants with schizophrenia: monotherapy) Sample Allocation Schedule

Panel	n	Days 1-3	Days 4-6	Days 7-9	Days 10-12	Days 13-15
D	12	8 mg	16 mg	24 mg	36 mg	48 mg
D	8	PBO	PBO	PBO	PBO	PBO

6.3.2 Stratification

Intervention allocation/randomization will be stratified based on ethnicity for Panel A.

No stratification based on age, sex, or other characteristics will be used for Panel B, Panel C and Panel D.

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.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

Paracetamol/acetaminophen and antacids (e.g. magnesium hydroxide) may be used for minor ailments without prior consultation with the Sponsor. Note: for participants in Panel C, the investigator should confirm the use of antacids should not interact with participant's AAP as per the AAP prescribing information.

For participants with schizophrenia (Panel B, Panel C and Panel D), 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 [redacted] and/or [redacted] are not allowed as [redacted] In addition, MK-8189 is a mild inducer of [redacted] in human hepatocytes at drug concentrations of ≥ 10 µM and therefore co-medication with substrates for [redacted] should be avoided [redacted]).

For Panel C only, subjects will continue the use of their permitted AAP medication (i.e., use of risperidone > 6 mg/day or use of clozapine is not permitted).

For healthy participants (Panel A), no concomitant medication/vaccinations are permitted, except for the necessary treatment of AEs (see also Section 6.5.1 on rescue medication).

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, 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.

Panel B and Panel D participants 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 inhibitors or inducers of CYP3A and 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)

All dose titration decisions will be made jointly by the investigator and the Sponsor. Each dose titration decision for each individual participant will occur after 3 days of dosing per dose level.

Dose titration decisions for each participant will be based on available (as per the SoA) safety variables: VS, 12-lead safety ECG, laboratory safety tests, AEs, C-SSRS, BPRS, and EPS evaluations from the previous dose levels. Pharmacokinetic and pharmacodynamic data may be included in the dose titration decisions.

If, as judged by the Sponsor and 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 following 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 8.1.11). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.10, 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 8.1.10.

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

- The participant 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.10, or if available, a protocol clarification letter.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she 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 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 future biomedical research, are outlined in Section 8.1.10. 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 or trained 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 utilized 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 500 mL (Appendix 10).

- 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 consent from each potential participant prior to participating in a clinical study or future biomedical research .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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant 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 dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

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 written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/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. This should also include any psychiatric history of the participant.

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 14 days before starting the study for Panel A (healthy participants) and within 3 months of starting the study for Panel B, Panel C and Panel D (participants with schizophrenia). Use of any prescription or nonprescription medication during the washout period of Panel B and Panel D 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.

8.1.5.2 Concomitant Medications

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

8.1.6 Washout from Antipsychotics

All participants in Panel B and Panel D 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.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization.Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 provided in Section 8.10.1.

8.1.8 Assignment of Treatment/Randomization Number

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

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

8.1.9 Study Intervention Administration

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

8.1.9.1 Timing of Dose Administration

MK-8189/placebo dosing will occur once daily in the morning following an 8 hour fast. Participants will receive each oral dose of MK-8189 /placebo with ~240 mL water.

8.1.10 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 post-study visit (approximately 14 days after the last dose of study intervention is given) 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 14 days after the last dose of study intervention is given, the investigator should perform a follow-up telephone call 14 days after the last dose of study intervention to determine if any AEs have occurred since the post-study 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.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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.

8.1.11 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 drug 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s treatment assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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 principal 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.

8.1.12 Domiciling

Participants in Panel A will report to the CRU on Day -2 prior to the scheduled day of study intervention administration on Day 1. Participants in Panel B and Panel D will be confined to the CRU within a week of beginning their antipsychotic washout and at least 6 days prior to treatment with MK-8189 on Day 1. Participants in Panel C will report to the CRU on Day -1 prior to the scheduled day of study intervention administration on Day 1. All participants in Panel A, Panel B and Panel C will remain in the CRU until Day 21 (72 hours following the last dose). Participants in Panel D will remain in the CRU until Day 18 (72 hours following the last dose). At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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

8.1.13 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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy or immunogenicity assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Section 10.10.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

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

8.3.2 Body Mass Index (BMI)

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m2). Body Mass Index will be rounded to the nearest whole number according to the standard convention of 0.1-0.4 round down and 0.5-0.9 round up.

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

8.3.3 Vital Signs

- Oral temperature, pulse rate, respiratory rate, and BP will be assessed at prespecified timepoints noted in the SoA (Section 1.3).

- Blood pressure and pulse measurements will be assessed semi-recumbent with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.3.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semi-recumbent for at least 10 minutes prior to having VS measurements obtained. Semi-recumbent will include HR and BP. 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 in triplicate measurements, obtained at least 1-2 minutes apart on Day -1 as per the SoA. 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.

8.3.3.2 Body Temperature

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

8.3.3.3 Orthostatic Vital Signs

Orthostatic VS (HR and BP) will also be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright after the resting vitals for approximately 3 minutes prior to measurement of orthostatic VS.

8.3.4 Electrocardiograms

12-Lead Safety Electrocardiogram

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to 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 semi-recumbent for at least 10 minutes prior to 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.

In all Panels, baseline (prior to Day 1 dosing) ECGs will be obtained in triplicate at least 1-2 minutes apart as per the SoA. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

In Panels A, B and D, postdose ECG measurements will be single measurements. In Panel C, postdose ECG measurements will be obtained in triplicate at least 1-2 minutes apart as per the SoA.

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 10 minutes (applies to Panels A, B and D only as Panel C will have triplicate post dose ECG evaluations). The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If 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 (e.g., a cardiac or intensive care unit) 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 study cardiologist will be consulted by the Principal Investigator as needed to review ECG tracings with abnormalities.

24-Hour Holter Assessment (Panel A ,Panel B and Panel D only)

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 in each trial period. 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 by a blinded core ECG laboratory according to a pre-specified algorithm. To minimize artifacts, participants must rest quietly in a semi-recumbent position for ~10 minutes prior to the time points specified for extraction. No other study assessments or procedures should occur during the resting period.

Please see Trial Procedures Manual for Holter-specific procedures provided by the ECG vendor.

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

8.3.5 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum and/or urine β-hCG at specific timepoints outlined in the SoA. In the case of a positive or borderline serum β-hCG pregnancy test at the pre-trial (screening) visit, the subject must not enter the trial; in the case of a positive or borderline urine β-hCG pregnancy test during the trial, a serum β-hCG pregnancy test will be required. If the pregnancy has been confirmed the subject must be discontinued from the trial immediately and the pregnancy must be reported to the Sponsor as outlined in Section 8.4.5.

8.3.6 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (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 procedures 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.

8.3.7 Suicidal Ideation and Behavior Monitoring

8.3.7.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at the time points indicated in the SoA. In addition, C-SSRS will be administered at any unscheduled visit where safety assessments are performed. The C-SSRS will not be routinely administered at visits with a sole purpose of PK sampling and/or witnessed study intervention administration. Site staff should review the contents of the C-SSRS for completeness. If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, prior to their assessment of the participant and to further inform their evaluation. The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior at screening, the assessor should also inquire and document if this is also present at the time of the screening visit.

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an adverse event, either between visits or during visit interviews, must be assessed by the Investigator. Participants who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or mental health nurse practitioner (or comparable professional qualification in countries outside of the United States). Only participants whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at

serious risk for self-harm during the course of the study may continue in the study; others must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety. In addition, all AEs of suicidal ideation or behavior must be recorded as an Event of Clinical Interest (see Section 8.4.7). Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

8.3.8 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 if it is observed or a participant reports complaints of dystonia and or akathisia.

8.3.9 Assessment of Neuropsychological Effects

For the assessment of the psychological effects, all participants will complete the VAS at times specified in SoA. Prior to the initial administration of the VAS participants will be trained by study staff and will practice the assessment.

In addition, participants with schizophrenia will also complete the BPRS at times specified in SoA.

A General Neurological Exam will be performed at the Screening and Baseline visits for all participants. A targeted Neurological Exam will be administered at times specified in the SoA. Details of the neurological examinations are in Appendix 11 and Appendix 12.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, 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 of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered drug-related.

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

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

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	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (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
Serious Adverse Event (SAE) including Cancer and Overdose	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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (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
Event of Clinical Interest (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

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 AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), 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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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. Pregnancy outcomes of 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 (ECIs)

Selected nonserious and SAEs 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, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

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

3. Suicidal ideation and/or suicidal behavior as reported in the C-SSRS scores, TEAEs or any self-injurious behavior

4. Dystonia

5. New or worsening tardive dyskinesia

6. QTcF interval of ≥500 msec (the average of the three QTcFs will be used)

8.5 Treatment of Overdose

The participant has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeds the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189

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

8.6.2 Urine Collection for MK-8189 and metabolite profiling

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

8.7 Pharmacodynamics

Pharmacodynamic parameters, other than QTc and other ECG parameters, will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis

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 future biomedical research if the participant signs the future biomedical research consent.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the procedures manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- 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 4 weeks prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 5.1 and 5.2.

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

8.10.2 Treatment Period

Panel A: Healthy participants that meet selection criteria for enrollment will participate in Panel A, 16 participants in total. Participants will report to the CRU on Day -2 to undergo procedures in SoA.

Panel B and Panel D: Participants with schizophrenia that meet selection criteria for enrollment will participate in Panel B or Panel D, 16 participants or 20 participants, respectively, in total. Participants must be washed out from their antipsychotic medication for at least 5 days prior to the Day -1 Holter assessment. Participants will report to the CRU within a week of the start of their washout, minimally on Day -6.

Panel C: Participants with schizophrenia that meet selection criteria for enrollment will participate in Panel C, 12 participants in total. Participants will report to the CRU on Day -1 to undergo procedures in SoA.

On treatment days between Day 1 and Day 18 (Panel A, B and C) or Day 1 and Day 15 (Panel D), participants will be dosed once daily with MK-8189/placebo and have procedures

completed per the SoA. Participants will remain in the unit through Day 21 (Panel A, B, C) or Day 18 (Panel D) procedures and discharged at the discretion of the investigator.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.10.4 Poststudy

After completion of treatment, participants in Panel B and Panel D will resume the use of their own antipsychotic medication after the Day 18, 48 hour post-dose (Day 20 - Panel B) or Day 15, 48 hour post-dose (Day 17 - Panel D) PK sample has been collected. A phone call should occur after 5-7 days after CRU discharge to check for any side effects and medication compliance.

All 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.

8.11 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the timing of the ECG extraction from the 24-hour Holter recording, and blood sample for MK-8189 and ECG collection are the critical procedures. At any postdose time point, these assessments will be collected close to the exact time point as possible. The PK sample should follow immediately after the Holter extraction is complete.

These procedures will be performed in the following order (below) with regard to the prescribed time. These procedures can be done prior to or after the time point.

1. Holter ECG assessment (extraction period)
2. Resting VS
3. Orthostatic VS
4. Blood for MK-8189

As a blood sample for assessment of MK-8189 plasma concentration, 12-lead safety ECGs, and resting and orthostatic VS are planned at the same timepoint, the order of execution is as follows:

1. 12-lead safety ECG

2. Resting VS

3. Orthostatic VS

4. Blood for MK-8189

All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

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

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

The following variance in procedure collection times will be permitted.

- Predose standard safety evaluations: 12-lead safety ECGs within 2 hours prior to dosing; laboratory safety tests within approximately 48 hrs prior to dosing

- Postdose standard safety evaluations: 12-lead safety ECG, and VS

  a. Day 1 postdose through Day 18 (Panels A, B and C) postdose or Day 1 postdose through Day 15 (Panel D) postdose may be obtained +/- 15 min of the theoretical sampling time

  b. Day 19 postdose through Day 21 (Panels A, B and C) or Day 16 postdose through Day 18 (Panel D) may be obtained +/- 30 min of the theoretical sampling time

- Postdose laboratory safety tests on Days 1 through 18 may be obtained:

  a. For blood: within -90 minutes from the theoretical sampling time

  b. For urine: within -120 minutes from the theoretical sampling time.

- Predose and Postdose ECG Holter extractions may be obtained -15/+5 minutes from the theoretical sampling time.

- PK collections:

  a. May be obtained -5/+10 minutes from the theoretical sampling time.

  b. Must be obtained no more than +10 minutes after the end of the ECG Holter extraction window at each theoretical timepoint.

  c. Must NOT be taken prior to the end of the ECG Holter extraction window.

d. Must be obtained no more than +15 minutes after the 12-lead safety ECG at each theoretical timepoint and must be collected following vital sign assessments.

- Study intervention administration: +/- 30 mins

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

This is a Phase 1 assessment of MK-8189 in humans, and the PK, PD, 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 in any given day/panel.
- Entire panel may be omitted.
- Adjustment of the dosing interval (e.g., divided doses [BID to QD, QD to BID, TID, or vice versa]).
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data.
- Modification of the PK/PD sample processing and shipping details based on newly available data.
- A single dose may be skipped, and dosing may continue at the same dose level or adjusted downwards.

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

Up to additional 50 mL of blood may be drawn for safety, PK, and/or PD 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 (Section 10.10).

The timing of procedures for assessment of safety procedures (e.g., VS, 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 employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2).

Safety: Summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). For Panels A, B, and C, Day -1 8hr serves as a baseline for post-dose vital sign readings. For Panel D, Day -1 8 hr, 10 hr, and 16 hr readings will serve as time-matched baselines for the corresponding post-dose vital sign readings.

For all panels, summary statistics and plots will be generated for Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) and Simpson Angus Scale (SAS), Bond and Leader Visual Analogue Scale (VAS), and Brief Psychiatric Rating Scale (BPRS) 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.

PK Summary:

Panel A (healthy participants: Japanese and non-Japanese) : Separately for each PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level (and day where applicable) will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose, population (Japanese, Non-Japanese), and population by dose and a random effect for subject.

Panels B and D (schizophrenia participants: monotherapy), Panel C (schizophrenia participants: add-on therapy),: Separately for each panel and PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level (and day where applicable) will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose and a random effect for subject.

For each population and PK parameter, geometric means (GM) and corresponding ninety-five percent confidence intervals (CI) for each dose will be provided.

Cardiodynamic Analysis:

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. Separate models may be evaluated for each population. 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.

9.2 Responsibility for Analyses

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

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

9.3 Hypotheses/Estimation

Objectives:

To evaluate the safety and tolerability of rising multiple once-daily oral doses of MK-8189 in participants with schizophrenia (monotherapy and add-on) and healthy Japanese and non-Japanese participants

To estimate the pharmacokinetics for MK-8189 following multiple once-daily oral doses in participants with schizophrenia (monotherapy and add-on) and in healthy Japanese and non-Japanese participants

To evaluate the effect of MK-8189 concentrations on QTc interval and other ECG parameters

9.4 Analysis Endpoints

Primary Endpoints

Safety: Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, 12-lead ECGs, and VS. Baseline is defined as day 1 predose (Day -1 for VS) reading.

BARS, AIMS, SAS, VAS and BPRS for all participants. The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (i.e., ideation and behavior). Responses on the C-SSRS are classified according to 11 prespecified categories as described in procedure manual. The most severe treatment-emergent ideation and behavior event reported at a visit

will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it newly emerged or is more severe compared to recent history (i.e., protocol-defined recent history prior to entering the trial as stated in the Inclusion/Exclusion criteria for suicidal ideation/behavior, up to and including the randomization visit).

Secondary Endpoints

Pharmacokinetics: The PK variables MK-8189 (AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd and t1/2) are of secondary interest.

Exploratory Endpoints

Cardiodynamics: QTc change from baseline (Holter ECGs for Panels A, B, and D and triplicate 12-lead safety ECG measurements for Panel C), HR, RR interval, PR interval, and QRS duration. U and T wave morphology are of exploratory interest

9.5 Analysis Populations

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment (dose level) will be included in the Per-Protocol dataset. This population will be used for the PK and Concentration-QTc analyses.

9.6 Statistical Methods

Safety

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

For all panels, summary statistics and plots will be generated for BARS, AIMS, SAS, VAS, and BPRS 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.

Pharmacokinetics

Model-Based PK Summary

The PK parameters in healthy (Panel A), and schizophrenia (Panels B, C, and D), will be evaluated separately as variability in PK parameters in schizophrenia participants may differ from those in the healthy participants and these panels also differ in the day when the PK are collected. Furthermore, the PK parameters in Panel B and D will be evaluated separately as these panels differ in the day when the PK data are collected.

Panel A (healthy participants: Japanese and non-Japanese): Separately for each PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level (and day where applicable) will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose, population (Japanese, Non-Japanese), and population by dose 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. For each population, ninety-five percent 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 CIs about the GMs on the original scale.

Panels B and D (schizophrenia participants: monotherapy), Panel C (schizophrenia participants: add-on therapy),): Separately for each panel and PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level (and day where applicable) will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose, and a random effect for subject. Geometric means (GM) and corresponding 95% CIs for each dose will be provided.

Descriptive Statistics

For each panel individual values will be listed for each PK parameter AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd, and t1/2 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).

General

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

Cardiodynamic Analysis

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. Separate models may be evaluated for each population. 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 subjects on each treatment is consistent with those deemed to be adequate in the Scientific White Paper on Concentration-QTc Modeling [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 Corp., a subsidiary of Merck & Co., Inc. (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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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. Unless required by law, only the investigator, Sponsor (or representative), 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 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 (eg, 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, commonly 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

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 report form 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 prior to 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 International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (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 trial 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 Debarmen

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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); 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 Studies.

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 signed ICF, 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. 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 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 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.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception 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 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Urine alcohol, cotinine (Panel A only) and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines; If the clinical site's drug screen evaluation routinely detects additional agents, the relevance of positive findings for exclusion will be discussed with the Sponsor.) Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)
• WBC Differential: absolute or % acceptable per institutional standard. • Creatinine: GFR (measured or calculated) or creatinine clearance can be used in place of creatinine. NOTES: 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 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, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

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

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, 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 electronic data collection (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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 nonhormonal highly effective contraception methods if they wish to continue their HRT during the study and if HRT use is permitted per protocol. 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 *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,d] • 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 can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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.
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 If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c Male condoms must be used in addition to the hormonal contraception. d 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 condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' 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 gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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 this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

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

7. Retention of Specimens

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

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

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: 12-Lead Electrocardiogram Abnormality Criteria

If criteria listed in table below differ from inclusion/exclusion criteria, the most conservative criteria should be used.

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
RHYTHM		
Sinus Tachycardia	>110 beats per minute (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 Left Anterior Hemiblock (LAHB)	New onset LAHB
Right Axis Deviation	RBBB with Left Posterior Hemiblock (LPHB)	New onset LPHB
CONDUCTION		
1st degree A-V Block	PR ≥230 ms	PR ≥230 ms + increase of >15 ms; or PR increase of >25%
2nd degree A-V Block	Mobitz Type II	Mobitz Type II
3rd degree A-V Block	All	All
LBBB	All	All
RBBB	RBBB with LAHB/LPHB as defined above	New onset RBBB (not including rate-related)

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
Incomplete Right BBB (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
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
Baseline is defined as Predose Day 1 ms=milliseconds, mm=millimeter		

10.9 Appendix 9: Algorithm for Assessing Out of Range Laboratory Values

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

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

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The participant may be excluded from the study;

   2. The participant may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. 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 (e.g., elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

      OR

   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

   a. If the repeat test value is within the normal range, the participant may enter the study.

   b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: Blood Volume Table

All Panels	Pre-trial	Treatment Period	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests (included FSH and β-hCG)	1	4	1	6	12.5	75.0
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	8.5	8.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-8189 (Panels A and B)		43		43	4.0	172.0
Blood for MK-8189 (Panel C)		35		35	4.0	140.0
Blood for MK-8189 (Panel D)		49		49	4.0	196.0
					Total Blood Volume Participant (Panels A and B)†	264.0 mL
					Total Blood Volume Participant (Panel C)†	232.0 mL
					Total Blood Volume Participant (Panel D) †	288.0 mL
† If additional PK and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.						

10.11 Appendix 11: General (Full) Neurological Exam

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

MODULE 1 – MENTAL STATUS EXAMINATION

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

B. Thought Processes and Language: Generally assess logic, relevance, organization and coherence of volunteer's use of language throughout the interview.

C. Orientation (time, place, person)

D. Attention/Concentration

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

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

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

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

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)

1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

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

F. VIII – Auditory Acuity (assessed using a bed-side screening test e.g. by rubbing fingers on each side of subject's head or by whispering numbers)

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)

***Score*: left and right (except for G, H, J)**

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

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

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

   Score: ***left and right***

   Grade: **NORMAL, INCREASED or DECREASED**

B. Muscle Strength

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

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

2. Test proximal limb strength by having the volunteer flex and extend the knees and elbows against your resistance.

   Test bilaterally, and compare one side to the other.

   Score: ***left and right***

   Grade: ***5/5: normal;***

   4/5: movement against resistance impaired;

   3/5: movement against gravity but not against resistance;

   2/5: visible movement but not against gravity;

   1/5: visible contraction;

   0/5: no visible activity

3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer's feet; finger abduction and handgrip strength against your resistance.

   Test bilaterally, and compare one side to the other.

   Score: ***left and right***

   Grade: ***5/5: normal;***

   4/5: movement against resistance impaired;

   3/5: movement against gravity but not against resistance;

   2/5: visible movement but not against gravity;

   1/5: visible contraction;

   0/5: no visible activity

C. Pronator Drift

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

2. Instruct the volunteer to keep both arms still while you tap them briskly downward. The volunteer should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

   Score: ***left and right***

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

MODULE 4 - REFLEXES

A. Biceps

B. Knee

Note: *Other deep tendon reflexes may be tested at Investigator's discretion (e.g. elbow, wrist or Achilles tendon)*

Score: left and right

Grade: **NORMAL, INCREASED, DECREASED or ABSENT**

C. Babinski

Score: left and right

Grade: **NORMAL or ABNORMAL**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

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

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

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

B. Point-to-Point Movements

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

   Score: left and right

   Grade: **NORMAL or IMPAIRED**

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

C. Romberg

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

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

   Grade: **NORMAL or IMPAIRED**

D. Gait

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

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

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

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

MODULE 6 - SENSORY

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

B. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

C. Temperature: warm or cool object touched to skin of forearms and legs, bilaterally.

D. Vibration: tuning fork vibration detection in hands, feet bilaterally.

E. Position sense: perception of thumb and toe movement, bilaterally.

F. Stereognosis: (identify common objects placed in hand, e.g., coin, key).

Score: left and right

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

10.12 Appendix 12: Targeted Neurological Exam

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

MODULE 1 – MENTAL STATUS EXAMINATION

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

MODULE 2 – CRANIAL NERVE ASSESSMENT

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)

    1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

MODULE 3 - MOTOR SYSTEM

B. Muscle Tone

    1. Ask the volunteer to relax.

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

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

        Score: left and right

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

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

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

   Score: left and right

   ***Grade:* NORMAL or IMPAIRED**

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

D. Gait

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

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

MODULE 6 - SENSORY

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

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
AAP	atypical anti-psychotics
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BPRS	Brief Psychiatric Rating Scale
CRF	case report form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EPS	extrapyramidal symptoms
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
NOAEL	no observed adverse effect level
PANSS	positive and negative symptoms scale
PK	pharmacokinetic
RNA	ribonucleic acid
SAE	serious adverse event
SAS	Simpson Angus Scale
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
UDS	urine drug screen
VAS	Visual Analogue Scale
WONCBP	woman/women of non-childbearing potential
WOCBP	woman/women of childbearing potential

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