Official Protocol Title:	A Double-Blind, Cross-Over Placebo-Controlled and Active-Controlled Trial To Evaluate The Effect Of A Supratherapeutic Dose Of MK-8189 On The QTc Interval In Participants With Schizophrenia
NCT number:	NCT05893862
Document Date:	16-Aug-2023

TITLE PAGE

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Protocol Title: A Double-Blind, Cross-Over Placebo-Controlled and Active-Controlled Trial To Evaluate The Effect Of A Supratherapeutic Dose Of MK-8189 On The QTc Interval In Participants With Schizophrenia

Protocol Number: 019-02

Compound Number: MK-8189

Sponsor Name: Merck Sharp & Dohme LLC

(hereafter called the Sponsor or MSD)

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	NA
EU CT	NA
EudraCT	NA
JAPIC-CT	NA
WHO	NA
UTN	NA
IND	118,986

Approval Date: 16 August 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	16-AUG-2023	Clarified predose hCG pregnancy testing
Amendment 1	03-MAY-2022	Increased sample size from 54 to 84
Original Protocol	03-MAR-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

Clarification of predose hCG pregnancy testing for consistency with inclusion criteria #14. A previous PCL incorrectly clarified the hCG timepoints.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3 Schedule of Activities	hCG pregnancy test moved from Day -2 to Day -1 and note updated to be consistent with inclusion criteria #14.	This change corrects a previous PCL error and ensures predose hCG pregnancy testing is obtained within 24 (urine) or 72 (serum) hours predose per inclusion criteria #14.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3, Schedule of Activities	Blood for Plasma MK-8189 – added Days 3, 4, and 5 timepoints	Protocol inconsistency. Footnote ‘k’ indicated blood collection through 72 hours (Day 5).
Section 1.3, Schedule of Activities	Blood for Plasma Moxifloxacin – added Days 3, 4, and 5 timepoints	Protocol inconsistency. Footnote ‘l’ indicated blood collections through 72 hours (Day 5).
Section 1.3, Schedule of Activities	Randomization number assignment updated from Day -1 to Day 1	This represents the day the participant is deemed eligible to receive the first dose of study intervention and will occur prior to dosing on Period 1 Day 1.
Section 1.3, Schedule of Activities	UDS was added to Day -6 and note was updated to provide additional clarification of UDS predose testing.	Predose UDS will be done at the time of admission to the clinic (Day -6 or Day -2).
Section 1.3, Schedule of Activities	24-Hour Holter ECG Extraction on Day 4 was removed.	Protocol inconsistency. Footnote ‘e’ indicated Holter ECG extractions through Day 2 24 hours (Day 3). No extractions will occur on Day 4.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Footnote 'i' was updated to clearly indicate triplicate HR measurements are required at all timepoints, including screening and poststudy, and at the timepoints indicated on specific days.	Additional clarification provides consistency with Section 8.3.2.1 of the protocol that more clearly specifies the triplicate HR measurements.
Section 1.3, Schedule of Activities	In footnote 'k', the bullet "Leftover main study plasma will be stored for future biomedical research' was removed.	In amendment (01), storage of leftover main study plasma was clarified to indicate for main study use and FBR as previously indicated in Section 8.9. The footnote should have been removed in the protocol amendment.
Section 1.3, Schedule of Activities	Visit window added for the poststudy visit (column heading)	To provide flexibility of +/- 2 days
Section 1.3, Schedule of Activities Section 4.1, Overall Design	The 5-day washout between periods was clarified as it is relative to the last dose of study medication (Day 2) in each period.	Washout is based on the terminal half-life of both MK-8189 and moxifloxacin and the not the actual end of the period (Day 5)
Section 1.3, Schedule of Activities	Added text to footnote 'c' clarifying participants not currently being treated with antipsychotic therapy will also remain domiciled through 72 hours post the last dose in Period 3.	Domiciling requirement for all participants is through 72 hours post the last dose in Period 3.
Section 5.2, Exclusion Criteria	EC 17 – removed 2 paragraphs referring to eGFR	eGFR is not being used to calculate CrCl in the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Double-Blind, Cross-Over Placebo-Controlled and Active-Controlled Trial To Evaluate The Effect Of A Supratherapeutic Dose Of MK-8189 On The QTc Interval In Participants With Schizophrenia

Short Title: MK-8189 Thorough QT Study in Participants with Schizophrenia

Acronym: TQT

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in participants with schizophrenia.

Primary Objective	**Primary Endpoint**
To evaluate the effect of a supratherapeutic dose of 80-mg MK-8189 on the QTc interval Hypothesis: Administration of an 80-mg MK-8189 dose on Day 2 does not prolong the QTc interval to a clinically significant degree. Specifically, the true mean difference (MK-8189 - placebo) in QTc change from baseline is less than 10 msec	QTc (QT interval corrected for heart rate) change from baseline at post dose time points
To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia	Adverse events leading to discontinuation of study intervention Adverse events
Secondary Objectives	**Secondary Endpoints**
To evaluate the effect of moxifloxacin on the QTc interval Hypothesis: Administration of a single 400-mg dose of moxifloxacin is associated with an increase in QTc interval. Specifically, the true mean difference (Moxifloxacin-placebo) in QTc change from baseline is greater than 5 msec at least at one time point	QTc (QT interval corrected for heart rate) change from baseline at post dose time points
To estimate the pharmacokinetics of MK-8189 following multiple doses of MK-8189 in participants with schizophrenia	AUC0-24, AUC0-last, Cmax, C24, Tmax, t1/2 of MK-8189

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Schizophrenia
Population	Participants with schizophrenia or schizoaffective disorder
Study Type	Interventional
Intervention Model	Cross-Over This is a multi site study
Type of Control	Placebo
	Active Control
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects, Investigator, Monitor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 84 participants with schizophrenia will be allocated/randomized to 1 of 6 treatment sequences, such that approximately 10 to 14 participants are evaluable and complete the study in each treatment sequence as described in Section 9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Sequences 1 to 6	MK-8189	12 mg	48 mg	Oral	Treatment A Day 1	Test Product
Sequences 1 to 6	MK-8189	12 mg 4 mg	80 mg	Oral	Treatment A Day 2	Test Product
Sequences 1 to 6	Moxifloxacin	400 mg	400 mg	Oral	Treatment B Day 2	Diagnostic – to assess endpoints
Sequences 1 to 6	MK-8189 Matched Placebo	0 mg	0 mg	Oral	Treatment C Days 1-2	Placebo
Sequences 1 to 6	Standard image placebo	0 mg	0 mg	Oral	Treatment B Day 1	Placebo

Total Number of Intervention Groups/Arms	4
Duration of Participation	Each participant will participate in the study for approximately 11 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

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

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

Study accepts healthy participants:

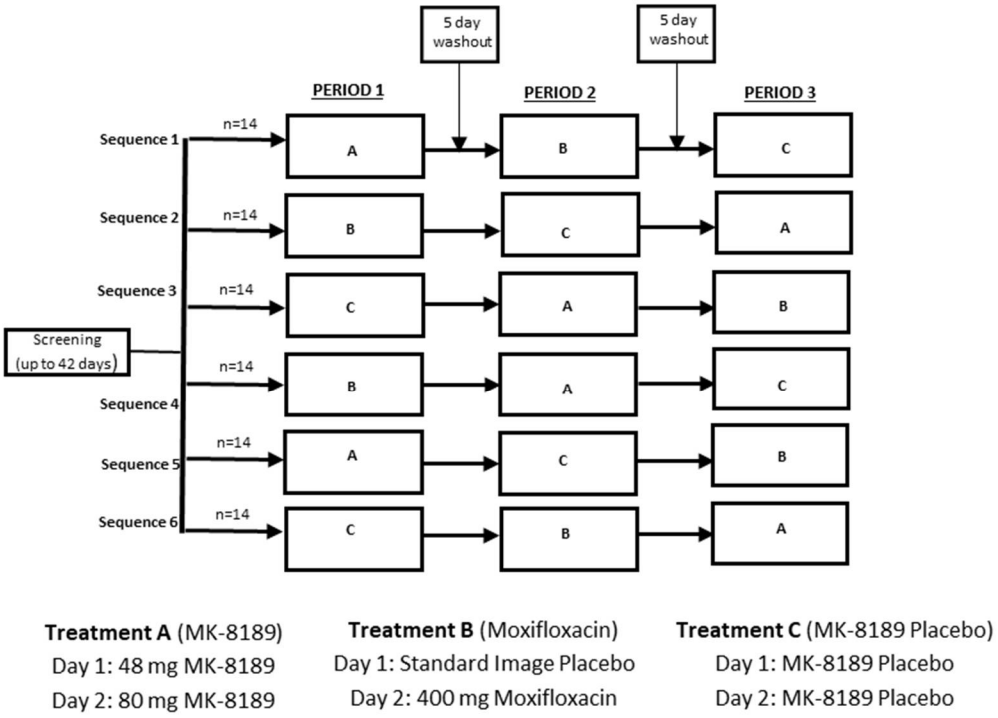
No

A list of abbreviations is in Appendix 12.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



1.3 Schedule of Activities

All Sequences											
	Prior to Period 1			**All Periods[a]**						**After Period 3**	
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**	
Administrative/Study Procedures											
Informed Consent	X										Section 5.1, 8.1.1.1
Informed Consent for FBR	X										Section 5.1, 8.1.1.2
Participant ID Card	X										Section 8.1.3
Inclusion/Exclusion Criteria	X			X							Specific criteria may be reviewed before randomization in Period 1 Section 5.1 & Section 5.2
Medical History (includes psychiatric history and substance abuse)	X										Substances: Drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X----------X										Section 5.2, 6.5, 8.1.5
Assignment of Screening Number	X										Section 8.1.6
Washout from current antipsychotics therapy		X									Medication discontinued at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1 Section 8.1.5.1
Assignment of Randomization Number					X						Period 1 only Section 5.5, 8.1.7
Study Medication Administration/Dispensing					X	X					Section 4.1
Standard Meals[b]		X----------X									Section 5.3.1
Domiciling[c]		X----------X									Section 8.1.11
Follow Up Phone call – Period 3 only									X		Should occur 5-7 days after discharge Section 8.10.2

All Sequences											
	Prior to Period 1			**All Periods[a]**						**After Period 3**	
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**	
Safety Procedures											
Full physical examination	X			X					X	X	Day -1: Period 1 only Day 5: Period 3 only Section 8.3.1
Height	X										
Weight	X			X					X	X	BMI to be taken only at Screening
Full Neurological Examination	X			X							Performed at Screening and Day -1: Period 1 only Section 10.11
Targeted Neurological Examination[d]				X	X	X	X	X	X	X	Day -1: Period 2 and Period 3 only Day 5: Period 3 only All other intervention days: Up to 3 hours predose Section 10.11
Vital Signs (heart rate, blood pressure)[e]	X			X	X	X	X	X	X	X	Period 1 Day -1: may be done on Day -2 Section 8.3.2
Orthostatic Vital Signs (heart rate, blood pressure) [f]	X			X	X	X	X	X	X		Period 1 Day -1: may be done on Day -2 Section 8.3.2
Vital Signs (respiratory rate, temperature) [e]	X			X	X[g]	X[g]	X[g]	X[g]	X[g]	X	Period 1 Day -1: may be done on Day -2 Section 8.3.2
12-lead Safety ECG[h]	X			X	X	X	X	X	X	X	Period 1 Day -1: may be done on Day -2 Section 8.3.3
24-Holter ECG Extraction[i]				X	X	X	X				Section 8.3.3
Serum hCG (as needed in POCBP only)	X									X	Section 5.1 & Section 8.3.5
Urine or Serum hCG (as needed in POCBP only)				X							Predose hCG testing should be per IC #14. Sections 5.1, 8.3.5, & 10.2

All Sequences											
	Prior to Period 1			**All Periods[a]**						**After Period 3**	
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**	
Serum FSH - (PONCBP only)	X										Postmenopausal participants only Section 10.2
HIV, Hepatitis B and C screen (per site SOP)	X										Section 10.2
UDS/BDS (per site SOP)	X	X	X								To be completed once upon admission (Day -6 or Day -2) Additional UDS/BDS are conducted per site SOP
Laboratory Safety Tests (hematology, chemistry, urinalysis)	X			X					X	X	Period 1 Day -1: up to 72h prior to dosing. Per I/E, results must be reviewed prior to Period 1 dosing. In Periods 2 and 3, results are not required to be reviewed prior to dosing. Day 5: Period 3 only Section 10.2
AE/SAE review	X----------									----------X	
BPRS[d]	X			X					X		The assessment can be done at any time during the day however an attempt should be made for consistent timing across days and periods. Day 5: Period 3 only Section 8.3.9
C-SSRS Baseline Version	X										Section 8.3.6.1
C-SSRS Since Last Assessment Version[d]				X		X	X		X	X	Up to 3 hours predose Section 8.3.6.1
Barnes Akathisia Rating Scale (BARS)[j]				X		X			X	X	The assessment can be done at any time during the day however an attempt should be made for consistent timing across days and periods. Day 5: Period 3 only Section 8.3.7

All Sequences											
	Prior to Period 1			**All Periods[a]**						**After Period 3**	
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**	
Abnormal Involuntary Movement Scale (AIMS)[j]				X		X			X	X	The assessment can be done at any time during the day however an attempt should be made for consistent times across days and periods. Day 5: Period 3 only Section 8.3.7
Simpson Angus Scale (SAS)[j]				X		X			X	X	The assessment can be done at any time during the day however an attempt should be made for consistent times across days and periods. Day 5: Period 3 only Section 8.3.7
Pharmacokinetics											
Blood for Plasma MK-8189 and/or Metabolites Assay[k]					X	X	X	X	X		Sample to be collected within 10 minutes of end of ECG extraction window. Plasma for MK-8189 will be collected in Treatment A & C Periods Days 1 and 2
Blood for Plasma Moxifloxacin Assay[l]						X	X	X	X		Sample to be collected within 10 minutes of end of ECG extraction window. Plasma for moxifloxacin will be collected in Treatment B Period Day 2 only Section 8.6.1

All Sequences											
	Prior to Period 1			**All Periods[a]**						**After Period 3**	
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**	
Biomarkers											
Blood for Genetic Analysis					X						Period 1 only Collect predose from enrolled participants only Section 8.8

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BDS=blood drug screen; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia Suicide Severity Rating Scale; CRU=clinical research unit; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; PK=pharmacokinetic; SAE=serious adverse event; SAS=Simpson Angus Scale; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs; POCBP=participant of childbearing potential; PONCBP=participant of non-childbearing potential.

a. There will be a 5-day washout between Periods 1 and 2 & 2 and 3. The 5-day washout between periods is relative to the last dose of study medication (Day 2) in each period.

b. Meals should be given at approximately the same time every day starting from time of domiciling through last dose including breakfast will be given at ~1-hour postdose, lunch at ~4-hour postdose; a snack at ~6-hour postdose and dinner at ~9-hour postdose. On non-dosing days, meals will be time-matched to mealtimes on dosing days. It is important that meal timing is standardized relative to Holter ECG extractions. If a mealtime and Holter ECG extraction/PK assessment coincide, the Holter ECG extraction will be conducted prior to the meal.

c. Participants currently treated with antipsychotic therapy will be domiciled from Day -6 prior to Period 1 (to start washout period) and will remain in the CRU until 72 hours post the last dose in Period 3. Participants not currently being treated with antipsychotic therapy may be domiciled minimally starting on Day -2 through 72 hours post the last dose in Period 3. Participants may stay longer at PIs discretion.

d. During the intervention period on days when a dose is not given, assessment should be time-matched to the predose or postdose time point. Poststudy assessments are not required to be time-matched.

e. All HR measurements will be in triplicate. VS (HR, BP and RR) - On the following days, specific timepoints are noted:
- Day -1: time-matched to predose and 9 hours postdose. BP will also be taken in triplicate at both timepoints.
- Days 1 & 2: 9 hours postdose.
- Days 3 & 4: time-matched to predose and 9 hours postdose
- Day 5: time-matched to predose

Temperature will only be taken on Day -1 time-matched to 9 hours postdose.

All Sequences												
	Prior to Period 1			**All Periods[a]**						**After Period 3**		
Study Period:	**Screening**	**Washout Check-In**		**Pre-dose**	**Intervention**					**Poststudy**	**Notes**	
Scheduled Day:	**Up to -42**	**-6**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**+14 post last dose (+/-2)**		

f. Orthostatic VS (HR, BP) - On the following days, specific timepoints are noted:
- Day -1: time-matched to predose and 9 hours postdose
- Days 1 & 2: 9 hours postdose
- Days 3 & 4: time-matched to predose and 9 hours postdose
- Day 5: time-matched to predose

g. Respiratory rate only

h. 12-Lead safety ECG measurements - On the following days, specific timepoints are noted:
- Day -1: Triplicate measurements, time-matched to 9 hours postdose
- Days 1 & 2: 9 hours postdose
- Days 3 & 4: time-matched to 9 hours postdose
- Day 5 (Period 3 only): Upon discharge from the clinic

i. Continuous Holter ECG measurements will be performed on Day -1 (Period 1 only) for approximately 24 hours. No rest or extraction times are specified. Moderate ambulation and physical activity are encouraged to show a range of heart rate on Day -1 of Period 1 only.
In each Period, continuous 24-hour Holter ECG measurement will be performed from approximately 70 minutes prior to first dose administration and until 24 hours post last dose administration. Replicate 12-lead Holter ECG recordings will be extracted over a 5-minute interval following 15 minutes of rest.
- Day 1: Predose (-50 min, -30 min, -10 min), 0.5, 1, 2, 3, 4, 6, 8, 12, 14 hours postdose
- Day 2: Predose, 1, 2, 3, 4, 8, 11, 14, 16, 24 hours postdose

j. Additional BARS, AIMS, and SAS assessments should be conducted, as soon as reasonably possible, when there are observed or reported complaints of dystonia and/or akathisia

k. PK for MK-8189 (Treatments A & C)
- Day 1: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 14 hours postdose
- Day 2: Predose, 0.5, 1, 2, 3, 4, 8, 11, 14, 16, 24, 36, 48, 72 hours postdose

l. PK for Moxifloxacin:(Treatment B)
- Day 1: none
- Day 2: Predose, 0.5, 1, 2, 3, 4, 8, 11, 14, 16, 24, 36, 48, 72 hours postdose
- Blood samples will be archived.

2 INTRODUCTION

MK-8189 is a selective inhibitor of PDE10A that is in development for the treatment of schizophrenia.

2.1 Study Rationale

This study is being conducted to support efforts to de-risk the potential for MK-8189 to prolong QT as required by International Council for Harmonisation (ICH E14). The study will assess the potential effect of a supratherapeutic dose of MK-8189 on QTc prolongation in participants with schizophrenia in a randomized, double-blind (MK-8189 and placebo) placebo-controlled and active-controlled, crossover design. Participants will receive open-labeled moxifloxacin as an active control.

To appropriately interrogate the potential for a drug to prolong QT, a TQT study requires the administration of a supratherapeutic dose that is expected to cover the high clinical exposure scenario; this reflects the exposure of the drug when affected by the intrinsic or extrinsic factor that causes the greatest increase in plasma concentrations. Thus, this study will evaluate safety, tolerability, and PK of MK-8189 at a dose that will result in concentrations that are greater than those expected when MK-8189 is co-administered with a cytochrome P450 (CYP) 3A inhibitor [redacted] increase in maximum plasma concentration [Cmax], P006), the factor which is expected to cause the greatest increase in MK-8189 concentrations. [redacted]

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 monohydrate) (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) or second-generation antipsychotic (SGA) treatment.

2.2.2 Preclinical and Clinical Studies

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

Summary of Completed Phase 1 Clinical Studies

Three single-dose clinical studies (P001, P002, P004) in healthy participants, a single dose study in healthy participants and participants with moderate hepatic impairment (P012) two CYP3A drug-drug interaction (DDI) studies in healthy participants (P006, P015), and four multiple- dose clinical studies in participants with schizophrenia and healthy participants (P003, P007, P011 and P016) have been completed with MK-8189. P011 included elderly (>60 years of age, n=12) participants with schizophrenia and healthy elderly (> 60 years of age, n=18) participants. Overall, across the completed studies, 231 participants have received at least one dose of MK-8189; 124 participants without schizophrenia and 107 participants with schizophrenia. Please see IB and section 2.2.4 for a summary of completed studies.

Overview of Pharmacokinetics:

CCI [redacted] Based on completed studies, data suggest that the exposures at steady state for a given dose are generally comparable between healthy participants and participants with schizophrenia administered MK-8189 as monotherapy. MK-8189 is a CYP3A substrate and in a DDI study (P006) the coadministration of extended release 240-mg diltiazem, a moderate CYP3A inhibitor, increased MK-8189 area under the curve (AUC) and Cmax by approximately CCI [redacted] respectively. Additionally, a subsequent DDI study (P015) demonstrated that coadministration of itraconazole, a strong CYP3A inhibitor, increased MK-8189 AUC and Cmax by approximately CCI [redacted] respectively, and these results were generally consistent with the results observed in the diltiazem study. Collectively, these results confirm that MK-8189 is a CYP3A substrate. Data collected from a single-dose hepatic impairment study (P012) demonstrated that MK-8189 AUC and Cmax were approximately CCI [redacted] in participants with moderate hepatic impairment compared to healthy matched controls, respectively. Results collected from a study in adult and elderly participants (P011) suggest that 1) the PK of MK-8189 in elderly participants with and without schizophrenia were generally similar to one another and 2) the PK of MK-8189 in young and elderly participants with schizophrenia were generally similar to one another.

Overview of Safety:

Across completed and ongoing studies, MK-8189 was generally well tolerated up to 24 mg in healthy participants and up to 80 mg in participants with schizophrenia. The most common treatment-related adverse events (AEs) (≥5%) following treatment of MK-8189 (n=231) across the completed Phase 1 studies which included, healthy participants (non-elderly and

elderly), participants with schizophrenia (non-elderly and elderly) and participants with hepatic impairment, were headache (13.0%) somnolence (13.4%), dystonia (10.4%), decreased appetite (9.5%), nausea (8.7%), fatigue (5.6%), dizziness (6.5%), vomiting (6.1%), diarrhea (4.8%), akathisia (6.1%), anxiety (5.2%) and insomnia (5.2%). Most AEs were mild to moderate in severity. There were no deaths and one treatment-related SAE across the Phase 1 studies; In P007, one participant discontinued due to a treatment-related SAE of increased psychosis which resulted in hospitalization. The SAE occurred following treatment with the 36-mg dose. The AE was considered severe and had a duration of 6 days. The SAE resolved following initiation of an antipsychotic and benzodiazepine.

Participants with schizophrenia (n=107) were only evaluated in multiple-dose studies. The most commonly (≥ 5%) reported treatment-related AEs reported in participants with schizophrenia administered MK-8189 as monotherapy (n=75) or adjunct therapy (n= 32) were headache (16.8%), somnolence (15.0%), decreased appetite (12.1%), nausea (9.3%), dystonia (8.4%), akathisia (7.5%), dizziness (6.5%), vomiting (6.5%), and constipation (5.6%). In comparison, the most commonly reported AEs in participants administered placebo (n=37) were somnolence (13.5%), headache (10.8%), anxiety (5.4%), decreased appetite (5.4%), dizziness (5.4%), nausea (5.4%), and rash (5.4%). There is no clear trend for a relationship between MK-8189 dose and specific AEs.

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

2.2.3 Ongoing Clinical Studies

As of January 1, 2023, 4 Phase 1 trials and one Phase 2 trial are ongoing (includes clinically complete) and 3 Phase 1 trials completed. All data presented for ongoing trials are preliminary.

2.2.3.1 Protocol 010

P010 was a Phase 1 study to evaluate the Absorption, Metabolism and Excretion of a single 4.5-mg IR/~ 50 µCi dose of [14C]MK-8189 in healthy adults. This study is clinically complete and preliminary results are provided below.

The study was a non-randomized, single-site, open-label, 1-period study of MK-8189 dosed in 6 healthy adult males. Participants received a single-oral dose of 4.5-mg (~50-µCi) of [14C]MK-8189, fasted. Blood (plasma), urine, and fecal samples were collected at specified

timepoints. Total radioactivity and metabolite profiling was assessed in plasma, urine, and fecal samples. MK-8189 concentrations were also measured in plasma.

In general, a single dose of 4.5-mg (~ 50-µCi) of [14C]MK-8189 was generally well tolerated in healthy male participants. Six (100.0%) participants experienced 1 or more AEs during the study and 5 (83.3%) reported AEs that were considered related to study intervention by the investigator. Four of 6 participants experienced mild extrapyramidal symptoms. All AEs were mild in intensity except 1 moderate AE of lethargy and all AEs resolved by study completion. AEs reported by >1 participant were akathisia (n=4), fatigue and hyperhidrosis (n=2 each).

Four participants experienced intervention-related mild akathisia starting within 20 minutes (minutes) after dosing with a duration ranging from 15 to 50 minutes. All events resolved without intervention. One participant experiencing akathisia also experienced lethargy (moderate for 3.82 hours followed by mild for 18.25 hours), mild irritability for 20 minutes and euphoric mood for 9.92 hours on Day 1. One participant experiencing akathisia also experienced mild hyperhidrosis for 45 minutes, fatigue for 22.83 hours and dyskinesia for 39 minutes on Day 1.

There were no clinically meaningful abnormalities (i.e., reported as AEs) in routine laboratory safety, ECG, vital signs, or physical examinations. There were no deaths or SAEs reported and no discontinuations due to an AE.

2.2.3.2 Protocol 013

P013 was a multiple-dose clinical study to evaluate the safety, tolerability, and pharmacokinetics of MK-8189 in healthy Chinese participants.

This study enrolled 16 healthy Chinese male and female participants and were randomized to receive MK-8189 8 mg or placebo (Days 1-3), MK-8189 12 mg or placebo (Days 4-6), MK-8189 16 mg or placebo (Days 7-9) and MK-8189 24 mg or placebo (Days 10-12). MK-8189 oral administration of titrated doses up to 24 mg was generally tolerated in healthy Chinese participants. No reports of serious adverse events (SAEs) or deaths were identified. All 12 participants treated with MK-8189 reported 1 or more AEs and the investigator found at least 1 event related. These events were generally mild to moderate in severity and recovered without concomitant medication.

All 12 participants had 1 or more AE considered related to MK-8189 by the investigator. The most frequently reported (> n=1) treatment related AEs after MK-8189 were somnolence (n=10, 83.3%), insomnia (n=9, 75.0%), decreased appetite (n=5, 41.7%), nausea (n=4, 33.3%), dystonia (n=4, 33.3%), tremor (n=3, 25.0%), anxiety (n=3, 25%), blood bilirubin increased (n=2, 16.7%), akathisia (n=2, 16.7%), headache (n=2, 16.7%), hyperhidrosis (n=2, 16.7%). Of the 2 participants who discontinued the study, 1 discontinued due to a treatment related AE of moderate delusions (15.5 hours duration) after MK-8189 8 mg. Another participant discontinued due to other reason (no longer wanted to take the study drug) and is described below.

Five participants reported dystonia (n=4 after MK-8189 and n=1 after placebo), an ECI:

- One participant experienced dystonia (mild, related) after MK-8189 8 mg. Signs and symptoms included difficulties in closing eyes, tremor around eyes after closing them, abnormal muscle tension around mouth and unnatural occlusion and restricted mouth and eye movement, abnormal head and facial muscle tone. The participant remained under observation (no laboratory tests were performed, or treatment given) and recovered from dystonia after 7 hours and 30 minutes.
- One participant experienced occlusal muscle dystonia (mild) after placebo. The occlusal muscle was abnormal and could not be closed for 6 seconds; the participant reported it was difficult to close the eyes, and the eyes trembled after closing the eyes. The participant remained under observation (no laboratory tests were performed, or treatment given) and the event had self-remission after 6 seconds.
- One participant experienced dystonia (mild, related) after the last dose of MK-8189 16 mg. There was no complaint of discomfort, and a physical examination found increased muscle tension of the limbs, and the arm fell slightly slowly. No treatment was given, and no laboratory tests were performed. Another physical examination was performed with no abnormalities and the symptoms resolved after 59 minutes.
- One participant experienced dystonia (mild, related) and akathisia (mild, related) after MK-8189 8 mg. The participant had difficulty closing eyes, stiff wrists, and poor arm movement. A physical examination showed no abnormalities. On that day, SSAS assessment showed that the subject had slow falling arms, stiff swinging shoulders, stiff elbows, stiff wrists, slight swinging of the legs, and slight resistance to head rotation. BARS assessment showed akathisia. AIMS showed slight restriction of facial muscle movement. No laboratory tests were taken, and no treatment given. The participant remained under observation and symptoms of dystonia and akathisia resolved after 1 hour 40 minutes. The day after the participant experienced thinking sluggish (mild, 1 day duration) and anxiety (mild, 8 hours duration).
- One participant experienced dystonia (mild, related) after MK-8189 8 mg. The participant presented numb mouth, difficulty closing eyes, tight mouth, and difficulty opening mouth. Also present was abnormal perioral muscle tone when looking up. The physical examination showed no abnormalities. The investigator conducted AIMS, which showed slightly increased tongue movement, the BARS showed the inner restlessness, and the SAS assessment report indicated that when the subject walked, the swing was slightly reduced, the arm dropped slightly slowly, the contact sound was weak, and the rebound was weak. The participant was under observation and received trihexyphenidyl hydrochloride (benzhexol hydrochloride). The symptoms of dystonia resolved 2 hours and 4 minutes later. This participant reported a second episode of dystonia (mild, related) after MK-8189 12 mg. The participant claimed their eyes were trying to look up involuntary, and also noted difficulty closing the eyes. The BARS, SAS and AIMS were conducted, and the SAS indicated gait obvious diminution in swing, arm fall slowed slightly with less audible contact and little rebound, shoulder shaking slight stiffness, elbow rigidity slight stiffness, wrist rigidity slight stiffness, head rotation slight resistance to movement although the time to rotate may be normal. The participant was kept under

observation and received trihexyphenidyl hydrochloride (benzhexol hydrochloride) to treat the dystonia. A physical examination was completed and showed no abnormality. Symptoms of dystonia recovered after 23 hours and 30 minutes. This participant also reported the following AEs and ultimately discontinued from the study after the Day 6 dose due to Other reason (as noted above): 3 occurrences of dizziness (11.5 hours, 5.5 hours and 1 week duration), 3 occurrences of headache (11.5 hours, 5.5 hours and 5 days duration), 2 occurrences of vomiting (1 hour and 7 hour duration), somnolence (5 days duration), anxiety (5 days duration), insomnia (3 days duration), decreased appetite (3 days duration), nausea (4 days duration) and diarrhea (4 days duration). All AEs were considered related to study intervention except the diarrhea which occurred a day after study intervention was stopped.

- One participant reported suicidal ideation (mild) after MK-8189 24 mg. It was reported that after a dream the participant had mood swings and was crying. The concept of transient suicide appeared. The participant was observed during the clinical course and did not receive treatment for the event. The suicidal ideation lasted for 5 seconds, and the moderate mood swings (related) recovered after 21 minutes. As the outcome was recovered, no further follow-up information was reported. The investigator considered the suicidal ideation related to study intervention as the participant had not reported previous suicidal thoughts.

There were no clinically meaningful trends for study-intervention related changes in the vital sign measurements, physical examination assessments, or other observations related to safety in this study.

2.2.3.3 Protocol 014

P014 is a randomized, placebo-controlled, parallel-group, multisite, double-blind, multiple-panel study of MK-8189 in participants with schizophrenia to support efforts to de-risk the potential for MK-8189 to prolong QT as required by ICH E14. Thus, this study is being conducted to 1) evaluate a supratherapeutic dose regimen in participants with schizophrenia to support, if required, a TQT in participants with schizophrenia and 2) perform a concentration-QTc analysis in participants with schizophrenia receiving supratherapeutic doses.

Panel A and A-1 are clinically complete. Panel A enrolled 11 participants who were randomized to receive MK-8189 48 mg or placebo (Day 1) and MK-8189 60 mg or placebo (Day 2). Panel A-1 enrolled 10 participants who were randomized to receive MK-8189 48 mg or placebo (Day 1) and MK-8189 80 mg or placebo (Day 2). Panel C is ongoing and will enroll up to 30 participants who will be randomized to receive MK-8189 or placebo; MK-8189 48 mg or placebo (Days 1 to 2) and MK-8189 80 mg or placebo (Day 3).

To date, no SAEs or deaths have occurred. In Panel A, 11 schizophrenic participants enrolled in Panel A have completed dosing per protocol. Four participants reported a total of 5 treatment-emergent adverse events. All AEs were considered mild in intensity. Discomfort, tremor, restlessness, somnolence, and headache were considered related to study intervention; exacerbation of insomnia and musculoskeletal pain were considered unrelated

to study intervention. All AEs resolved without interruption to study intervention. In Panel A-1,10 participants were randomized and completed dosing per protocol. Five participants reported at least one treatment-emergent AE. All AEs were mild and resolved. AEs reported included headache (n=1), constipation (n=1), insomnia (n=1), nausea (n=1), asthenia (n=1), somnolence (n=2), anxiety (n=1), feeling jittery (n=1) and akathisia (n=1). The AE of akathisia began following the 80 mg dose, no treatment was provided, and the AE lasted for approximately 3 weeks.

To date, in Panel C, 28 participants have been randomized, 26 have completed dosing per protocol, and 25 have completed the study. Two participants have discontinued due to an AE, and 1 participant withdrew consent. Treatment emergent AEs have been reported in 10 participants and include dry mouth (n=1), increased appetite (n=1), dizziness (n=1), headache (n=3), vaginal discomfort (n=1), fatigue (=1), anxiety (n=1) dyspepsia (n=1), lip twitching (n=1), somnolence (n=1), asthenia (n=1), and vomiting (n=1). One participant was reported to have mild nystagmus and miosis which began ~ 1 day following their last dose with a duration of 2 days. The participant who experienced the vaginal discomfort (unrelated to study treatment) following completion of study treatment was discontinued from the study as the participant was prescribed fluconazole and metronidazole. Two participants experienced dystonia: One participant experienced moderate oromandibular dystonia with a duration of ~16 hours which began 4 hours following their first 48 mg dose of MK-8189/placebo. The participant withdrew consent due to this AE and the participant was treated with a single dose of benztropine 1 mg. A second participant also experienced mild dystonia approximately 7 hours following their first dose of MK-8189/placebo. The participant complained of intermittent stiffening of her neck shoulders hands and jaws for approximately 4 hours. No treatment was administered. No dystonia symptoms were reported the following day and the participant completed study treatment pre protocol. The participant also experienced intermittent episodes of vomiting following administration of MK-8189/placebo. With the exception of the moderate oral mandibular dystonia, all AEs were mild, and all AEs with the exception of vaginal discomfort (participant lost to follow-up) were resolved.

Across the panels there have been no trends for clinically significant changes, in safety laboratory parameters, vitals or ECGs.

2.2.3.4 Protocol 017

P017 is an ongoing Phase 1 randomized, placebo-controlled, parallel-group, multisite, double-blind study of MK-8189 in participants with Alzheimer's Disease with and without neuropsychiatric symptoms.

Preliminary blinded safety data from the ongoing Phase 1 study (P017) in participants (n=29) with AD, suggest that MK-8189 doses titrated from 8 mg to 24 mg were generally well tolerated. An initial cohort of 8 participants (6 active: 2 placebo) received. Based on good safety and tolerability data from those first 8 participants, all additional participants (n=21) were to be titrated up to MK-8189 24 mg/placebo as follows: MK-8189 8 mg/placebo Days 1 to 3 MK-8189 16 mg/placebo Days 4 to 6 and MK-8189 24 mg/placebo Days 7 to 28. Based on available data to date, 13 men and 15 women were enrolled, 19 were White and 9 were Black or African American and participants were between the ages of 65 and 85 years. There

were no deaths or treatment-related SAEs. Of the 29 participants, 27 completed study treatment for 28 days and of those 26 completed study treatments per protocol. One participant down-dosed from MK-8189 24 mg/placebo to MK-8189 8 mg/placebo due to an AE first reported on Day 8 but experienced since Day 6 and this participant completed 28 days of dosing. One participant withdrew consent, and one participant withdrew following administration of the MK-8189 16 mg/placebo dose due to AEs (duration) of moderate nausea (4 days), mild diarrhea (2 days) and mild dizziness (3 days). Eleven participants reported at least one AE. Most AE reported were mild, and one AE was severe (intermittent electrical shock sensation with duration of 8.5 hours following administration of 16 mg/placebo dose) which resulted in down dosing as described above. No participant reported AEs of EPS. There have been no trends for clinically meaningful changes in laboratory safety values, vital signs or ECGs.

2.2.3.5 Protocol 008

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

A total of 576 participants from approximately 80 sites across the USA, Europe and Asia will be recruited into this trial. Recruitment was initiated in December 2020. Treatment duration will be for a period of 12 weeks and includes a 6-week acute treatment period followed by a 6-week extension period. Eligible participants will be randomized to receive one of five treatment sequences with target doses of MK-8189 (8 mg, 16 mg, and 24 mg QD), risperidone (6 mg QD), or placebo. Placebo completers at 6 weeks will be allocated to receive MK-8189 24 mg for the remainder of the trial. This trial is being conducted in a hospital/acute care setting followed by an outpatient setting.

2.2.4 Completed Clinical Studies

2.2.4.1 Protocol 011

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

Part 1 Panel A: Participants with schizophrenia. Intervention MK-8189 16 mg/placebo (Days 1 to 3), 24 mg/placebo (Days 4 to 10).

Overall, multiple oral doses of MK-8189 titrated from 16 mg to 24 mg were generally well tolerated in participants with schizophrenia. Of the 8 participants included in the safety analysis in Panel A, 6 (75%) experienced 1 or more AEs during the study; 5 participants

(83.3%) after MK-8189 and 1 participant (50%) after placebo. All AEs were mild or moderate in intensity and resolved prior to the end of the study. No participants were discontinued from the study intervention due to an AE.

Five participants (62.5%) reported 1 or more AEs that the investigator considered study intervention related; 4 participants (66.7%) after MK-8189 and 1 participant (50%) after placebo. The most commonly (>1 participants) reported study intervention related AEs were decreased appetite (n=1 [16.7%] following MK-8189 24 mg and n=1 [50.0%] following placebo), dystonia (n=2 [33.3%] following MK-8189 16 mg), and somnolence (n=2 [33.3%] following MK-8189 16 mg).

Dystonia and new or worsening tardive dyskinesia per protocol were defined as ECIs. There were 2 (33.3%) participants administered MK-8189 who experienced a nonserious ECI. One participant, who prior to the study was being treated with benztropine to prevent EPS, experienced mild intermittent bilateral dystonia of the upper extremities after MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 2 days. The participant had also experienced moderate somnolence (3-day duration; related to MK-8189) which resulted in this participant remaining at the 16 mg dose for all 7 days of dosing. This participant was also taking a sedating antihistamine, hydroxyzine, for the duration of the AE. One participant had moderate dystonia of the tongue, lips, facial muscles, and left hand after MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 22 h. The participant was titrated to MK-8189 24 mg per protocol and completed the study without recurrence of dystonia. The investigator considered both events related to study intervention.

Part 1 Panel B: Participants with schizophrenia. Intervention MK-8189 24 mg/placebo (Days 1 to 7)

Overall, multiple oral doses of MK-8189 24 mg were generally well tolerated in participants with schizophrenia. Of the 18 participants included in the safety analysis in Panel B, 10 (55.6%) experienced 1 or more AEs during the study; 9 participants (64.3%) after MK-8189 and 1 participant (25%) after placebo. All AEs were mild or moderate in intensity. One participant had a moderate ligament sprain continuing at the end of the study. The investigator considered the event not related to study intervention. All other AEs resolved prior to the end of the study.

Five (35.7%) participants administered MK-8189 24 mg reported 1 or more AEs that the investigator considered study intervention related. The most commonly (>1 participants) reported study intervention related AE was somnolence (n=2, [14.3%] following treatment with MK-8189 24 mg).

One (7.1%) MK-8189 treated participant, who had a history of gastroesophageal reflux disease, discontinued intervention due to mild vomiting following administration of MK-8189 24 mg. The investigator treated the participant with ondansetron 4 mg and symptoms resolved after 3 days. This participant also reported nausea on Day 2. The investigator considered both AEs not related to intervention.

One (7.1%) participant had a mild AE of increased alanine aminotransferase (ALT) (116 IU/L; normal range [NR] 7-52 IU/L) following treatment of MK-8189 24 mg that the investigator considered related to study intervention. This participant had mildly elevated screening (61 IU/L) and predose (98 IU/L) values of ALT which continued to increase during the study. The AE was reported on the last day of study intervention and resolved in ~2 weeks. Alkaline phosphatase followed a similar pattern. Aspartate aminotransferase was normal at screening and predose but the participant experienced an elevation throughout the study. Bilirubin remained within normal range throughout the study.

Part 1 Panel C: Not initiated

Part 2 Panel D: Elderly participants with schizophrenia. Intervention MK-8189 8 mg/placebo (Days 1 to 3), 16 mg/placebo (Days 4 to 6), 24 mg/placebo (Day 7 to 13)

Overall, multiple oral doses of MK-8189 titrated from 8 mg to 24 mg were generally well tolerated in elderly participants with schizophrenia. Of the 16 participants included in the safety analysis in Panel D, 10 (62.5%) experienced 1 or more AEs during the study; 7 participants (58.3%) after MK-8189 and 3 participants (75%) after placebo. The majority of AEs were mild or moderate in severity; an AE of severe intensity is discussed below. One participant (8.3%) in the MK-8189 intervention group had a mild skin disorder (verbatim term: small bump on the left side of the forehead) not resolved at the end of study. The AE was reported following the last dose of study intervention (MK-8189 24 mg) and the investigator considered this event not related to study intervention. All other AEs resolved prior to the end of the study.

Six participants (37.5%) reported 1 or more AEs that the investigator considered study intervention related; 4 participants (33.3%) after MK-8189 and 2 participants (50%) after placebo. The most commonly (>1 participants) reported study intervention related AEs were somnolence (n=2 [16.7%] following MK-8189 8 mg, and 24 mg and n=1 [25%] following placebo), dystonia (n=1 [8.3%] following MK-8189 8 mg and n=1 [25.0%] following placebo) and restlessness (n=2 [16.7%] following MK-8189 8 mg and 16 mg).

One participant (8.3%) in the MK-8189 intervention group experienced an AE of severe intensity (somnolence) and a nonserious related ECI (dystonia). On Day 1 following administration of the MK-8189 8 mg dose, the participant experienced severe somnolence which resolved after 3 days with continued dosing. No action was taken regarding study intervention. On Day 3 following the 8 mg dose, this participant experienced moderate bilateral upper extremity dystonia. The event lasted for 3 days and resolved with cyclobenzaprine 10 mg. This participant also reported moderate akathisia beginning on Day 3 with a duration of 3 weeks. This same participant did not receive the Day 6 dose (MK-8189 16 mg) due to moderate AEs of conjunctivitis (3-day duration) and a maculo-papular rash (4-day duration). The investigator considered all AEs related to study intervention. The participant did not titrate to the MK-8189 24-mg dose and was dosed with 16 mg on Day 7. The participant withdrew consent on Day 8 and discontinued from study intervention.

Three participants (n=2 [16.7%] following MK-8189 and n=1 [25.0%] following placebo) were discontinued from study intervention due to an AE. One participant discontinued intervention due to moderate pain that the investigator did not consider related to study medication. The AE started on Day 3 following administration of MK-8189 8 mg and resolved after ~ 1.5 weeks. The subject discontinued prior to the 16 mg intervention administration on Day 5. One participant discontinued intervention due to moderate restlessness after administration of MK-8189 16 mg (Day 3). This participant also experienced moderate dyskinesia (verbatim: involuntary movement of lower extremities) (Day 6). Both AEs resolved after 23 hours with no action taken. The investigator considered both AEs related to study intervention. One participant discontinued intervention due to mild dystonia (described below) after administration of placebo.

Two participants (n=1 [8.3%] following MK-8189 and n=1 [50.0%] following placebo) reported ECIs. One participant experienced moderate dystonia following treatment with MK-8189 8 mg and is described above. One participant had mild dystonia of the throat after placebo study intervention (Day 3) which initially responded to treatment with benztropine but then recurred. The event resulted in discontinuation from study intervention and resolved after 2 weeks. The investigator considered the event related to study intervention.

One participant (25.0%) in the placebo treatment group had 2 laboratory AEs: mild decreased estimated glomerular filtration rate (eGFR) on 2 occasions. One reported on Day 4 with a duration of 4 days. The other reported after the last dose of study intervention along with a mild increased blood glucose. The increased blood glucose resolved in 2 weeks however the decreased eGFR lasted around 1.25 months and was considered recovered/resolved with sequelae. The participant had a screening eGFR value of 55 mL/min/1.73 (NR: >59) with a creatinine of 1.23 mg/dL (NR: 0.76 to 1.27). The eGFR was low at screening but within 10% of the lower limit of normal permitted by the protocol. The participant had a medical history of diabetes and hypertension. The investigator felt the eGFR decreases were due to the poorly controlled diabetes, hypertension, and reluctance to hydrate. All AEs were not related to study intervention.

Part 2 Panel E: Not initiated.

Part 2 Panel F: Healthy elderly participants. Intervention MK-8189 8 mg/placebo (Days 1 to 3), 16 mg/placebo (Days 4 to 6), 24 mg/placebo (Day 7 to 13)

Overall, multiple oral doses of MK-8189 titrated from 8 mg to 24 mg were generally well tolerated in healthy elderly participants. Of the 6 participants included in the safety analysis for Panel F, 4 of 5 participants administered MK-8189 (80%) experienced 1 or more AEs during the study. The 1 participant that received placebo did not report an AE. All AEs were mild or moderate in intensity and all but 1 AE resolved prior to the end of the study as described below.

Three (60%) participants after MK-8189 reported 1 or more AEs that the investigator considered study intervention related. No specific related AEs were reported in more than 1 participant.

One participant (20%) administered MK-8189 discontinued from study intervention due to an AE of moderate nausea after administration of MK-8189 24 mg. This participant had multiple AEs throughout the course of the study. Following treatment with MK-8189 8 mg, the participant had an AE of mild decreased appetite (~ 1-week duration) considered related by the investigator. Following the third dose of MK-8189 24 mg, this participant reported AEs of moderate dizziness (~ 8-hour duration), moderate nausea (5-day duration; reason for discontinuation), mild vomiting on 2 occasions (1- and 2-min durations), mild dyspepsia (3.5-hour duration), and mild ongoing hyponatremia (133 mmol/L on Day 10 and 130 mmol/L at discharge [NR 135-146] mmol/L). The investigator considered all AEs after MK-8189 24 mg related to study intervention. This participant also had mild diarrhea (considered unrelated to study intervention) beginning on Day 6 (16 mg) with a duration of 5 days which may have contributed to the hyponatremia. The participant also experienced a mild macule (verbatim: asymptomatic macular erythematous lesions on upper left chest) on Day 5 which was considered unrelated to treatment.

One participant reported moderate involuntary muscle contractions (3.5-hour duration) along with moderate EPS (~ 2-week duration) following MK-8189 16 mg (Day 5). The participant also experienced a second episode of moderate involuntary muscle contractions on Day 6 (~2-week duration). Following the participant's first MK-8189 24 mg dose and due to the ongoing EPS, the participant did not feel comfortable continuing at the 24-mg dose and was down-titrated to 16 mg for the duration of the study. The EPS was characterized by intermittent internal and visible tremor, intermittent stiffness and intermittent cogwheeling. The participant was given benztropine as needed until these AEs resolved. This participant also reported mild salivary hypersecretion (2-hour duration) following MK-8189 16 mg (Day 10). The investigator considered all AEs related to study intervention.

Part 2 Panel G: Healthy elderly participants. Intervention MK-8189 16 mg/placebo (Days 1 to 3), 24 mg/placebo (Days 7 to 13)

Overall, multiple oral doses of MK-8189 titrated from 16 mg to 24 mg in healthy elderly may be less well tolerated than initiating titration of MK-8189 at a dose of 8 mg. Of the 15 participants included in the safety analysis for Panel G, 12 (80%) experienced 1 or more AEs during the study; 11 participants (84.6%) after MK-8189 and 1 participant (50%) after placebo. The majority of AEs were mild or moderate in intensity; AEs of severe intensity are described below. All AEs resolved prior to the end of the study.

Ten participants (66.7%) reported 1 or more AEs that the investigator considered study intervention related; 9 participants (69.2%) after MK-8189 and 1 participant (50%) after placebo. The most commonly (>1 participants) reported study intervention related AEs were somnolence (n=4 [30.8%] following MK-8189 16 mg), akathisia (n=3 [23.1%] following MK-8189 16 mg [n=2] and 24 mg [n=1]), tremor (n=3 [23.1%] following MK-8189 24 mg), myalgia (n=2 [15.4%] following MK-8189 16 mg and 24 mg), headache (n=2 [15.4%] following MK-8189 24 mg), hypertonia (n=1 [7.7%] following MK-8189 24 mg and n=1 [50%] placebo), and oromandibular dystonia (n=2 [15.4%] following MK-8189 16 mg and 24 mg).

Three participants (23.1%) administered MK-8189 experienced 1 AE of severe intensity. One participant experienced severe somnolence on Day 1 (MK-8189 16 mg) which resolved after 8.75 hours. The participant also reported mild akathisia (3-hour duration), mild dyspepsia (3-hour duration) and restlessness (~ 1-week duration) also on Day 1 and an AE of mild tremor (4-day duration) on Day 5 (MK-8189 24 mg). One participant experienced severe somnolence on Day 1 (MK-8189 16 mg) which resolved after 10 hours. This participant had no other reported AEs. The investigator considered all AEs for both participants related to study intervention. No action was taken with study intervention for these 2 participants. One participant experienced a severe hypnagogic hallucination after MK-8189 24 mg (discussed below).

Three (23.1%) participants administered MK-8189 discontinued study intervention due to an AE. One participant discontinued due to a severe hypnagogic hallucination on Day 8. This participant experienced mild akathisia (20-hour duration) and moderate headache (8-hour duration) on Day 7 after MK-8189 24 mg. The participant was treated with benztropine 1 mg as needed for the akathisia. Overnight, prior to the Day 8 24-mg administration, the participant experienced moderate tactile hallucination (5-min duration), moderate hyperhidrosis (5-hour duration) and mild palpitations (2-min duration). Early morning upon waking on Day 8, the participant experienced a severe hypnagogic hallucination (5-min duration). The participant did not receive the Day 8 dose due to these AEs. Later that day (Day 8), the participant experienced moderate tactile hallucination (15-min duration), moderate hyperhidrosis (15-min duration), mild hypertonia (5-day duration) and moderate sinus tachycardia (39-min duration). Since similar AEs reoccurred on Day 8, the participant decided not to continue dosing due to the possibility of a reoccurrence of the hypnagogic hallucination. This participant also reported a mild ECI of oromandibular dystonia (30-min duration) on Day 1 (MK-8189 16 mg) and a mild headache on Day 10 (MK-8189 24 mg). The investigator considered all AEs related to study intervention except the mild headache on Day 10. One participant discontinued intervention due to mild akathisia following Day-3 administration of MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 2 days. The investigator considered the AE related to study intervention. This participant also reported mild fatigue (6-day duration) and moderate wheezing (2-day duration) 8 days following intervention discontinuation. The investigator considered these AEs not related to study intervention. One participant discontinued intervention due to moderate ECI of oromandibular dystonia of the jaw on Day 4 following administration of MK-8189 24 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 6.5 hours. The participant also reported moderate anxiety (~11-hour duration; treated with lorazepam 1 mg), mild myalgia (14.5-hour duration; treated with ibuprofen 800 mg) and mild apathy (23-hour duration) on Day 4. The investigator considered all Day-4 AEs related to study intervention. Prior to the Day-4 AEs, the participant experienced on Day 2 moderate apathy (2-day duration), mild dysphonia (6-day duration), mild involuntary muscle contractions (verbatim: fasciculation, 2-day duration) and mild parosmia (~1-week duration), all considered related to intervention by the investigator. On Day 3, the participant experienced mild back pain (3-day duration; treated with paracetamol 1000 mg), salivary hypersecretion (3-day duration) and mild muscle tightness of the legs (10.5-hour duration). The only AE considered related to intervention on Day 3 by the investigator was the salivary hypersecretion.

One participant (7.7%) had a mild laboratory AE of decreased eGFR on Day 12 after MK-8189 24 mg which was not considered related to study intervention. The decreased eGFR lasted around 1.5 months and was considered recovered/resolved with sequelae by the investigator. The participant had a normal screening eGFR value of 75 mL/min/1.73 (NR: >59) with a creatinine value of 0.81 mg/dL (NR: 0.76-1.27). The eGFR fluctuated between 65 and 75 mL/min/1.73 throughout the study but was never below the NR until Day 12 (eGFR value of 58 mL/min/1.73; creatinine value of 1.01 mg/dL). The participant had a history of hypertension, and the investigator felt the eGFR decrease was related to their baseline hypertension. The investigator referred the participant to their primary care physician (PCP) for further treatment of hypertension (participant was prescribed lisinopril by the PCP).

Across all Panels, there were no dose-related trends for increases in specific AEs. There were no clinically meaningful trends for MK-8189-treatment related changes in safety laboratory values, vital signs, including orthostatic vital signs, ECGs, or physical exams. There were no SAEs or deaths reported and no participant reported suicidal ideation or behavior per the C-SSRS.

2.2.4.2 Protocol 012

P012 was an open-label single-dose Phase 1 study to evaluate the safety, tolerability, and PK in participants with hepatic impairment and matched healthy participants.

Overall, MK-8189 4 mg was generally well tolerated in the moderate hepatic impairment and healthy participants in the study. No deaths or serious adverse events or events of clinical interest were reported. No participant discontinued from the study due to an AE. Of the 14 participants included in the safety analysis, 4 (28.6%) experienced 1 or more AEs during the study: 4 (57.1%) in the moderate hepatic impairment group and none in the healthy participants group. Ten (71.4%) participants did not report an AE. All AEs were mild in intensity and all AEs resolved by the end of the study. The most frequently (>1 participant) reported AE amongst the moderately hepatic impaired participants was vomiting (n=2/7; 28.6%). One participant vomited on Day 1, ~5 hours after dosing and another participant on Day 3. All other AEs were reported by 1 participant only.

Intervention-related AEs were reported by 2 of 14 (14.3%) participants as detailed below. Six AEs (2 of 7 [28.6%] participants with moderate hepatic impairment) were considered intervention-related by the investigator: One participant developed mild AEs of vomiting, ~5 hours after dosing (1 episode, 1 min), muscle spasm (10 minutes), and hot flush (40 minutes). One participant had mild AE of headache (19.5 hours) on Day 1, followed by anxiety (30 minutes) and affect lability (30 minutes) on Day 2.

No clinically meaningful trends were observed as a function of study intervention for laboratory safety tests, vital signs, or ECGs.

2.2.4.3 Protocol 016

P016 was a randomized, placebo-controlled, parallel-group, single-site, double-blind, multiple-ascending dose study of MK-8189 in healthy participants. Up to approximately

25 healthy participants were planned to be enrolled to ensure 20 participants completed the study. Participants were randomized to receive single rising doses of MK-8189 or placebo on Days 1 through 6 (Day 1=8 mg, Day 2=16 mg, Day 3=24 mg, Days 4, and 5=48 mg, and Day 6=72 mg). Participants were domiciled from Day -2 until Day 9.

Adverse Events: In general, MK-8189 up to doses of 24 mg was well tolerated in healthy male and female participants in the study. The rapid titration regimen above 24 mg was not generally well tolerated due to central nervous system and gastrointestinal AEs.

Of the 12 participants included in the safety analysis, 100.0% (n=12/12) experienced 1 or more AEs during the study. In general, more AEs were observed with higher doses of MK-8189, and all participants receiving placebo reported AEs; 28.6% (n=2/7) for MK-8189 8 mg (Day 1), 57.1% (n=4/7) for 16 mg (Day 2), 42.9% (n=3/7) for 24 mg (Day 3), 100.0% (n=6/6) for 48 mg (Days 4 and 5), 100% (n=4/4) for 72 mg (Day 6), and 100.0% (n=5/5) for placebo. Most AEs were mild or moderate in intensity; one AE of akathisia was rated severe. All but 1 unrelated AE of leukocyturia resolved by study completion. There were no deaths or other serious AEs.

Three participants receiving MK-8189 discontinued study intervention due to AEs that were considered related to study intervention by the investigator: One participant experienced a moderate AE of vomiting (duration 23.17 hours) following administration of the second 48-mg dose and was not titrated further by decision of the investigator. This participant also experienced mild nausea (2 days) following the second dose of 48 mg. One participant experienced a moderate AE of anxiety (duration 9.92 hours) following administration of the second 48-mg dose and was not titrated further by decision of the investigator. This participant also experienced moderate vomiting (duration 10 minutes) following the second dose of 48 mg. One participant discontinued study intervention following the 24-mg dose due to severe akathisia that started 23.5 hours after dosing (duration 22.5 hours) and was treated with 3 doses of 10-mg propranolol hydrochloride. This participant also experienced moderate affect lability which began after the 16-mg dose (duration 4 days) and a few days later (Day 9) mild affect lability with a duration of 3.43 weeks, as well as mild restlessness which started after the 24-mg dose (duration 3 days).

One participant receiving placebo had a dose reduction when still blinded (from 48 mg on Day 4 to 24 mg MK-8189/placebo on Days 5 and 6) due to AEs of mild restlessness and moderate somnolence, both assessed by the investigator as related to study intervention, that started on Day 4 and lasted 40 min and 7 hours, respectively.

AEs reported by >1 participant treated with MK-8189 or placebo were: nausea (MK-8189: 71.4%, placebo: 40.0%); decreased appetite (MK-8189: 71.4%, placebo: 20.0%); insomnia (MK-8189: 57.1%); headache (MK-8189: 42.9%, placebo: 40.0%); nightmare (MK-8189: 42.9%, placebo: 20.0%); diarrhea and pyuria (MK-8189: 42.9% each); restlessness (MK-8189: 28.6%, placebo: 20.0%); vomiting, eructation, increased systolic blood pressure, hematuria, and leukocyturia (MK-8189: 28.6% each); dizziness and somnolence (placebo: 40.0% each). AEs in the system organ classes of gastrointestinal disorders, metabolism and nutrition disorders, and psychiatric disorders were most frequently reported, by 6 participants each.

A total of 83.3% (n=10/12) participants reported AEs that were considered related to study intervention by the investigator. In general, more AEs were observed with higher doses of MK-8189; 14.3% (n=1/7) for MK-8189 8 mg, 42.9% (n=3/7) for 16 mg, 28.6% (n=2/7) for 24 mg, 83.3% (n=5/6) for 48 mg, 100% (n=4/4) for 72 mg, and 60.0% (n=3/5) for placebo. Study-intervention-related AEs reported by >1 participant treated with MK-8189 or placebo were: nausea (MK-8189: 71.4%, placebo: 40.0%); decreased appetite (MK-8189: 71.4%, placebo: 20.0%); insomnia (MK-8189: 57.1%); headache (MK-8189: 42.9%, placebo: 40.0%); nightmare (MK-8189: 42.9%, placebo: 20.0%); diarrhea (MK-8189: 42.9%); restlessness (MK-8189: 28.6%, placebo: 20.0%); vomiting, eructation, increased systolic blood pressure (MK-8189: 28.6% each); dizziness and somnolence (placebo: 40.0% each).

Dystonia was an event of clinical interest. One participant experienced an AE of dystonia in the legs approximately 14 hours after receiving MK-8189 72 mg on Day 6 with a duration of 17 minutes. Earlier in the day (~6-hours postdose), this participant experienced intermittent tremors in the legs (duration 40 minutes) and 10 minutes later also muscle twitches in the right leg (duration 7.67 hours). All AEs were of mild intensity, considered related to study intervention and resolved without intervention. Although not considered dystonia, the following dystonic-like reactions were also observed. One participant receiving MK-8189 experienced AEs of intermittent muscle tightness in the arms on Day 2 ~30 minutes predose (ie, 23.5 hours after the 8-mg dose) (duration 3 hours), muscle spasms in the right hand on Day 2 44 minutes after the 16-mg dose (duration 1 minute) and blepharospasm on Day 4 after the first 48-mg dose (duration 3 days). The participant also experienced orofacial dyskinesia on Day 2 predose. All AEs were of mild intensity, considered related to study intervention and resolved without intervention. This participant discontinued study medication after the second dose of MK-8189 48 mg due to an AE of vomiting. One participant receiving placebo experienced mild muscle spasms in the calves on Day 7 with a duration of 5 days. This participant also developed moderate intermittent akathisia on Day 7 with a duration of 5 days that was treated with 60-mg propranolol hydrochloride on Days 7 to 11. Both events were considered related to study intervention and resolved. Two other participants randomized to MK-8189 received propranolol hydrochloride to treat AEs. One participant to treat severe akathisia (see above). Another participant received a single dose of 10-mg propranolol hydrochloride on Day 7 to treat an acute stress disorder of moderate intensity that started 33 hours after the last dose (72 mg on Day 6) and resolved in 4 hours. The AE was not considered related to study intervention.

Laboratory Safety Tests and Physical Examination: Overall there were no clinically meaningful trends observed as a function of study intervention for laboratory safety tests and physical examination. Although there were some AEs reported related to laboratory safety tests, none of these were considered related to study intervention.

12-lead ECGs and semi-automated Holter ECGs: 12-lead ECGs were collected from Day 1 to Day 6 24 hours with Day 1 predose as baseline. Semi-automated Holter ECGs were collected on Days 1, 3, and 6 (up to 72-hours postdose) with time-matched baseline. QTcF categorical analyses were performed for the Holter ECGs only.

QT corrected using Fridericia's formula (QTcF): Mean change from time-matched baseline for QTcF from the semi-automated Holter ECGs was similar for MK-8189 and placebo. A similar pattern was observed for the 12-lead ECGs. All QTcF values during the study were ≤450 msec (Holter). All changes in QTcF from time-matched baseline (Holter) were <30 msec, except for 1 participant receiving MK-8189 8 mg who had an increase >30 msec and ≤60 msec on Day 1 8 hours (actual increase: 33 msec, time-matched baseline value: 395 msec) and 14 hours (actual increase: 40 msec, time-matched baseline value 391 msec). This participant continued dosing up to 72 mg without any further QTcF increases of >30 msec.

12-lead ECG parameters were generally similar for MK-8189 and placebo. However, mean change from baseline for ventricular rate was higher for MK-8189 than for placebo at higher doses (starting on Day 5 10 hours) up to 72 hours after the 72-mg dose, which was also present on the Holter ECGs on Day 6. The rationale for the ventricular/heart rate increase is unknown.

Mean change from time-matched baseline for resting systolic and diastolic blood pressure was generally similar for MK-8189 and placebo. It was numerically higher from Day 6 6 hours onwards, and Day 6 14 hours onwards, respectively.

Orthostatic Hypotension: One participant (MK-8189 48 mg) experienced orthostatic hypotension (ie, a decrease of ≥20 mmHg between standing and semi-recumbent systolic blood pressure or decrease of ≥10 mmHg between standing and semi-recumbent diastolic blood pressure). All events were asymptomatic, and no occurrences were considered AEs.

2.2.5 Information on Other Study-related Therapy

Moxifloxacin is being used as an active control in this trial because it produces a mild but robust increase in QTc interval in healthy study participants at Tmax [redacted]. Moxifloxacin is a synthetic broad-spectrum antibacterial agent that is frequently used as an active control in TQT trials such as this.

Moxifloxacin is metabolized via glucuronide and sulfate conjugation. The CYP P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. In vitro studies with CYP P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the PK of drugs metabolized by these enzymes. Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The mean (± standard deviation [SD]) elimination [redacted]

Adverse reactions (AR), judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 3% of moxifloxacin treated patients were: nausea (7%), diarrhea (6%), and dizziness (3%). See the moxifloxacin hydrochloride package insert for additional information [U.S. Prescribing Information 2020].

2.3 Benefit/Risk Assessment

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

The data generated will be used to inform the cardiac safety profile of MK-8189.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in participants with schizophrenia.

Primary Objective	**Primary Endpoint**
To evaluate the effect of a supratherapeutic dose of 80-mg MK-8189 on the QTc interval Hypothesis: Administration of an 80-mg MK-8189 dose on Day 2 does not prolong the QTc interval to a clinically significant degree. Specifically, the true mean difference (MK-8189 - placebo) in QTc change from baseline is less than 10 msec	QTc (QT interval corrected for heart rate) change from baseline at post dose time points
To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia	Adverse events leading to discontinuation of study intervention Adverse events
Secondary Objectives	**Secondary Endpoints**
To evaluate the effect of moxifloxacin on the QTc interval Hypothesis: Administration of a single 400-mg dose of moxifloxacin is associated with an increase in QTc interval. Specifically, the true mean difference (Moxifloxacin-placebo) in QTc change from baseline is greater than 5 msec at least at one time point	QTc (QT interval corrected for heart rate) change from baseline at post dose time points
To estimate the pharmacokinetics of MK-8189 following multiple doses of MK-8189 in participants with schizophrenia	AUC0-24, AUC0-last, Cmax, C24, Tmax, t1/2 of MK-8189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4 STUDY DESIGN

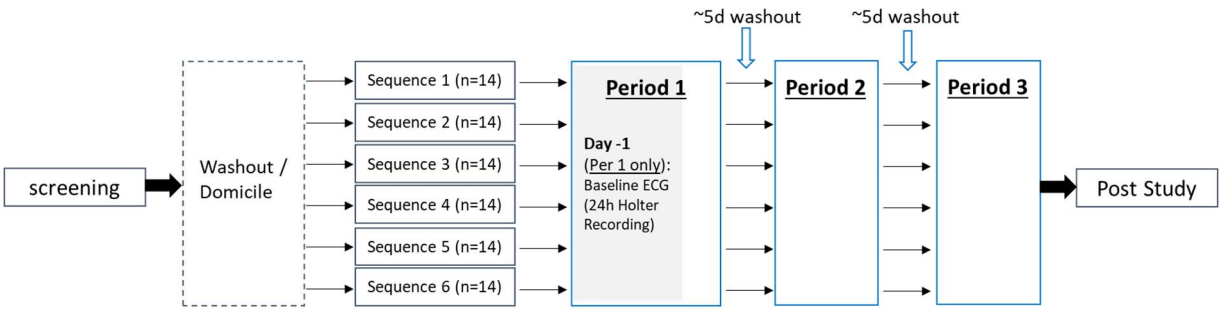
4.1 Overall Design

This is a three-period, randomized, double-blind, active-controlled and placebo-controlled, 3-way crossover, multisite study of participants with schizophrenia.

The study will consist of 6 sequences and 3 treatment periods with 5-day washout between doses in each period in a cross-over design. The 5-day washout period is selected based on the terminal half-lives of both MK-8189 and moxifloxacin.

Participants will be randomized to 1 of 6 sequences according to a randomized allocation schedule. In each treatment sequence, the dosing periods will consist of:

- Treatment A: MK-8189 48 mg on Day 1, MK-8189 80 mg on Day 2
- Treatment B: Standard image placebo on Day 1 and moxifloxacin 400 mg on Day 2
- Treatment C: MK-8189 matched placebo on Day 1 and Day 2



If applicable, participants will be washed off their current antipsychotic therapy. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants should not receive antipsychotic therapy for at least 5 days or 3 half-lives (whichever in longer) prior to Day -1. For longer half-life antipsychotics (eg, aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment of the antipsychotics as an outpatient but should be confined to the clinical research unit within a week of stopping treatment and minimally beginning on Day -6. If participants are not currently receiving antipsychotic therapy, they may be domiciled as late as Day -2 prior to Period 1.

Participants will be domiciled approximately 5 days (or 1 day if no washout required) prior to Day -1 of Period 1 through 72 hours following the last dose administration in Period 3 (including all washout periods) to facilitate the intensive PK sampling and Holter recordings. On Day -1 of Period 1 only, participants will have Holter recordings for approximately 24 hours without prespecified extraction periods to generate a wide range of heart rate and QT values that will be used to generate an individualized heart rate correction for QT. These data may be required if the Fridericia heart rate correction is not considered sufficient. In addition, Holter monitoring recordings and blood sample for PK will be conducted on days and

timepoints specified in the SoA up to 24 hours and 72 hours, respectively, following the last dose administration in each Period. Blood sampling for PK will be within 10 minutes of the end of ECG extraction period. The ECG reader will be blinded to all treatment (placebo, study intervention and active positive control) groups.

Following 72-hour assessments in Period 3, antipsychotic standard of care may be restarted, and participants may be discharged from the unit. At the investigator's discretion, the participants may be domiciled for a longer duration if further observation is required. Participants will return to the clinical research unit for a follow-up visit approximately 14 days following the last dose administration of the study intervention.

Because this is a Phase 1 assessment of MK-8189 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

A thorough assessment of the cardiac safety of MK-8189 is required as part of drug development and registration. Some non-antiarrhythmic drugs have the potential to delay cardiac repolarization, prolonging the QT interval on the ECG. Such QT prolongation has been associated with development of potentially life-threatening cardiac arrhythmias, in particular Torsades de Pointes (TdP). There is in general a qualitative relationship between substantial QT prolongation and the risk of TdP [ICH Expert Working Group 2005]. This study is being conducted, therefore, to rigorously characterize the effect of MK-8189 on the QT and heart rate corrected QT (QTc) intervals. The study design will accomplish this objective consistent with ICH E14 guidelines.

The study will be a 6-treatment sequence arm, 3-period, double-blind (to MK-8189 treatment arm), randomized cross-over design. Participants will be randomized to 1 of 6 sequence arms, and will receive MK-8189, placebo, and moxifloxacin. This 3-period, cross-over design is selected as each participant receives all 3 treatments and serves as their own control, thus a smaller number of patients are required as compared to a parallel group study.

Based on the half-life of MK-8189 [redacted]) and moxifloxacin (~12 hours), a 5-day washout should be sufficient between periods. While the positive control, moxifloxacin, will be administered in an open-label manner, the central ECG reader will be blinded to all treatments. The standard image placebo to moxifloxacin is included to ensure study procedures are followed uniformly.

Further, the following design features prescribed in the ICH E14 guidance have been incorporated into this study:

1. A supratherapeutic dose of MK-8189 will be administered to assess the effect of MK-8189 on QTc at concentrations in excess of those anticipated when the maximum clinical dose is administered under steady-state conditions and the influence of the intrinsic or extrinsic factor that causes the greatest increase in exposure as described in Section 4.3.2.

2. Moxifloxacin will be included as a positive control with an expected mean effect on the QT/QTc interval of 5 msec.

3. To reduce variability in the QT interval measurements, replicate ECGs will be extracted from 24-hour Holter tracings and a centralized core laboratory will be used to assess the QT interval. Readings at this core reading facility will be by a skilled reader and to the extent possible, all measurements from a single individual will be made by the same reader.

4. To reduce bias, the reader will be blinded to treatment, time, and subject identifier.

Furthermore, as food can affect QT, mealtimes will be standardized across treatment periods. In addition, as this study will also explore the relationship between MK-8189 concentration and QTc, there is an attempt to achieve a wide range of concentrations during the initiation of dosing and the washout period, therefore sampling will be collected early following the first dose through 72 hours following the final dose. Blood sampling for PK will be within 10 minutes of the end of the ECG extraction period to support this analysis.

As all participants are domiciled throughout the trial, there is adequate monitoring for any safety concerns and participants will be continued to be domiciled for 72 hours following the last dose of study intervention.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints in this study.

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical AEs as well as through the conduct of neurological exams, physical exams, ECGs, VS, and laboratory safety tests. The C-SSRS will be administered to monitor mood and suicidal ideation and behavior in all trial participants (see Section 4.2.). In addition, scales will be included to evaluate extrapyramidal symptoms (EPS) and general well-being.

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

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

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

4.2.1.3 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK of MK-8189. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to derive the PK parameter values AUC0-24, AUC0-last, Cmax, C24, Tmax and t1/2. MK-8189 concentrations are being collected to also support a concentration-QTc analysis.

4.2.1.4 Pharmacodynamic Endpoints

The primary objective of this trial is to evaluate the potential effect of a supratherapeutic dose of MK-8189 on the QTc in participants with schizophrenia.

Thus electrocardiogram data (eg, QT, QRS, RR and PR intervals and heart rate [HR]) will be obtained with a digital Holter device on study days specified in the SoA. An approximate 24-hour Holter will also be conducted on Day -1 to support the determination of QTCI as discussed in Section 4.1.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

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

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

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

4.2.1.6 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

Moxifloxacin is included as a positive control with an expected mean effect on the QT/QTc interval of 5 msec. Use of a positive control with this magnitude of effect is recommended by the E14 guidelines to ensure that a thorough QT study is conducted in such a way as to be adequately sensitive to detect a change in QT/QTc that meets the definition of being of regulatory concern.

Placebo to moxifloxacin will be used in an open-labeled manner, as the reading of ECGs is performed in a blinded manner. The placebo to moxifloxacin is included to ensure that specified study procedures are followed uniformly.

Placebo to MK-8189 will be used to blind study participants and site staff to study treatment. This ensures an unbiased safety assessment.

Furthermore, ECGs collected following administration of placebo will be used to provide off-drug assessments at the same timepoints and under similar conditions (eg, in relation to food, activity and time of day all known to affect the QT interval) to those obtained following administration of study drug.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

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

4.3 Justification for Dose

The rationale for dose regimen selection is detailed in Section 4.3.1 and Section 4.3.2.

As this is a Phase 1 assessment of MK-8189 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.1 Starting Dose for This Study

The starting dose for this study will be MK-8189 48mg/placebo. This starting dose, CCI [redacted] has been shown to be generally well tolerated in an ongoing protocol, P014: See Section 2.2.3.5 for a summary of the study design for P014 as well as the preliminary blinded safety data associated with this starting dose.

A starting dose of 48 mg will allow for a shortened titration scheme and duration of treatment while achieving the target supratherapeutic dose to support a thorough QT study as discussed in section 4.3.2.

4.3.2 Maximum Dose Exposure for This Study

To ensure the risk of QT prolongation is appropriately evaluated, the maximum dose selected for this study should provide a Cmax value that would exceed the Cmax anticipated following administration of the highest clinical dose at steady-state under the condition of the intrinsic or extrinsic factor that results in the greatest increase in Cmax concentrations. The anticipated maximum therapeutic dose of MK-8189 is CCI [redacted] with CCI [redacted] accumulation observed at steady state resulting in a predicted median steady-state Cmax of CCI [redacted] (geometric mean (GM) Cmax = CCI [redacted] Under conditions of CYP3A inhibition, the factor anticipated to cause the greatest increase (CCI [redacted]) in MK-8189 PK, the median steady state Cmax is predicted to be CCI [redacted] (GM Cmax = CCI [redacted] Based on preliminary results from P014 in Panel A-1 (48 mg Day 1/80 mg Day 2), the observed median Cmax on Day 2 following the 80 mg dose was CCI [redacted] (GM Cmax = CCI [redacted] providing an CCI [redacted] relative to the median Cmax at the highest clinical dose under

steady state conditions. Preliminary data from P014 demonstrated that administration of an 80 mg dose is generally well tolerated as described in Section 2.2.3.5.

Based on preliminary results from P014 in Panel A-1 (48 mg Day 1/80 mg Day 2), the observed GM AUC0-24 exposure at 80 mg was CCI and therefore the margin to the AUC0-24 for an 80 mg dose, as derived from the 6-Week and chronic toxicology studies, would be CCI and CCI, respectively, further supporting evaluation of this supratherapeutic dose. Brief summaries of the 6-Week and chronic toxicology studies supporting dose escalation are provided below:

In the 6-Week rat study, doses of 25, 50 and 1000 mg/kg/day of MK-8189 were evaluated. There were no adverse findings in the study; therefore, the no observed adverse effect level (NOAEL) was CCI (AUC0-24hr = CCI) and CCI in males (AUC0-24hr = CCI) over the supratherapeutic GM exposure of CCI . The functional observational battery (FOB) evaluation conducted on Study Day 1 showed findings at all dose levels that consisted of non dose-dependent decreases in the mean number of line crosses and rears, and very slight, dose-dependent decreases in mean body temperature. In addition, an absence of motor activity (akinesis) was noted in 1 of the 6 high-dose animals tested. Collectively, these observations are consistent with mild sedation. Importantly, these animals retained normal ability to respond to external stimuli as evidenced by normal responses to the noise, touch, and approach stimuli. These findings were considered transient as they were not present before the subsequent dose on Study Day 2.

In the 6-Week monkey study, doses of 10, 30 and 300 mg/kg/day were administered. Pharmacologically-mediated physical signs were observed across all dose groups and consisted of somnolence, increased/decreased activity, unsteady gait, increased licking/chewing/chomping motion, vocalization, intermitted recumbency, intermitted whole body trembling, and/or salivation. These physical signs were considered transient, reversible, and consistent with the expected pharmacology of PDE10A inhibition. The NOAEL in this study was CCI (AUC0-24hour = CCI) providing an exposure margin of CCI over the supratherapeutic GM exposure of CCI .

In the 6-month rat study, doses of 0, 25, 100 and 750 mg/kg/day were evaluated. CCI Therefore the CCI mg/kg/day dose was considered the NOAEL for this study (AUC0-24hr = CCI providing an exposure margin of CCI over the supratherapeutic GM exposure of CCI

In the 9-month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK-8189 were administered. Similar to the 6-Week study, pharmacologically-mediated transient and reversible physical signs were observed in all dose groups in the study. In addition, beginning in Study Week 8 of this study, reversible physical signs of uncoordinated movements were observed down to the low-dose level. Due to the severity of the uncoordinated movements, the low-dose level had to be lowered (30 to 3 mg/kg/day) to increase tolerability of the test article. Based on these findings, the NOAEL CCI . Renal

tubular degeneration was observed in the high-dose group (600/300 mg/kg/day). The NOAEL[CCI), providing an exposure margin of[CCI over the[CCI

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[CCI [CCI . The IC50 value is[CCI over the unbound mean Cmax ([CCI at the anticipated[CCI and[CCI over the unbound mean Cmax ([CCI) at a supratherapeutic dose of MK-8189 of 80 mg QD, based on preliminary results from P014 in Panel A-1 (48 mg Day 1/80 mg Day 2).

The M3 metabolite decreased hERG current amplitude in a concentration-dependent manner ([CCI [CCI however, an IC50 value could not be determined. Assuming IC50[CCI , the margin over the estimated unbound M3 Cmax concentration at 80 mg QD ([CCI , [CCI , based on preliminary results from P014 in Panel A-1 (48 mg Day 1/80 mg Day 2).

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[CCI respectively. Thus, the NOEL/NOAEL in this study[CCI providing an exposure margin of[CCI over the estimated GM[CCI at the anticipated[CCI and[CCI relative to the GM clinical Cmax at the 80 mg dose of[CCI In anesthetized rhesus monkeys, MK-8189 had no effect on CV parameters during rising intravenous (IV) doses up to a[CCI plasma concentration (~[CCI

In a telemetry study in monkeys, single oral doses of 2, 5, and 20 mg/kg were evaluated and[CCI 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[CCI mg/kg[CCI estimated from a 6-week toxicity study[CCI the[CCI [CCI and[CCI value of[CCI at a dose of MK-8189 of 80 mg). Several studies were conducted to determine the underlying cause (see MK-8189 IB for additional details). The general conclusion from these studies was that[CCI likely occur due to a[CCI [CCI subsequent to PDE10A target engagement in conscious rhesus monkeys and therefore, these changes in[CCI are not relevant to humans.

Furthermore, a concentration-QTc analysis was conducted in P007 and as shown in Figure 2 there is no evidence for a relationship between concentration and QTc at MK-8189 exposures achieved with the 48 mg dose. Therefore, preclinical and clinical data support dose escalation to 80 mg in the current study. In addition, during the study safety and tolerability will be

carefully assessed. Dose escalation may be stopped within an individual or the study based on tolerability.

4.3.3 Rationale for Dose Interval and Study Design

MK-8189 is formulated as a controlled-release tablet intended for QD administration. To date most multiple ascending dose studies have been conducted as a within participant titration. The within participant titration was introduced based on results from the single-ascending dose trial (P001) in healthy participants, where following treatment with the 3-mg and 6-mg IR formulation, dystonia was observed around the time of peak MK-8189 concentration (See IB for details).

In addition to successfully reducing through development of the CR formulation (a titration approach in the target patient population was implemented in the multiple ascending dose studies (P003 and P007) and the POC (P005) study, which significantly reduced the rate of observed EPS and dystonia and permitted evaluation of doses and exposures significantly greater than could be achieved tolerably with the IR formulation. Of note, in P007, where the as well as supratherapeutic doses up to 48 mg have been evaluated, no MK-8189-related dystonia has been reported in healthy participants or

participants with schizophrenia. The peak concentration values at the CCI dose are CCI those observed following CCI of the IR formulation, suggesting the absolute concentration is not a driver of dystonia. Across P003 and P007 the starting dose of the CR formulation has increased from 2 mg to 4 mg to 8 mg without an increase in the incidence in dystonia. Furthermore, Part 1 of P011 was conducted to evaluate the need for titration in participants with schizophrenia. As described in section 2.2.3 4, initiating dosing at CCI was generally well tolerated in participants with schizophrenia. In this panel of participants, no AEs of EPS were reported. Furthermore, as described in Section 2.2.3, the titration regimen in this study was demonstrated to be generally well tolerated in P014, an ongoing study. As described in Section 4.3.5, this regimen should provide appropriate exposures to evaluate the potential of MK-8189 to prolong QT.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Meets diagnostic criteria for schizophrenia or schizoaffective disorder according to the 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. Participants on more than 1 antipsychotic will need to be reviewed and approved by PI and Sponsor.
2. Has a total BPRS score of <48 with a BPRS score <4 for #10 (hostility) and #14 (uncooperativeness) at the screening visit.
3. 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 antipsychotics medication to treat symptoms of schizophrenia for two months prior to screening.
    b. no increase in level of psychiatric care due to worsening of symptoms of schizophrenia for three months prior to screening.

    Note: Participants that are stable but not currently taking antipsychotic medications are eligible.
4. Be in good health based on medical history, physical examination, and laboratory safety tests obtained at the screening visit and prior to randomization. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.
5. Have a Body Mass Index (BMI) ≥18.5 kg/m^2 and ≤40 kg/m^2 inclusive and total body weight of ≥50 kg (110 lbs) at screening. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

6. Have no clinically significant abnormality on 12-lead ECG performed at the screening visit and 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, 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 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria, however the more restrictive criteria of this Appendix and Inclusion/ Exclusion criteria will be followed.
7. Have a normal resting blood pressure (systolic blood pressure is ≥90 mmHg and ≤140 mmHg; diastolic blood pressure is ≥60 mmHg and ≤90 mmHg) and normal resting heart rate (≥45 bpm and ≤100 bpm) in the supine position at the pre-trial (screening) visit and prior to randomization. Repeat evaluations may be done if the values for a participant are, per investigator discretion, minimally outside of the triplicate measures. The assessment prior to randomization is based on the mean of the triplicate measures. In addition, orthostatic vital sign changes should be asymptomatic with a standing systolic blood pressure of ≥90 mmHg.
8. Has a history of receiving and tolerating antipsychotics medication within the usual dose range employed for schizophrenia.
9. Has a stable living situation in which the participant or contact person can be reached by the investigator if there is a need for follow up.
10. Participants with hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other medical conditions could be considered as a candidate 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.
11. Has regular bowel movements and, in the opinion of the investigator, no clinically significant diarrhea or constipation.
12. Participants is able to discontinue the use of all antipsychotic medication at least 5 days or 3 half-lives (which ever in longer) prior to the start of the treatment period and during the study.

Demographics

13. Participant is an individual of any sex/gender, from 18 years to 60 years of age inclusive, at the time of providing the informed consent.
14. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
  - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5 and Appendix 2.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

Additional Categories

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

5.2 Exclusion Criteria

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

Medical Conditions

1. 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 with one month of screening.

2. Has evidence or history of intellectual disability, borderline personality disorder, anxiety disorder, or organic brain syndrome.
3. Has a history of neuroleptic malignant syndrome or moderate to severe tardive dyskinesia (TD).
4. Has a substance-induced psychotic disorder or behavioral disturbance thought to be due to substance abuse.
5. Has a DSM-5 defined substance abuse or dependence disorder (excluding nicotine and caffeine) within 3 months of screening.
6. Has a history of seizure disorder beyond childhood or is receiving treatment with any anticonvulsant to prevent seizures.
7. Has an untreated or uncompensated clinically significant renal, endocrine, hepatic, respiratory, gastrointestinal, psychiatric, neurologic, cardiovascular, hematological, immunological, or cerebrovascular disease, malignance, allergic or other chronic and/or degenerative process at screening.
8. Has any clinically significant abnormal laboratory, vital signs, 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. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.
10. History of cancer (malignancy). Participants with adequately treated disease deemed as "cured," or who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study may be enrolled at the discretion of the investigator.
11. 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.
12. The participant meets any of the following cardiac parameters: a history of risk factors for Torsades de Pointes (e.g, heart failure/cardiomyopathy or family history of long QT syndrome), is taking concomitant medications that prolong the QT/QTc interval.
13. At Screening or prior to randomization has uncorrected hypokalemia or hypomagnesemia, or abnormal serum calcium.
14. Has a history of repeated or frequent syncope, vasovagal episodes, or epileptic seizures.
15. Has a family history of sudden cardiac death.
16. Has a history of any illness that, in the opinion of the investigator or Sponsor, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
17. Participant has an estimated CrCl ≤80 mL/min based on the Cockcroft-Gault Equation.

Cockcroft-Gault Equation:

$$\text{CrCl} = \frac{(140 - \text{age<yr>})(\text{body wt <kg>})}{(72)(\text{serum creatinine <mg/dL>})}$$

When creatinine is measured in µmol/L, use this formula:

$$\text{CrCl} = \frac{(140 - \text{age<yr>})(\text{body wt <kg>})}{(72)(\text{serum creatinine <µmol/L>} \times 0.0113)}$$

For females, multiply the result by 0.85.

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

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

18. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
19. Has a positive test(s) for HBsAg, hepatitis C antibodies or HIV.
20. 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

21. Has received or is currently receiving treatment with clozapine for any length of time. Has received treatment with monoamine oxidase inhibitors within 3 months of screening or cariprazine within 2 months of screening.
22. Is unable to be washed off their parenteral depot antipsychotic medication prior to screening or requires a dose of a parenteral depot antipsychotic medication during the study
23. Is unable to refrain from the use of co-medication that is a moderate or strong inhibitor or inducer of CYP3A or moderate or strong inducer of CYP2C9 beginning approximately 2 weeks or 5 half-lives, whichever is longer, prior to administration of the initial dose of trial drug and throughout the trial (Section 6.5).
24. Has received any non-live vaccine starting from 14 days prior to study intervention or is scheduled to receive any non-live vaccine through 30 days following study intervention. Exception: COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination. Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

Prior/Concurrent Clinical Study Experience

25. 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

Not applicable

Other Exclusions

26. Under the age of legal consent.
27. Has been in incarceration or imprisonment within 3 months prior to screening.
28. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
29. 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.
30. Is a regular user of cannabis (in the opinion of the PI; cannabis use >2x per month requires Sponsor consultation), a user of 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) (with the exception of prescribed medications permitted at the discretion of the PI and Sponsor and/or cannabis) prior to randomization.
31. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions). 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.
32. 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

Participants will fast from all food and drinks, except water, for at least 8 hours before study intervention administration. Approximately 240 mL of water will be provided during study drug administration but will be restricted 1 hour prior to and 1 hour after study drug administration.

Meals and snack(s) will be provided by the investigator at time points indicated in the SoA after any coinciding Holter and/or PK procedure. Participants will fast from all food and

drinks, except water, between meals and snacks. Meals and snacks should be standardized in caloric content, composition, and timing and the meal content will be consistent within a given clinical site. After the 48-hour postdose procedures have been completed in each period, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing except Day 5 breakfast which will be served after all 72-hour postdose procedures.

Meal and water restrictions on Day -1 will be time-matched to days when treatment is administered. Similarly, on the days following the last dose in each per period, meal and water restrictions will be time-matched to days when treatment is administered.

Fasting requirements for laboratory safety evaluations are at least 8 hours prior to collection.

5.3.1.2 Fruit Juice Restrictions

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

Participants will refrain from the consumption of all fruit juices 24 hours before study drug administration and through the completion of the 72-hour postdose procedures in each period.

On all other 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 before the prestudy and poststudy visits.

Participants will be permitted to consume approximately 2 units of caffeinated beverages or xanthine-containing products only between 1 hour and 2 hours postdose on study intervention administration days and time-matched on non-study intervention administration days.

After 72 hour postdose procedures, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

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

5.3.2.3 Tobacco Restrictions

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

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc.) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), and until the poststudy visit. Note: On Day -1 of Period 1, moderate ambulation and physical activity are encouraged to show a range of HR.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

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

6 STUDY INTERVENTION

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

Clinical supplies, MK-8189 and matching placebo and standard image placebo for moxifloxacin will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
Sequences 1 to 6	Experimental	MK-8189	Drug	Tablet	12 mg	48 mg	Oral	Treatment A Day 1	Test Product	IMP	Provided centrally by the Sponsor
Sequences 1 to 6	Experimental	MK-8189	Drug	Tablet	12 mg 4 mg	80 mg	Oral	Treatment A Day 2	Test Product	IMP	Provided centrally by the Sponsor
Sequences 1 to 6	Active Comparator	Moxifloxacin	Drug	Tablet	400 mg	400 mg	Oral	Treatment B Day 2	Diagnostic – to assess endpoints	NIMP/AxMP	Provided locally by the site
Sequences 1 to 6	Placebo Comparator	MK-8189 Matched Placebo	Drug	Tablet	0 mg	0 mg	Oral	Treatment C Days 1-2	Placebo	NIMP/AxMP	Provided centrally by the Sponsor
Sequences 1 to 6	Placebo Comparator	Standard image placebo	Drug	Tablet	0 mg	0 mg	Oral	Treatment B Day 1	Placebo	NIMP/AxMP	Provided centrally by the Sponsor

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

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

The sample allocation schedule is depicted in Table 2.

Table 2 Sample Allocation Schedule

Treatment Sequences	n	Period 1	Period 2	Period 3
Sequence 1	14	A	B	C
Sequence 2	14	B	C	A
Sequence 3	14	C	A	B
Sequence 4	14	B	A	C
Sequence 5	14	A	C	B
Sequence 6	14	C	B	A

Treatment A (MK-8189)
Day 1: 48-mg MK-8189 (4 x 12 mg) = 4 tablets
Day 2: 80-mg MK-8189 (6 x 12 mg, 2 x 4 mg) = 8 tablets
Treatment B (Moxifloxacin)
Day 1: Standard image placebo = 1 tablet
Day 2: 400-mg Moxifloxacin = 1 tablet
Treatment C (MK-8189 Placebo)
Day 1: MK-8189 Placebo matching 48-mg MK-8189 = 4 tablets
Day 2: MK-8189 Placebo matching 80-mg MK-8189 = 8 tablets

6.3.2 Stratification

The allocation schedule will be stratified to females and males. Female participants will be assigned the low allocation range and male participants will be assigned the upper allocation range to attempt to enroll at least 30% females.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-8189 and MK-8189 matched placebos will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

The administration of moxifloxacin will be open label therefore, the Sponsor, investigator, and participant will know the moxifloxacin intervention administered. A standard image placebo will be administered on Day 1 of the moxifloxacin period (Treatment B).

6.4 Study Intervention Compliance

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

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

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

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 5 days after the last dose of study intervention.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

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

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

- Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:
  - Reason for use
  - Dates of administration including start and end dates
  - Dosage information including dose and frequency

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

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 are stable for at least 3 months prior to screening and there are no expected changes in co-medication during the study. Inclusion of participants being administered concomitant medications that have not been stable for 3 months must be discussed with the Sponsor. Moderate to strong inhibitors or inducers of CYP3A and/or CYP2C9 are not allowed as MK-8189 is being metabolized by these CYP enzymes and co-administration of inhibitors or inducers may potentially alter the metabolism and PK of MK-8189.

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

For the treatment of EPS, such as acute dystonia, all participants may be treated with an anticholinergic. If the symptoms are unresponsive to anticholinergic treatment, a benzodiazepine can be used. CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

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 resolve with the β-adrenergic blocker, treatment with an anticholinergic may be used. An anticholinergic may be used as first-line treatment in the case that a β-adrenergic blocker is not a preferred treatment based on a participant's medical history and/or concomitant medication.

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

Participants will be washed off from their antipsychotic treatment (Section 8.1.5.1). 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. 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)

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

- Skip a single dose and dosing may continue at the same dose level
- Receive the same dose level to further explore safety and tolerability at that level
- Dosing may be stopped

If appropriate medical care necessitates dosing to be stopped or a lower dose given, the investigator may do so without consultation with the Sponsor. Participant discontinuation criteria are outlined in Section 7.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- Participants with severe EPS symptoms will be discontinued if not attenuated with dose reduction, titration, or medical management.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen (with the exception of prescribed medications permitted and/or cannabis at the discretion of the PI and Sponsor) at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, 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 or participant's legally acceptable representative withdraws consent from the study.

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in Appendix 8.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history, including psychiatric history and substance abuse, will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

Washout from Antipsychotics:

All participants will be washed out from their antipsychotic medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1 in Period 1. The washout may start with a down titration of the antipsychotic treatment during the screening period per direction of the investigator. For longer half-life antipsychotics (eg, aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment (ie, cessation of AAP) as an outpatient, but should be confined to the clinical research unit within a week of stopping treatment and minimally beginning on Day -6.

Participants may restart their antipsychotics therapy following completion of the 72-hour postdose study procedures in Period 3.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff. Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Approximately 240 mL of water will be provided during study drug administration but will be restricted 1 hour prior to and 1 hour after study drug administration. Details on water and dietary restrictions are outlined in Section 5.3.1. Site staff will ensure that participants have swallowed study treatment.

8.1.8.1 Timing of Dose Administration

All doses of the study medication will be given in the morning at approximately the same time in each treatment period and will occur after an 8-hour overnight fast, as described in the SoA.

8.1.9 Discontinuation and Withdrawal

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

CCI [redacted]. Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

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

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

8.1.11 Domiciling

Participants currently treated with antipsychotic medication will be domiciled in the CRU from Day -6 prior to Period 1 (to start the washout period of current antipsychotic

medication) and will remain in the CRU until 72 hours post the last dose in Period 3. Participants not currently being treated with antipsychotic medication may be domiciled minimally starting on Day -2. 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.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

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

Body Mass Index (BMI)

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

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

8.3.2 Vital Signs

- Body temperature, heart rate, respiratory rate, and blood pressure will be assessed at prespecified timepoints noted in the SoA (Section 1.3).
- Blood pressure and heart rate measurements will be assessed in a supine position as well as orthostatic positions with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

In each Period, the predose (baseline) 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 BP measurements will be single measurements. In each Period (all timepoints), and at screening and poststudy, HR will be measured in triplicate, obtained at least 1-2 minutes apart.

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained at timepoints per the SoA. Participants should be supine for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

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

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

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

The correction formula to be used for QTc is Fridericia.

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

Predose ECGs, in each period, will be obtained in triplicate at least 1 to 2 minutes apart per the schedule of activities on Day -1. These measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

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

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

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

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

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

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

24-Hour Holter Assessment

For the entire 24-hour Holter recording duration, participants should not wear metal jewelry such as watches, necklaces, and/or bracelets from the waist up. Participants must also not use electronic devices such as cell phones, computers/laptops, MP3 players, etc. during Holter recording. Holter recording will be turned on approximately 70 minutes prior to trial drug administration. Participants will be encouraged to shower according to a schedule agreed upon by the Investigator, Sponsor, and Holter vendor so as not to interfere with intensive Holter monitoring periods. Details can be found in the procedure manual provided by the ECG vendor.

Holter data will be extracted (in replicates) and analyzed using automated and semi-automated methods by a blinded core ECG laboratory according to a pre-specified algorithm. To minimize artifacts, participants must rest quietly in a supine position for ~20 minutes prior to the time points specified in the SoA. The extraction window will be ~5 minutes following ~15 minutes of rest. No other study assessments or procedures should occur during the resting and extraction windows (~20 minutes).

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

See the procedure manual provided by the ECG vendor for specific instructions.

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

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

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Suicidal Ideation and Behavior Monitoring

8.3.6.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at the time points indicated in the SoA. In addition, C-SSRS will be administered at any unscheduled visit where safety assessments are performed. The C-SSRS will not be routinely administered at visits with a sole purpose of PK sampling and/or witnessed study intervention administration. Site staff should review the contents of the C-SSRS for completeness.

If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, before their assessment of the participant and to further inform their evaluation.

The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior at screening, the assessor should also inquire and document if this is also present at the time of the Screening Visit.

Participants who, at any time during this study, report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). After that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety.

In addition, all AEs of suicidal ideation or behavior must be recorded as an ECI (see Section 8.4.7). Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

8.3.7 Rater Expectations and Training for Clinical and Cognitive Assessments

For this study, potential raters of clinical assessments (BARS [Section 8.3.8], SAS [Section 8.3.8], AIMS [Section 8.3.8], BPRS [Section 8.3.9] and C-SSRS [8.3.6.1]), will be identified based on review of their reported credentials against target minimum credentials for education, prior experience with schizophrenia or similar populations and direct, hands-on experience with study-specific or similar assessments. Persons whose credentials meet or exceed those targets will then be considered 'qualified' as raters in this trial. It is recommended that the same rater conducts the same assessments throughout the study for a given participant, where feasible.

8.3.8 Monitoring of Extrapyramidal Symptoms

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

8.3.9 Assessment of Neuropsychological Effects

A general (full) Neurological Exam will be performed at the Screening and Baseline visits. A targeted Neurological Exam will be administered at times specified in the SoA.

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

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

8.3.10 Photograph of Rash

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

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

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

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

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

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

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

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

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

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

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

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

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Not applicable

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

1. Severe EPS or EPS leading to study discontinuation
2. Treatment-emergent adverse event of new or worsening tardive dyskinesia
3. Suicidal ideation, suicidal behavior
4. Moderate or severe depression
5. Moderate or severe mood swings
6. Dystonia
7. Akathisia

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

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

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189 and Moxifloxacin

Blood collection time points for plasma MK-8189 and moxifloxacin are outlined in the SoA (Section 1.3). Sample collection, storage, and shipment instructions for plasma samples will be provided in the Operations/Laboratory manual.

8.7 Pharmacodynamics

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

8.8 Biomarkers

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

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CCI 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 CCI Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1, but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples are listed in Section 8.8

8.10 Visit Requirements

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

8.10.1 Screening

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

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period

Refer to the Schedule of Activities (Section 1.3)

Participants must be washed out from any antipsychotic therapy for at least 5 days or cover at least 3 half-lives of the drug (whichever is longer) prior to Day -1. Participants will report to the CRU on Day -6 to start their washout period. However, if participants are not currently being treated with antipsychotic medications and therefore do not require a washout, they may be domiciled on Day -2.

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

Participants will resume the use of their own antipsychotic medication after the completion of the last PK sample collection (72h postdose). A phone call should occur 5-7 days after CRU discharge to check for any side effects and medication compliance.

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

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

8.10.4 Poststudy

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

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the ECG parameter values extracted from the 24-hour Holter collection, and time-matched blood samples for MK-8189/moxifloxacin are the critical procedures. Every effort should be made to complete the 20-minute supine resting period at the nominal time point. For example, for the 1-hour postdose time point, the supine rest period should begin at 40 minutes postdose and end at 1-hour postdose. The PK should be collected within 10 minutes of the end of the supine rest period. For example, if the supine rest period ends at 1 hour postdose the PK should be collected by 1 hour and 10 minutes postdose.

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

1. Holter ECG (extraction period) **and** blood for plasma PK
2. 12-Lead Safety ECG
3. Vital signs –
   a. Resting Blood Pressure and Heart Rate
   b. Orthostatic BP and HR
4. Laboratory safety tests
5. Neurological exams: C-CSSRS, BPRS, BARS, AIM, SAS

Vitals signs may occur immediately before 12-Lead Safety ECG depending on participant positioning.

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: VS and ECG triplicate measurements on Day -1 timepoint(s) within 1 hour; laboratory safety tests and physical examination within 72 hours.
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical examination
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to 72-hours postdose may be obtained within 2 hours of the theoretical sampling time
- Study intervention administration (multiple-dose studies only): at 30 minutes.

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

This is a Phase 1 assessment of MK-8189 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

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

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

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

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

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

9 KEY STATISTICAL CONSIDERATIONS

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

Responsibility for Analyses

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

9.1 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3

Primary hypothesis:

Administration of an 80 mg MK-8189 dose on Day 2 does not prolong the QTc interval to a clinically significant degree. Specifically, the true mean difference (MK-8189 – placebo) in QTc change from baseline is less than 10 msec.

Secondary hypothesis:

Administration of a single 400 mg dose of moxifloxacin is associated with an increase in QTc interval. Specifically, the true mean difference (Moxifloxacin-placebo) in QTc change from baseline is greater than 5 msec at least at one time point.

9.2 Analysis Endpoints

Cardiodynamics, PK and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.2.1 Cardiodynamics

ECG Extractions:

The central ECG laboratory (eResearch Technologies, Inc., a Clario company, Philadelphia, PA, USA) will use TQT Plus, an advanced computer-assisted and statistical process utilized to extract ECGs from continuous recordings collected in thorough QT (TQT) studies. During protocol-specified ECG extraction windows, up to 10 non-overlapping 14-second digital 12-lead ECG tracings will be extracted from continuous recordings. The TQT Plus method enables the extraction of a high-quality data set by identifying periods of recordings with the lowest available HR variability and noise.

The ECGs will be extracted according to the following principles:

- The actual times of dosing, extraction windows, and PK sampling will be communicated to the central ECG laboratory by the study center personnel.
- The TQT Plus process identifies periods of stable HR on the continuous 12-lead ECG tracing within the 5-minute extraction window. Stability will be defined as beat-to-beat variation of HR and other ECG parameters lower than a predefined threshold. If the TQT Plus method results in a low number of consecutive, readable cardiac cycles in the 5 minute window, the time point will be fully reviewed manually.
- Replicate, non-overlapping ECGs will be extracted in close succession within each extraction window.

Early Precision QT Analysis

Twelve-lead ECGs will be extracted in up to 10 replicates from each nominal time point pre specified in the protocol with TQT Plus methods. The median value of each parameter from the set of approximately 100 evaluable beats in each extracted replicate will be calculated, and then the mean of all available (up to 10) medians from the nominal time point will be used as the participant's reportable value at that time point.

Early Precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates (1 replicate consists of one 14 second ECG). All readable cardiac cycles from these ECG replicates will be assessed for multiple quality metrics, including beat stability, HR changes, noise, and other parameters, and will be categorized into high and low confidence rank. All low confidence beats will be fully reviewed and adjudicated manually by Clario technicians using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis.

Statistical quality control procedures will be used to review and assess all beats and identify "high" and "low" confidence beats using several criteria including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat to beat
- HR derived from RR using the formula HR (bpm)=60000/RR(msec)

The primary analysis lead will be Lead II. If Lead II is not analyzable, then the primary lead of analysis will be changed to V5 for the subject's entire data set. If Lead V5 is not analyzable, then Lead V2 will be used for the subject's entire data set. If both alternate leads cannot be used, the Clario cardiologist has the option to deem the data non-analyzable or can decide to use the most appropriate lead for the subject's entire data set. The lead used for analysis is listed in the data listings transferred from Clario.

Placement of fiducials and measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates will be performed using the iCOMPAS software. All beats that are deemed "high confidence" will not be reviewed by a Clario cardiac safety specialist. All low confidence beats will be reviewed manually by a Clario cardiac safety specialist and adjudicated using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis. The beats confirmed to meet fail criteria will not be included in the analysis.

For the purpose of measuring PR and QRS intervals and to assess T-wave morphology and presence of U-waves, the TQT Plus algorithm will select the 3 of the 10 ECG replicates with the highest quality score from the ECG extraction window. These 3 ECGs will be analyzed using a semi-automated process to determine these parameters. If 3 consecutive usable beats cannot be identified in at least 2 of the 3 replicates, then all beats in all replicates will be reviewed for that time point using a manual analysis.

If manual analysis is required, then all beats in a minimum of 3 replicates will be reviewed using the iCOMPAS software. The Clario cardiac safety specialist will review all usable beats in Lead II (or an alternate lead) for each replicate and will review and/or adjust the fiducial placements (onset of P, onset of Q, offset of S, and offset of T-wave that were electronically marked) of each waveform and also document the T wave morphology and the presence of U-waves for each beat.

Endpoints

QTc (QT interval corrected for heart rate) change from baseline is the primary endpoint. Fridericia's correction to the QT interval (QTcF) will be used as the default correction method, and is applied by dividing the QT interval by the cube root of the RR interval, QTcF = (QT/RR1/3).

Replicates Holter ECG readings will be extracted at each specified time point, and replicate values will be averaged before any calculation and model fitting.

The baseline value for each participant during each period will be defined as the average of measurements obtained over three predose time points: 20 minutes, 10 minutes and 5 minutes prior to Day 1 dosing in that period. Change from baseline at each time point will be computed as post-dose minus baseline value for all analyses.

The QTc comparison of MK-8189 to placebo will be conducted at all time points as indicated by the study flow chart. For the comparison of moxifloxacin to placebo, only the time points 1, 2, 3, and 4 hours post-dose will be considered.

HR, PR interval, QRS duration, and U and T wave morphology are exploratory endpoints.

9.2.2 Pharmacokinetic Endpoints

Plasma concentrations at ECG-matched time points for MK-8189. (Note: Moxifloxacin concentrations will be assessed only if concentration-QTc analysis is required for moxifloxacin)

PK parameters (e.g., AUC0-24, AUC0-last, Cmax, C24, Tmax and t1/2) for MK-8189 are the PK endpoints of interest.

9.2.3 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs.

9.3 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.

Per-Protocol (PP) – The population includes the subset of participants who receive study treatment and who comply with the protocol sufficiently to ensure that generated data will likely 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 clinical study report. 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 study treatment will be included in the PP dataset. This population will be used for the PK and cardiac safety analyses.

9.3.1 Safety Analysis Populations

All Participants as Treated (APaT) – Safety Analyses will be conducted in the APaT population, which consists of all randomized/allocated participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

Analyses of laboratory test results, vital signs, and ECG measurements will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

9.4 Statistical Methods

9.4.1 Statistical Methods for Cardiodynamics Analyses

ECG data will be examined for outliers and unusual values. Any data excluded from the analysis will be listed, along with the reason for exclusion, in the report. Replicates QT

measurements taken at a prescribed time point will be averaged prior to any further analysis. If additional unscheduled ECGs are collected post dose, they will be excluded from the analysis. No imputations will be made for missing ECG data.

9.4.1.1 Adequacy of QT Correction Method

Fridericia's correction to QT is made in order to correct for heart rate. The formula is (QTcF(msec)=QT(msec)/[(RR(sec))^(1/3)]). The appropriateness of the correction factor (i.e. 1/3) will be assessed graphically and via a linear mixed effects model with QTcF as the response variable and RR interval as a covariate, and subject as a random effect. Day -1 readings, pre-dose Day 1 measurements in each period, and placebo data will be used for this analysis. Though not to be formally tested, a slope close to 0 indicates that the Fridericia's correction is adequate. If the above methods provide evidence that Fridericia's correction is inadequate or heart rate is shown to be affected by MK-8189 administration, then additional correction methods such as individual correction (QTcI) may be explored.

If mean change from baseline in HR at any timepoint is above 10 bpm, then analysis will be performed using QTcI. For this analysis, QT and RR values thus obtained from continuous ECG measurements on Day -1 for 24 hour period (prior to dosing on Day 1 in period 1) will be used to estimate the coefficients for each participant and these coefficients will be used to correct QT for HR for the participant.

9.4.1.2 Primary Analysis

The baseline for the assessment of MK-8189 80 mg, placebo, and moxifloxacin QTc effect will be the QTc values obtained at predose on Day 1 in each treatment period.

A linear mixed effects model will be used to estimate the mean between-treatment difference in QTc change from baseline at each time point, using separate models for each pairwise treatment comparison of interest (MK-8189 versus Placebo and Moxi versus Placebo) and each time point. Post dose data from Day 2 from all six sequences will be included in the model. The dependent variable is QTc (y), and the independent variables in the model include fixed effect terms for seqstar, periodstar and treatment; seqstar and periodstar are defined for the MK-8189 vs. Placebo comparison in the table below, and analogous definitions are used for the moxi vs. Placebo comparisons. In addition, the between-periodstar difference in baseline QTc (Xdiffstar) will be used as a covariate in the model along with periodstar by Xdiffstar interaction. This approach is an extension of the methodology for the analysis of 2x2 crossover designs with period-specific baseline measurements [Mehrotra, D. V. 2014]. Of note, this linear mixed effects modeling analysis is notably more powerful than a corresponding analysis for a 3x3 crossover design that uses change from baseline as the dependent variable with fixed effects terms for sequence, treatment and period.

An unstructured covariance matrix will be used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). The least

square mean (95% CI) of QTc for both treatments and the least square difference (90% CI) between the two treatments will be obtained from the LSMEANS statement. Sample SAS code is given below for the comparison of MK-8189 versus Placebo.

```
PROC MIXED DATA=all;

 by timepoint;

 CLASS seqstar periodstar treatment subjid;

 MODEL y=seqstar treatment  periodstar  Xdiffstar  Xdiffstar *periodstar/ ddfm=kr;

 REPEATED treatment/SUBJECT= subjid(seqstar) TYPE=UN;

 LSMEANS treatment/ DIFF CL ALPHA=0.10;

RUN;
```

	Period			seqstar	periodstar	
Sequence	1	2	3		1	2
1	MK-8189	Placebo	Moxi	1	MK-8189	Placebo
2	Placebo	Moxi	MK-8189	0	Placebo	MK-8189
3	Moxi	MK-8189	Placebo	1	MK-8189	Placebo
4	MK-8189	Moxi	Placebo	1	MK-8189	Placebo
5	Moxi	Placebo	MK-8189	0	Placebo	MK-8189
6	Placebo	MK-8189	Moxi	0	Placebo	MK-8189

y=response at post-baseline (at a given time point)

Variable seqstar is derived from the original treatment sequences. For example, when comparing MK-8189 with Placebo, seqstar=1 for sequences in which MK-8189 appears before Placebo and seqstar=0 for sequences in which Placebo appears before MK-8189, as shown in the table above

Variable periodstar is derived by the order of treatments in a sequence. For example, when comparing MK-8189 with Placebo, the periodstar=1 for MK-8189 when MK-8189 appears before Placebo and periodstar=2 when MK-8189 appears after Placebo, as shown in the table above.

Xdiffstar= difference between the QTc baselines of the consecutive periodstars in which MK-8189 can appear before or after Placebo.

Primary Hypothesis

To address the primary hypotheses that administration of an 80 mg dose of MK-8189 does not prolong the QTc interval to a clinically significant degree, specifically, means and two-sided 90% CIs (equivalent to one-sided upper 95% CIs) for the true mean difference (MK-8189 – placebo) in QTc change from baseline will be provided at each prespecified time point. These CIs will be calculated using the appropriate error term from the above mixed effect model and referencing a t-distribution. If all of the upper limits of the 90% CIs fall below 10 msec, the primary hypothesis that administration of an 80 mg dose of MK-8189 does not prolong the QTc interval to a clinically significant degree will be supported. However, if any of the upper limits exceed 10 msec, then there will be insufficient evidence to accept the primary hypothesis.

Secondary Hypothesis

To address the secondary hypothesis, the one-sided p-value for the mean difference between moxifloxacin and placebo in QTc change from baseline compared to 5 msec will be computed at each of the following time points (1, 2, 3, and 4 hours post-dose) based on the above mixed effect model. Hochberg's step-up method will be applied to preserve the overall alpha level at 0.05 for the hypothesis testing. The p-values obtained will be ranked in ascending order $P(1) \leq P(2) \leq P(3) \leq P(4)$.

If the maximum p-value P(4) is less than or equal to $\alpha = 0.05$, then it will be concluded that the secondary hypothesis has been met.

If the maximum p-value P(4) is greater than $\alpha = 0.05$, the next largest p-value P(3) will then be compared with $\alpha/2 = 0.025$. If P(3) is less than or equal to 0.025, then it will be concluded that the secondary hypothesis has been met.

Testing will continue with P(i) compared to $\alpha = 0.05/(n-i+1)$ in each step, until one time point supports the hypothesis, or until all p-values have been evaluated.

The hypothesis that administration of moxifloxacin is associated with an increase in QTc interval will be accepted if there is at least one i such that P(i) is less than or equal to $\alpha = 0.05/(n-i+1)$. Ninety percent confidence intervals for the mean between-treatment difference (moxifloxacin – placebo) will also be provided at each time point.

9.4.1.3 Sensitivity Analysis

A model-based timepoint by timepoint analysis will also be conducted using a linear mixed effects model to estimate the mean between-treatment difference (moxifloxacin – placebo and MK-8189 80 mg - placebo) in QTc change from baseline at each time point. Data from all 6 sequences will be included in the model. The dependent variable is ΔQTcF (change from baseline), and the independent variables in the model include treatment (moxifloxacin, MK-8189 80 mg, and placebo), sequence, period, time (as a categorical variable), and

treatment-by-time interaction as fixed effects and baseline QTcF as a covariate, and subject as a random effect. An unstructured covariance matrix will be used for the repeated within-period QTcF change from baseline measurements.

The least square mean (95% CI) of QTcF change from baseline for moxifloxacin, MK-8189 80 mg, and placebo and the least square difference (90% CI) between treatments (moxifloxacin – placebo and MK-8189 80 mg - placebo) will be obtained at each time point from the LSMEANS statement.

9.4.1.4 C-QTc Analysis for MK-8189

Before performing the C-QTC analysis, the following model assumptions will be checked [Garnett, C., et al 2017]. If not specified otherwise, all data including Day 1 data will be used in the analysis.

Graphical data exploration of model assumptions

The assumptions that MK-8189 does not affect HR, that the QT correction method for HR is adequate, that there is no delayed effect of PK on QTc (hysteresis), and that the relationship between concentration and QTc is in fact linear will first be explored graphically and/or statistically. If any of the model assumptions are not met, other models may be considered.

Assumption 1: No drug effect on HR

The assumption that MK-8189 has no effect on HR will first be assessed by providing an exploratory plot of mean change in HR (ΔHR) from baseline versus time by dose. In addition to this plot, the mean placebo-corrected change from baseline in heart rate (ΔΔHR) by dose will also be evaluated.

Mean increases or decreases in HR from baseline >10 bpm would be considered indicative of a meaningful change.

Assumption 2: QT correction is independent of HR

The adequacy of QT correction for heart rate will be evaluated both statistically and graphically. Fridericia's correction to QT (QTcF = QT / RR1/3) is usually adequate, and this correction for HR will be applied first. The appropriateness of the correction factor (i.e., 1/3) will be assessed via a linear mixed effects model with QTcF as the response variable and RR interval as a covariate and subject as a random effect. Day -1 readings, pre-dose Day 1 measurements in each period, and placebo data will be used for this analysis. Inclusion of zero in the 95% CI of the estimated slope would indicate that Fridericia's correction provides an adequate correction to the original QT data; otherwise, an appropriate transformation on RR may be further explored for each of the analyses. For the analyses, a scatter plot of individual QTc versus RR interval (Day -1 readings, pre-dose Day 1 measurements in each period, and placebo data) including the regression line from the above model will be provided.

A second scatterplot of individual QTc versus RR interval including all data (active, placebo, designated by separate symbols) will also be provided. A QTc-RR quantile plot will be provided. Individual RR values will be binned into deciles. The median of the RR observations in each bin will be plotted against the corresponding mean QTc (with 90% CI). Mean QTc will be presented separately for placebo and active treatments, distinguished with separate symbols. This plot will be overlaid with separate regression lines for active and placebo treatments and 90% confidence bands, which will be obtained from a linear mixed effects model having a fixed effect for treatment (active, placebo), RR interval as continuous covariate, interaction of treatment and RR, and a random effect for subject.

If there is increase in HR (mean change from baseline in HR >10 bpm) on intervention, then QT will be corrected for HR by applying individual correction. The QTcI correction factor may be derived from linear mixed effects modeling on the natural log scale log(QT) = log(a) + bi ·log(RR interval) with subject included as a random effect for both slope and intercept. This will be done for each participant using baseline data derived from Day-1 and Day 1 predose from period 1 automated QT and RR readings. The QTcI correction factor (ie, log[RR] coefficient) for each participant, bi, will then be used to calculate the individually corrected QT for each participant as follows: $QTcI = QT/RR^{bi}$. If this model is found to be inadequate, then other models may be used.

For C-QTcI analysis, the individual coefficients will be calculated from automated ECG readings will be used. For C-QTcF analysis, semi-automated ECG readings will be used.

Note that hereafter, “QTc” will refer to the HR corrected QT interval with the appropriate correction method determined through the above procedures.

Assumption 3: No time delay between drug concentrations

The potential for PK/PD hysteresis will be evaluated with the following plots:

- time course of mean and 90% CI ΔΔQTc by dose

- time course of geometric mean (90% CI) drug concentration by dose

- mean ΔΔQTc versus concentration connected in temporal order by dose

The assumption of a direct temporal relationship between drug concentration and QTc effect is supported if the time course of ΔΔQTc is concordant with the PK profile. If, however, there is a clear delay between peak concentration and peak QTc or QTc effect, the model would be modified to account for the possibility of a delayed temporal effect.

Assumption 4: Linear C-QTc relationship

The adequacy of using a linear model will be assessed by a scatterplot of individual paired ΔQTc and concentration data. It will be overlaid with a loess smooth line and 90% confidence band.

Dependent Variable

The dependent variable for analysis will be HR-corrected QTc change (ΔQTc) from baseline values with the appropriate correction determined using the methodology in [Sec. 9.5.1].

MK-8189 plasma concentration profiles will be examined for outliers and missing values. For C-QTc analyses, only paired ECG and PK concentrations will be included in the model. Participants on active treatment who have post-dose concentration values below LLOQ will have the value set at LLOQ/2 for the analysis. Participants on placebo will have their plasma concentration set to zero at each time point for that treatment period.

C-QTC Model

If the assumptions described above are met, C-QTc modeling will be conducted in an exploratory manner. PROC MIXED will be used to investigate the relationship between QTc and MK-8189 plasma concentrations. The individual QTc change from baseline will be evaluated using a linear mixed effects model with fixed effects for treatment (MK-8189, placebo) and time point, and continuous effects for QTc baseline and MK-8189 plasma concentration as well as random effects for subject and subject by period, and a double compound symmetry covariance structure will be assumed [Mehrotra, D. V., et al 2017].

The following is sample SAS code:

```
proc mixed data=datanew method=reml;
class subjid time trt;
model cfb = trt conc time bsl/ddfm=kr solution;
random subjid;
repeated / subject = subjid*period type=cs;
estimate "ddQTc at 80 mg cmax" trt -1 1 conc cmax_80 mg / alpha=0.1 CL;
run;
```

where:
cfb = QTc change from baseline
ddQTc = placebo-corrected QTc change from baseline
bsl = QTc baseline
trt = 0 if treatment is placebo or 1 if treatment is MK-8189
conc = concentration
time = 0.5, 1, 2, 3, 4, 6, 8, 12, 14 on Day 1; predose, 1, 2, 3, 4, 8, 11, 14, 16, and 24 on Day 2.

The adequacy of the model will be assessed, and other relationships (e.g., nonlinear or delayed effect) may be explored if needed.

9.4.1.5 Exploratory Analyses – Other

Means and 95% confidence intervals for QTc and QTc change from baseline will be descriptively summarized for each treatment by time point.

In addition to the analyses conducted at prespecified time points, means and two-sided 90% CIs for the difference between MK- 8189 and placebo in QTc change from baseline may be provided for other time points that are of clinical interest.

Other ECG parameters of interest HR and PR intervals, QRS duration, will be summarized in similar fashion. Counts will be provided by treatment and time point for HR > 100 bpm, PR > 220 ms and QRS > 110 ms. T wave morphology and U wave will be summarized.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point. For baseline, the category will be deemed as present if observed in any replicates from all time points that constitute baseline.

9.4.1.6 Categorical Analysis of QTc

Counts will be provided by treatment and time point for QTc values falling in the following ranges: ≤ 450, > 450, > 480 and > 500 msec. Counts will also be provided by treatment and time point for QTc change from baseline values falling in the following ranges: < 30, ≥ 30 and ≥ 60 msec.

9.4.2 Statistical Methods for Pharmacokinetics and Safety Analyses

Pharmacokinetics

Individual values will be listed for AUC0-24, AUC0-last, Cmax, C24, and Tmax of MK-8189, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Safety

Clinical and laboratory adverse experiences will be tabulated. Additionally, laboratory tests, 12-lead ECG parameters, and vital signs may be summarized for each treatment, as deemed appropriate.

Summary statistics and plots will be generated for BARS, AIMS, and SAS, as well as for change from baseline. Responses to the C-SSRS will be listed.

9.5 Interim Analyses

No interim analysis is scheduled.

9.6 Multiplicity

No multiplicity adjustment is needed, since the primary hypothesis needs to be supported at each time point. Hochberg's step-up method is applied to preserve the overall alpha level at 0.05 for the secondary hypothesis testing.

9.7 Sample Size and Power Calculations

Primary Hypothesis:

The following power calculation is based on assumed true standard deviation for QTcF change from baseline of 12 msec obtained from participants in schizophrenia.

With 60 completing subjects, and true mean differences (MK- 8189 - placebo) in QTcF change from baseline no worse than 3 msec at all nine time points, there is at least 89% probability of observing 90% confidence intervals for the true difference to fall completely below 10.0 msec at all nine time points.

With 60 completing subjects, and true mean differences (MK- 8189 - placebo) in QTcF change from baseline no worse than 2 msec at all nine time points, there is at least 99% probability of observing 90% confidence intervals for the true difference to fall completely below 10.0 msec at all nine time points.

Secondary Hypothesis:

With 60 completing subjects, and true difference in QTcF change from baseline (moxifloxacin – placebo) of 7.9 msec, 10.3 msec, 12 msec, and 11.2 msec at 1, 2, 3, and 4 hours postdose, there is at least 99% probability that the secondary hypothesis will be supported; that is, that the true mean difference (moxifloxacin – placebo) in QTcF change from baseline is greater than 5 msec for at least one time point.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit			WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose fasting	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)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed in PONCBP only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)			

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

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

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.
f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

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

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
- Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant 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.

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

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are 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. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[b,c] • IUS[b,d] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[e] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If hormonal contraception efficacy for a participant assigned female sex at birth is potentially decreased due to interaction(s) with study intervention(s) (eg, CYP3A4 inducers), penile/external condoms must be used in addition to the POCBP's hormonal contraception [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [d] IUS is a progestin releasing IUD [e] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[e]

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

CCI [redacted]. Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

Any questions related to the future biomedical research should be emailed directly to CCI [redacted]

13. References

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

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Blood Volume Table

Periods 1, 2, and 3	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Test including serum βhCG (POCBP) or serum FSH (PONCBP) and BDS	1	4 (1 sample in Periods 1 & 2, 2 samples in Period 3)	1	6	12	72
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	4.5	4.5
Blood for Planned Genetic Analysis		1 sample in Period 1		1	8.5	8.5
Blood for MK-8189 and/or Metabolites Assay (Treatments A & C)		48 (24 samples in 2 of the 3 Periods)		48	4	192
Blood for Moxifloxacin (Treatment B - Day 2 only)		14 samples in 1 of the 3 Periods		14	4	56
Total Blood Volume per Participant for Periods 1, 2, and 3[a]						**333 mL**

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

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	**Potentially Significant Postrandomization Findings**
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
QTc (B or F)		
Male	QTc ≥450 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥450 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 Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Nonspecific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	**All**	**All**

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fridericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.

Baseline is defined as Predose Day 1.

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

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

A. If all protocol-specified laboratory values are normal, the participant may enter the study.
B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.
C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
    a. The participant may be excluded from the study.
    b. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
    c. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

OR

    a. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
        a. If the repeat test value is within the normal range, the participant may enter the study.
        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

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

10.11 Appendix 11: General and Targeted Neurological Examinations

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

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

10.11.1 The General Neurological Examination

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

10.11.1.1 Module 1 – Mental Status Examination

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of impaired attention or concentration. For example, difficulty remembering or following instructions or distractibility may be signs of inattention).
B. Thought Processes and Language (generally assess logic, relevance, organization, and coherence of participant's use of language throughout the interview).
C. Orientation (time, place, person).
D. Attention/Concentration.
   Ask the participant to count backwards from 100 by 7's ("Serial 7's") or ask to recite months backwards or spell a 5 unique letter word (eg, "WORLD") backwards.
   Note: To avoid learning effects, switch between tests throughout the study.
E. Memory (test registration of 3 objects; then test immediate recall 5 minutes later).
   Grade: NORMAL or IMPAIRED and describe abnormality (for each, A to E, above).
   Normal performance on Serial 7's is getting to 65 with no more than 1 error.

10.11.1.2 Module 2 – Cranial Nerve Assessment

A. II – Visual Fields and acuity
B. II, III – Pupil Size and Reactivity
C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus).
   Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus
D. V – Facial Sensation, Jaw Strength
E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)
F. VIII – Auditory Acuity (assessed using a bed-side screening test [eg, by rubbing fingers on each side of participant's head or by whispering numbers])
G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

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

10.11.1.3 Module 3 – Motor System

A. Muscle Tone

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

   Score: left and right

   Grade: NORMAL, INCREASED or DECREASED

B. Muscle Strength

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

   Grade: NORMAL, IMPAIRED and describe abnormality

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

   Score: left and right

   Grade:

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

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

   Score: left and right

   Grade:

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

C. Pronator Drift

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

Score: left and right

Grade: NORMAL or IMPAIRED and describe abnormality

10.11.1.4 Module 4 – Reflexes

A. Biceps

B. Knee

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

Score: left and right

Grade: NORMAL, INCREASED, DECREASED, or ABSENT

C. Babinski

Score: left and right

Grade: NORMAL or ABNORMAL

10.11.1.5 Module 5 – Coordination and Gait

A. Rapid, Rhythmic Alternating Movements

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

   Score: left and right

   Grade: NORMAL or IMPAIRED

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

B. Point-to-Point Movements

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

   Score: left and right

   Grade: NORMAL or IMPAIRED

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

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

       Be prepared to catch the participant if they are unstable.

       Grade: NORMAL or IMPAIRED

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

       Grade: NORMAL or IMPAIRED and describe abnormality

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

       Grade: NORMAL or IMPAIRED and describe abnormality

10.11.1.6 Module 6 – Sensory

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

   Score: left and right

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

10.11.2 The Targeted Neurological Examination

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

10.11.2.1 Module 1 – Mental Status Examination

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

10.11.2.2 Module 2 – Cranial Nerve Assessment

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

10.11.2.3 Module 3 – Motor System

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

10.11.2.4 Module 5 – Coordination and Gait

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

10.11.2.5 Module 6 – Sensory

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

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
AAP	atypical antipsychotics
ADME	absorption, distribution, metabolism, and excretion
AME	Absorption, Metabolism, and Excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
AUC0-24hr	area under the curve from 0 to 24 hours
AV	atrioventricular
BARS	Barnes Akathisia Rating Scale
BDS	blood drug screen
bid	twice daily
BMI	body mass index
bpm	beats per minute
BP	blood pressure
BRPS	Brief Psychiatric Rating Scale
cAMP	cyclic adenosine monohydrate
CCU	Cardiac care unit
CF	compact flash
cfb	change from baseline
CG	Cockcroft-Gault
cGMP	cyclic guanosine monohydrate
CI	confidence interval

Abbreviation	Expanded Term
C_{max}	maximum plasma concentration
CNS	central nervous system
CL	clearance
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CR	controlled release
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPQT	extra precision QT
EPS	extrapyramidal symptoms

Abbreviation	Expanded Term
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSSB	Hepatic-specific Safety Board
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LLOQ	lower limit of quantitation
mRNA	messenger RNA
NCS	not clinically significant
NDA	New Drug Application
NOAEL	no observed adverse effect level

Abbreviation	Expanded Term
NR	normal range
PCL	Protocol Clarification Letter
PD	pharmacodynamic
PK	pharmacokinetic
POCBP	participant of childbearing potential
PONCBP	participant of non-childbearing potential
PP	per-protocol
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAS	Simpson Angus Scale
SD	standard deviation
SGA	second generation antipsychotics
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time to maximum plasma concentration
TdP	Torsades de Pointes
TD	Tardive dyskinesia
$t_{½}$	half life
UDS	urine drug screen
ULN	upper limit of normal
UTN	Universal Trial Number
VS	vital signs

Abbreviation	Expanded Term
WBC	white blood cell

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