Official Protocol Title:	A Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Participants with Bipolar I Disorder
NCT number:	NCT06273774
Document Date:	17-May-2024

TITLE PAGE

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Protocol Title: A Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Participants with Bipolar I Disorder

Protocol Number: 020-02

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):

IND	171279

Approval Date: 17 May 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	17-MAY-2024	This amendment allows for the evaluation of more conservative dose regimens (Dose Regimens 2 and 3) even if Dose Regimen 1 is generally well tolerated.
Amendment 1	29-FEB-2024	This amendment was primarily created to include assessments to monitor treatment-emergent mania and depression and to add participant-level and study-level stopping rules.
Original Protocol	12-JAN-2024	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

This amendment allows for the evaluation of more conservative dose regimens (Dose Regimen 2 and Dose Regimen 3) even if Dose Regimen 1 is generally well tolerated.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1 Overall Design	The overall design allows for the evaluation of more conservative Dose Regimens, even if the more rapid titration or no titration is generally well tolerated.	To further inform optimal dose selection for Phase 3 trials.
Additional Changes		
Section 1.1 Synopsis	Increase sample size from 32 to 48	Allow for the enrollment of more conservative Dose Regimens to further inform on dose selection for Phase 3
Section 4.2 Scientific Rationale for Study Design	Updated to include optimizing tolerability to explore a regimen with a titration.	To further inform optimal dose selection for Phase 3
Section 8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters	Allow for a panel to be repeated at the same Dose Regimen and allow for a more conservative non-protocol-specified Dose Regimen to be evaluated.	Allow for the evaluation of additional more conservative Dose Regimens to further inform on dose selection for Phase 3.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multiple Dose Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Participants with Bipolar I Disorder

Short Title: MK-8189 Study in Bipolar I Participants

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in male and female participants with bipolar I disorder:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of multiple doses of MK-8189 in participants with bipolar I disorder, manic or mixed features	Adverse events Adverse experiences leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
Not applicable	Not applicable

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Bipolar disorder
Population	Participants with Bipolar I Disorder
Study Type	Interventional
Intervention Model	Sequential This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5.5 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Up to approximately 48 adult participants with bipolar I disorder will be randomized such that 16 evaluable participants, in one dose regimen, complete the study 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
Active	MK-8189	4 mg 12 mg	All dose levels	Oral	Dose Regimens 1, 2 and 3	Test Product
Placebo	Placebo	0 mg	All dose levels	Oral	Dose Regimens 1, 2 and 3	Placebo

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study for approximately 10 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 42 days each participant will receive assigned intervention for approximately 14 days. After the end of treatment each participant will be followed for 14 days.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

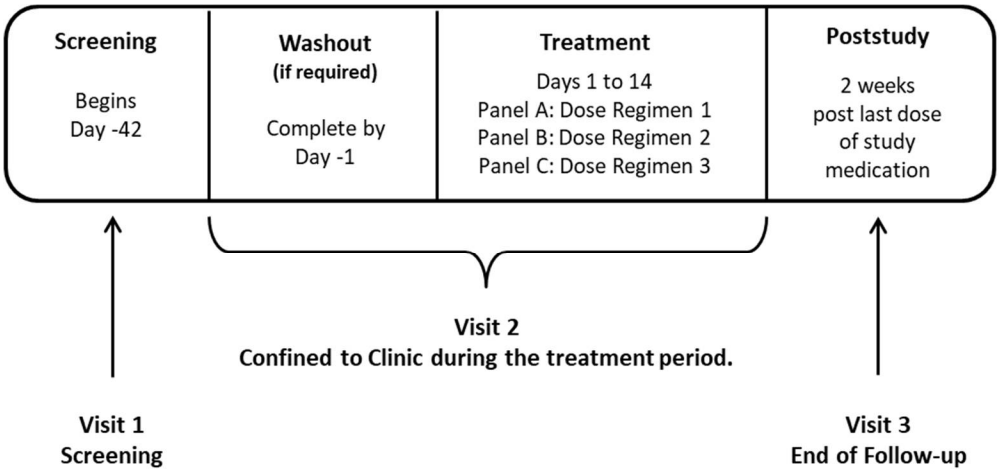
Study Accepts Healthy Participants: No

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

Panels A, B, C																				
Study Period:	**Screening/ Rescreening[a]**	**Washout**	**Intervention**																**Poststudy**	**Notes**
Scheduled Day	**Up to -42**	**-5 to -1**	**Day 1 Predose**	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15, 16**	**17**	**+14 post last dose**	
Administrative/Study Procedures																				
Informed Consent	X																			Sections 8.1.1.1
Informed Consent for FBR	X																			Sections 8.1.1.2
Participant ID Card	X		X																	Section 8.1.3
Inclusion/ Exclusion Criteria	X		X																	Sections 5.1, 5.2 Based on IC/EC, only specific criteria will be reviewed prior to randomization.
Medical History (includes psychiatric history and substance usage)	X																			Substances: Drugs, alcohol, tobacco, and caffeine
Prior/ Concomitant Medication Review	X	----------	----------	-	-	-	-	--	-	-	-	-	-	-	-	-	----	-	X	Sections 5.2, 6.5, 8.1.5
Washout from current antipsychotic therapy		X																		Section 8.1.5.1
Assignment of Randomization Number			X																	Section 8.1.7

Panels A, B, C																			
Study Period:	**Screening/ Rescreening[a]**	**Washout**	**Intervention**															**Poststudy**	**Notes**
Scheduled Day	**Up to -42**	**-5 to -1**	**Day 1 Predose**	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15, 16**	**17**	**+14 post last dose**	
MK-8189/Placebo Administration				X	X	X	X	X	X	X	X	X	X	X	X	X				Section 8.1.8
Standard Meals[b]				X						X						X				Sections 5.3.1, 5.3.2.1
Domiciling[c]		X	--	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X		Section 8.1.11 Participants will be domiciled minimally from Day -1 through Day 14 72 hours procedures are complete.
Safety Procedures																				
Full physical examination	X		X															X	X	Section 8.3.1 Day 1 predose: up to 24 hours prior to dosing
Height	X																			
Weight	X																	X		BMI to be taken only at Screening
Full Neurological Exam	X		X																	Section 10.11.1
Targeted Neurological Exam										X						X			X	Section 10.11.2
Resting VS (HR, BP)	X		X			X			X			X				X		X	X	Section 8.3.2 HR and BP will be taken in triplicate. Intervention days: predose. Day 17: approximately the same time as Day 14

Panels A, B, C																			
Study Period:	**Screening/ Rescreening[a]**	**Washout**	**Intervention**															**Poststudy**	**Notes**
Scheduled Day	**Up to -42**	**-5 to -1**	**Day 1 Predose**	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15, 16**	**17**	**+14 post last dose**	
Orthostatic VS	X		X			X			X			X				X		X	X	Section 8.3.2 Intervention days: predose. Day 17: approximately the same time as Day 14
Resting VS (RR, T)	X		X			X						X						X	X	Section 8.3.2 Intervention days: predose Day 17: approximately the same time as Day 14
12-lead ECG	X		X			X			X			X				X		X	X	Section 8.3.3 ECGs will be taken in triplicate. Intervention days: predose. Day 17: approximately the same time as Day 14
Serum hCG (POCBP only)	X																		X	Sections 5.1, 8.3.5, 10.2, 10.5.
Urine or Serum hCG Pregnancy Test[d] (POCBP only)			X																	Sections 5.1, 8.3.5, 10.2, 10.5 Day 1 predose: up to 24h (urine) or 72h (serum) prior to dosing.
Serum FSH (PONCBP only)	X																			Sections 10.2, 10.5
HIV, hepatitis B and C screen (per site SOP)	X																			Section 10.2
Drug screen (per site SOP)	X		X																	Day 1 predose: up to 72h prior to dose. Additional drug screens are conducted per site SOP.

Panels A, B, C																			
Study Period:	**Screening/ Rescreening[a]**	**Washout**	**Intervention**															**Poststudy**	**Notes**
Scheduled Day	**Up to -42**	**-5 to -1**	**Day 1 Predose**	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15, 16**	**17**	**+14 post last dose**	
Laboratory Safety (Hematology, Chemistry and Urinalysis)	X		X						X							X		X	X	Sections 8.3.4, 10.2 Day 1 predose: up to 72h prior to dose
AE/SAE review	X	----------	----------	-	-	-	-	--	-	-	-	-	-	-	-	-	------	-	X	
C-SSRS Baseline	X																			Section 8.3.6.1
C-SSRS Since Last Assessment			X				X			X				X		X		X	X	Section 8.3.6.1 Day 1 predose: up to 24h prior to dose Intervention days: predose Day 17: approximately the same time as Day 14
EPS Scales (BARS, AIMS, SAS)			X						X							X				Section 8.3.8 Day 1 predose: up to 24h prior to dose Intervention days: within 3 hours after dose.
CGI-BP-S	X		X						X							X				Section 8.3.9 Day 1 predose: up to 24h prior to dose Day 7, 14: predose
YMRS[e]	X		X						X							X				Section 8.3.9 Day 1 predose: up to 24h prior to dose Day 7, 14: predose

Panels A, B, C																			
Study Period:	**Screening/ Rescreening[a]**	**Washout**	**Intervention**															**Poststudy**	**Notes**
Scheduled Day	**Up to -42**	**-5 to -1**	**Day 1 Predose**	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15, 16**	**17**	**+14 post last dose**	
HAM-D17[e]	X		X						X							X				Section 8.3.9 Day 1 predose: up to 24h prior to dose Day 7, 14: predose
Pharmacokinetics																				
Blood for Plasma MK-8189 and/or Metabolites Assay[f]				X	X					X	X					X	X	X		Section 8.6
Biomarkers																				
Blood for Genetic Analysis			X																	Section 8.8 The PGA sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed.

AE=adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-BP-S: Clinical Global Impressions-Bipolar Version-Severity of Illness; C-SSRS=Columbia-Suicide Severity Rating Scale; EC=exclusion criteria; ECG=electrocardiogram; EPS = Extrapyramidal Symptoms; FBR=future biomedical research; FSH=follicle-stimulating hormone; h=hour; HAM-D17=Hamilton Depression Rating Scale; hCG=human chorionic gonadotropin; IC=inclusion criteria; ID=identification; PGA=planned genetic analysis; POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; SAS = Simpson-Angus Scale; SAE=serious adverse event; SOP=standard operating procedure; VS=vital signs; YMRS=Young Mania Rating Scale.

[a] Rescreening is defined as a separate screening period. All activities conducted during Screening must be completed as part of Rescreening. See Section 8.10.1.

[b] Meals should be given at approximately the same time on the days specified in the SoA. Breakfast will be given at ~ 1-hour postdose, lunch given at ~ 4-hours postdose, a snack given at ~ 8-hours postdose and dinner at ~ 12-hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

[c] Participants currently treated with antipsychotic therapy will be domiciled from Day -5 prior to Day 1 (to start washout period) and will remain in the CRU until 72 hours post the last dose on Day 14. Participants not currently being treated with antipsychotic therapy may be domiciled minimally starting on Day -1 through 72 hours post the last dose on Day 14. Participants may stay longer at PIs discretion.

[d] In the event the urine pregnancy test is positive or cannot be confirmed negative, a serum pregnancy test will be required.

[e] Additional assessment may be performed at the discretion of the investigator.

[f] PK sampling timepoints are below for all Panels.
Day 1: Predose and 2, 6, 8, 10, 12, 16, 24 (Day 2) hours postdose
Day 8: Predose and 2, 6, 8, 10, 12, 16, 24 (Day 9) hours postdose
Day 14: Predose and 8, 12, 24 (Day 15), 36 (Day15), 48 (Day 16), 72 (Day 17) hours postdose

2 INTRODUCTION

2.1 Study Rationale

MK-8189 is currently being evaluated in a Phase 2b study for the treatment of adults with Schizophrenia. A signal for efficacy was previously observed in a Phase 2 POC study (P005) where participants were titrated from 4 mg QD of MK-8189 to 12 mg QD of MK-8189. The Phase 2b study is currently evaluating safety and efficacy of MK-8189 when participants are titrated from 4 mg to 16 mg or 8 mg up to 24 mg QD. As there is substantial precedent for therapies effective in the treatment of schizophrenia to also be effective in the treatment of bipolar I disorder (i.e, olanzapine, risperidone, aripiprazole, quetiapine and cariprazine), MK-8189 will also be evaluated for the treatment of bipolar I disorder. Furthermore, the target dose range for these indications is usually the same for both indications and in some cases the starting dose may be higher for bipolar I disorder. A previous study (P011, Part 1) demonstrated that initiating dosing at the highest clinical dose in adult participants with schizophrenia was generally well tolerated, suggesting titration is not necessary for good tolerability. As there is an expected benefit to reaching the target clinical dose as quickly as possible during a manic episode, this study will also evaluate a starting dose of 24 mg QD, the highest clinical dose, in participants with bipolar I disorder. These data in conjunction with the Phase 2b data in schizophrenia participants will be used to support dose selection for Phase 3 trials.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

MK-8189 is a small molecule inhibitor of the PDE10A enzyme that is being developed for the treatment of schizophrenia and bipolar disorder. PDE10A is a member of the cyclic nucleotide phosphodiesterase family that functions to metabolically inactivate both cAMP and cGMP. PDE10A is highly expressed in the brain and has limited expression in peripheral tissues; in the brain, PDE10A is expressed at high levels in the medium spiny neurons of the striatum. Functional imaging studies have revealed that bipolar disorder is associated with exaggerated dopamine signaling in the striatum, consistent with schizophrenia, suggesting that striatal dysfunction may be a common neurobiology underlying psychosis [Karcher, N. R., et al 2019]. Preclinical studies have generated substantial evidence to support the hypothesis that PDE10A inhibition is a novel therapeutic target that regulates striatal activity. In vitro and in vivo assays demonstrate that PDE10A inhibition activates the Dopamine D2 receptor indirect pathway, similar to current antipsychotic medications, while also facilitating D1 receptor direct pathway and glutamatergic signaling in the striatum. PDE10A-deficient mice show reduced exploratory behavior when placed in a novel environment and have a blunted response to the psychomotor activating effects of NMDA receptor antagonists, phencyclidine and MK-801. In addition, administration of selective PDE10A inhibitors decrease psychomotor activity, reverse deficits in prepulse inhibition, and inhibit conditioned avoidance responding in rodents, models that are predictive of antipsychotic activity in the clinic. PDE10A inhibitors are also efficacious in nonclinical assays that test cognitive

domains impaired in psychiatric disorders, models of negative symptoms and decrease body weight in diet-induced obese animals. As described in Section 2.1, a signal for efficacy in participants with schizophrenia has been observed and based on precedent with many other antipsychotics, it is expected that efficacy would also be expected in participants with bipolar I disorder.

Bipolar disorder is a chronic lifetime condition affecting 1-4% of the population globally. Bipolar I Disorder is characterized by the occurrence of at least one manic or mixed episode, interspersed with periods of full or partial remission. Second-generation anti-psychotics are indicated to treat acute manic or mixed features. Atypical antipsychotic monotherapy currently available are associated with tolerability issues e.g., weight gain, metabolic issues, EPS, sedation, and hyperprolactinemia that can lead to reduced treatment adherence or discontinuation of therapy. A recent meta-analysis estimated typical weight gain of 3.8 kg in drug-naïve patients after starting antipsychotic treatment in the first 3 months of treatment. Obese bipolar patients have a 10-year shorter life span due to the higher CVD risk and vascular age. As a result, there is still a significant unmet need in this patient population.

2.2.2 Preclinical and Clinical Studies

The nonclinical safety profile of MK-8189 was determined in a series of safety pharmacology studies, genetic toxicology studies, oral repeat-dose toxicity/tolerability studies in rats and rhesus non-human primates (NHPs), reproductive and developmental toxicity studies in rats and rabbits, and repeat-dose tolerability studies in wild-type TgRasH2 mice. The pivotal nonclinical safety assessment studies, conducted in compliance with Good Laboratory Practice (GLP), support the use of MK-8189 in patients of ≥ 13 years old.

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

Four single-dose clinical studies (P001, P002, P004, P010) in healthy participants, a single dose study in healthy participants and participants with moderate hepatic impairment (P012), 2 CYP3A DDI studies in healthy participants (P006, P015), and 4 multiple-dose clinical studies in healthy participants and participants with schizophrenia (P003, P007, P011, P016) have been completed with MK-8189. One multiple-dose study in participants with Alzheimer's disease has also been completed (P017). Protocol 011 included elderly (>60 years of age, n=12) participants with schizophrenia and healthy elderly (> 60 years of age, n=18) participants. Protocol 017 included 29 elderly participants (≥65 years of age) with Alzheimer's disease. Please see IB for a summary of completed studies and Section 2.2.3 for a summary of ongoing studies.

Overall, across the completed studies, 259 participants have received at least one dose of MK-8189; 130 participants without schizophrenia, 107 participants with schizophrenia and 22 participants with Alzheimer's Disease.

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 AEs (≥5%) following treatment of MK-8189 (n=259) across the 12 completed Phase 1 studies which included, healthy participants (non-elderly and elderly),

participants with schizophrenia (non-elderly and elderly), elderly participants with Alzheimer's disease and participants with hepatic impairment, were headache (11.6% vs Placebo 8.9%) somnolence (13.4%vs Placebo 12.7%), dystonia (6.6% vs Placebo 1.8%), decreased appetite (8.9% vs Placebo 7.1%), nausea (8.1% vs Placebo 7.1%), fatigue (5.8% vs Placebo 0%), dizziness (6.6% vs Placebo 5.4%), vomiting (5.4%vs Placebo 0%), diarrhea (5.4% vs Placebo 1.8%), akathisia (6.9% vs Placebo 3.6%) and insomnia (5.8%vs Placebo 1.8%). 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 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.

Of the 107 participants with schizophrenia that received MK-8189, 32 participants were administered MK-8189 in addition to their standard of care. The MK-8189 dose was titrated from 2 mg to a maximum dose of MK-8189 24 mg. The most common treatment-related AEs (reported by 2 or more participants) were headache (21.9%), decreased appetite (18.8%), somnolence (12.5%), vomiting (12.5%), akathisia (9.4%), diarrhea (9.4%), nausea (9.4%), tremor (9.4%), anxiety (6.3%), insomnia (6.3%), upper abdominal pain (6.3%), constipation (6.3%), dystonia (6.3%) and orthostatic hypotension (6.3%). The common treatment-related AEs in the placebo group (n=10) were headache (20.0%) and somnolence (20.0%).

2.2.3 Ongoing Clinical Studies

Protocol 013

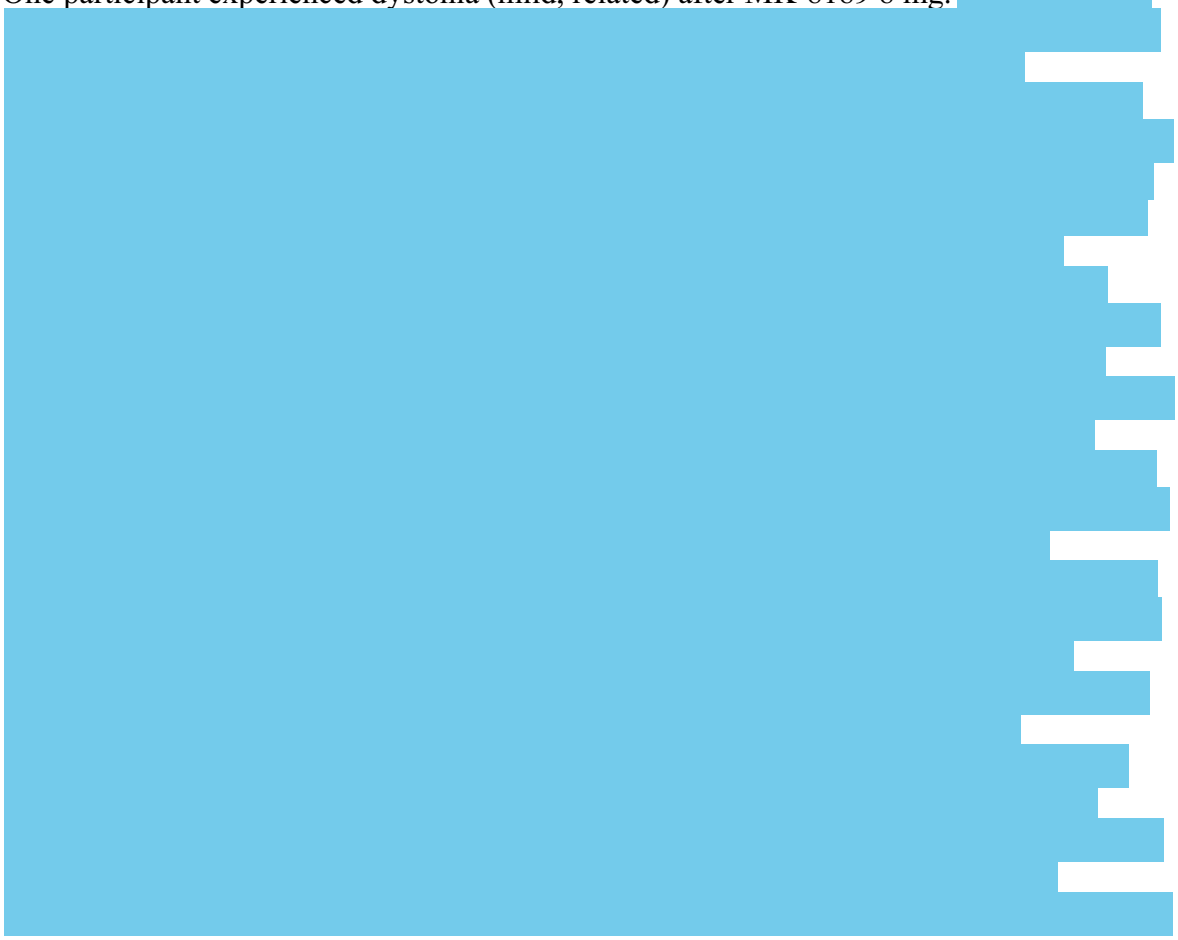
P013 was a multiple-dose clinical study to evaluate the safety, tolerability, and pharmacokinetics of MK-8189 in healthy Chinese participants. This study enrolled 16 healthy Chinese male and female participants and were randomized to receive MK-8189 8 mg or placebo (Days 1 to 3), MK-8189 12 mg or placebo (Days 4 to 6), MK-8189 16 mg or placebo (Days 7 to 9) and MK-8189 24 mg or placebo (Days 10 to 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%) and hyperhidrosis (n=2, 16.7%). Of the 2 participants who discontinued the study, 1 participant discontinued due to a treatment related AE of moderate delusions PPD PPD after MK-8189 8 mg. Another participant discontinued due to other reason (no longer wanted to take the study drug) and is described below.

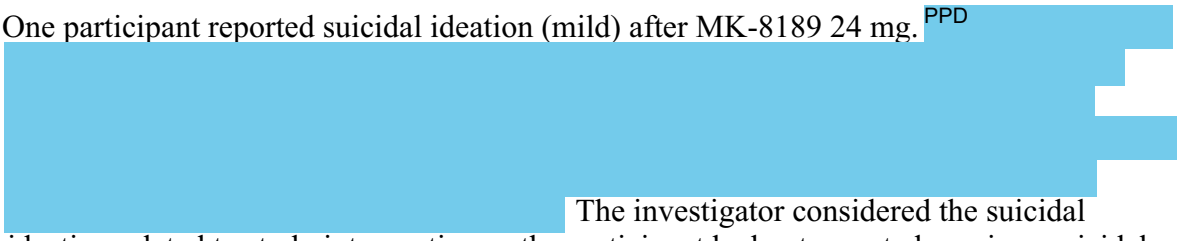
Five participants reported dystonia (n=4 after MK-8189 and n=1 after placebo), an ECI:

- One participant experienced dystonia (mild, related) after MK-8189 8 mg. PPD
- One participant experienced occlusal muscle dystonia (mild) after placebo. PPD
- One participant experienced dystonia (mild, related) after the last dose of MK-8189 16 mg. PPD
- One participant experienced dystonia (mild, related) and akathisia (mild, related) after MK-8189 8 mg. PPD

• One participant experienced dystonia (mild, related) after MK-8189 8 mg. PPD



• One participant reported suicidal ideation (mild) after MK-8189 24 mg. PPD



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.

Protocol 014

Preliminary unblinded safety data are available from P014, 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, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential For Non-Antiarrhythmic Drugs -Scientific Guideline. The study is clinically complete. Panel A enrolled 11 participants who were randomized to receive MK-8189 48 mg (Day 1), MK-8189 60 (Day 2) (n=8) or matched placebo (n=3). Panel A-1

enrolled 10 participants who were randomized to receive MK-8189 48 mg (Day 1), MK-8189 80 mg (Day 2) (n=8), or placebo (n=2). Panel C enrolled 32 participants who were randomized to receive MK-8189 48 mg (Days 1 to 2) MK-8189 80 mg (Day 3) (n=20) or placebo (n=12). Across all panels MK-8189 was generally well tolerated. No SAEs or deaths occurred were reported.

In Panel A, of the 11 participants included in the safety analysis, 27.3% (3/11) experienced 1 or more AEs during the study; 37.5% (3/8) after MK-8189 and 0% (0/3) after placebo. Three participants reported AEs after MK-8189 48 mg and 2 after 60 mg. All AEs were of mild intensity and no AE was reported by more than one participant. Treatment related AEs following MK-8189 administration included discomfort, somnolence, tremor and restlessness. There were no discontinuations due to AEs.

In Panel A-1, of the 10 participants included in the safety analysis, 50.0% (5/10) experienced 1 or more AEs during the study; 62.5% (5/8) after MK 8189 and 0% (0/2) after placebo. All AEs during the treatment period were of mild intensity. The most frequently (reported by >1 participant) AE for MK 8189 was somnolence (37.5%, n=3) which was considered treatment-related in all participants. Other treatment-related AEs reported by one participant each were asthenia, feeling jittery, akathisia, and anxiety. The AE of akathisia began following the 80 mg dose, no treatment was provided, and the AE lasted for approximately PPD weeks. There were no discontinuations due to AEs.

In Panel C, of the 32 participants included in the safety analysis, AEs were reported by 50.0% (16/32) of participants; 50.0% (10/20) after MK 8189 and 50.0% (6/12) after placebo. Seven participants reported AEs for MK-8189 48 mg and 6 for 80 mg n Panel C. AEs were mild to moderate in intensity. The most frequently (reported by >1 participant) AEs after MK-8189 were headache (15.0%, n=3) and dizziness (10.0%, n=2). No AEs were reported by >1 participant after placebo. Treatment- related AEs were reported by 30.0% (6/20) of participants after MK-8189 and 25.0% (4/12) of participants after placebo. The most frequently (reported by >1 participant) study intervention-related AEs after MK 8189 were headache and dizziness (10.0%, n=2). No study intervention-related AEs were reported by >1 participant after placebo. The other treatment-related AEs following MK-8189 (reported by 1 participant each) included skin irritation, nausea, vomiting, fatigue, muscle twitching, dystonia, oromandibular dystonia, parosmia, somnolence and anxiety. Of the 32 participants randomized in Panel C, 30 completed dosing per protocol; one participant discontinued due to an AE (dystonia described below) and one participant withdrew consent.

Two participants experienced dystonia: One participant experienced moderate oromandibular dystonia PPD which began 4 hours following their first 48 mg dose of MK-8189. The participant withdrew consent due to this AE and the participant was treated PPD. A second participant also experienced mild dystonia approximately 7 hours following their first dose of MK-8189. PPD the participant completed study treatment pre protocol.

Protocol 019

P019 is a randomized, double-blind, active- and placebo-controlled, 3-way crossover evaluating the effect of a supratherapeutic dose of MK-8189 on the QTc interval study in participants with schizophrenia. This study is ongoing and blinded. Approximately 45 participants have been enrolled and no deaths reported. The treatment-related AEs reported in more than 1 participant and available in the database are akathisia (n=3), dizziness (n=3), vomiting (n=3), dyskinesia (n=2), dystonia (n=2), feeling hot and cold (n=2), headache (n=2), nausea (n=2) and parkinsonian-like tremor (n=2). The patient remained blinded.

One SAE of anaphylaxis was reported which is considered related to study drug by the investigator. After approximately 6 hours after MK-8189 48mg or placebo, the participant reported nausea, vomiting, dizziness, and lightheadedness. PPD The participant was discontinued from the study.

There have been 6 discontinuations due to AEs (including the participant who experienced the SAE). The AEs that lead to discontinuation were akathisia (n=2), dystonia, ALT/AST increased and dyskinesia. Overall, MK-8189 doses titrated up to 80 mg are well tolerated in this study.

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 55 years of age who are experiencing an acute episode of schizophrenia according to DSM-V™ criteria. A total of 488 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. The MK-8189 8 mg treatment arm is no longer enrolling new participants. The determination of the minimally efficacious dose is planned to be established without completion of the current MK-8189 8 mg treatment arm. This trial is being conducted in a hospital/acute care setting followed by an outpatient setting.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in male and female participants with bipolar I disorder:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of multiple doses of MK-8189 in participants with bipolar I disorder, manic or mixed features	Adverse events Adverse experiences leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
Not applicable	Not applicable
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the PK profile of MK-8189 in participants	Cmax, AUC0-24, Tmax, t1/2, C24, Vz/F, CL/F
To evaluate the safety and tolerability of multiple doses of MK-8189	VS, ECG, Laboratory safety values, C-SSRS, BARS, SAS, AIMS, CGI-BP-S, YMRS, HAM-D17
Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multiple dose study to evaluate the safety and tolerability of MK-8189 in participants with stable bipolar I disorder. The study will evaluate up to 3 dose regimens within 3 Panels (Panels A, B and C). The intent will be for ~16 participants to complete at least one of the 3 specified dose regimens.

Panel A will enroll an initial cohort of 8 participants and receive 24 mg MK-8189 QD (2 x 12 mg tablet) for 14 days (Dose Regimen 1) or placebo (3:1). If Dose Regimen 1/placebo is generally well tolerated based on AE reporting, an additional 8 participants will be enrolled to receive Dose Regimen 1/placebo and the decision to also enroll Panel B or Panel C in parallel with Panel A will be determined to further explore optimal tolerability. If Dose Regimen 1/placebo is not considered to be generally well tolerated following the initial 8 participants, then 8 participants will be enrolled in Panel B or Panel C.

Panel B will receive 16 mg MK-8189 (1 x 12 mg tablet and 1 x 4 mg tablet) QD Days 1 to 3 and 24 mg MK-8189 (2 x 12 mg tablets) QD Days 4 to 14 (Dose Regimen 2) or placebo (3:1). If Dose Regimen 2/placebo is generally well tolerated based on AE reporting, an additional 8 participants will receive Dose Regimen 2/placebo in Panel B and the decision to also enroll Panel C in parallel with Panel B will be determined. If Dose Regimen 2/placebo is not well tolerated, an initial cohort of 8 participants will be enrolled in Panel C.

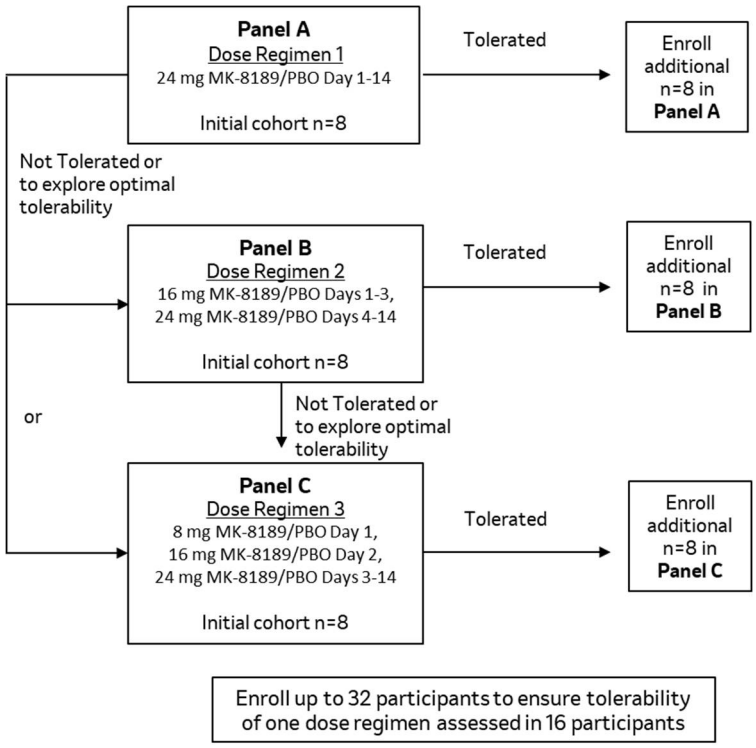
Panel C will receive 8 mg MK-8189 (2 x 4 mg) Day 1, 16 mg MK-8189 (1 x 12 mg tablet and 1 x 4 mg tablet) Day 2 and 24 mg MK-8189 (2 x 12 mg tablet) QD Days 3 to 14 (Dose Regimen 3) or placebo (3:1). If Dose Regimen 3/placebo is generally well tolerated based on AE reporting, an additional 8 participants will be enrolled in Panel C. If Dose Regimen 3/placebo is not well tolerated, no additional participants will be enrolled in Panel C and an alternate more conservative regimen may be evaluated per Section 8.10.6.

In Panels A, B and C, participants randomized to placebo will receive the same number of tablets matching the MK-8189 tablet strengths in the active group. See Study Design Diagram (Figure 2) below for the dose regimen decision tree.

If applicable, participants will be washed off their current antipsychotic therapy. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants should not receive antipsychotics for at least 5 days or 3 half-lives (whichever is longer) prior to Day 1. For longer half-life antipsychotics (eg, aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment (ie, cessation of atypical antipsychotic therapy) as an outpatient, but should be confined to the clinical research unit within a week of stopping treatment and minimally beginning on Day -5. Antipsychotic SOC may be restarted following the assessments that occur 72-hours following the last dose of study drug. At the investigator's discretion, the participant may be domiciled for a longer duration i.e., participants may be domiciled prior to Day -5 or for a longer period following end of study treatment while SOC is restarted.

Where applicable (Dose Regimen 2 or 3), titration to the next dose level within a regimen will occur per the investigator's medical discretion based on the tolerability of study intervention within an individual participant. If the investigator deems it necessary, dose titration within an individual may be paused temporarily for the duration of any tolerability issues (i.e, AEs) and resumed when deemed appropriate. Any changes to the dose regimen will not prolong an individual's participation in the trial and therefore it is acknowledged that failure to adhere to the protocol-defined dose regimen may result in some participants not reaching the escalation targets. Participants may be down-titrated by the investigator at any time without consultation of the Sponsor in the case of safety or tolerability issues. Regardless of the state of the dose escalation of each participant it is important to keep participants in the study as the data collected at all doses is valuable for the purposes of defining a clinical tolerability margin. Any changes to the protocol specified treatment regimen will be documented in a Protocol Clarification Letter.

Figure 2 Study Design Diagram



Following completion of 14 days of dosing in at least 6 participants, a decision to enroll an additional 8 participants in the current panel and enroll participants in a more conservative dose regimen (per Figure 2) will be made jointly by the investigator(s) and Sponsor. Dose regimen decisions will be based on the review of adverse event data. The Dose Regimen selected will be documented in a Protocol Clarification Letter.

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

Refer to Section 8.10.6 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

As described in Section 2.1, MK-8189 24 mg QD without titration was well tolerated in participants with schizophrenia and this study will explore the tolerability of this regimen in participants with Bipolar I disorder. An initial cohort of 8 participants will first be evaluated, such that if this regimen without titration is not well tolerated or if tolerability could be optimized, a regimen with titration can be explored as described in Figure 2. The adaptive nature of the study will minimize the number of participants exposed while identifying the optimal regimen to evaluate in Phase 3 trial in Bipolar participants. A matched placebo-control will be included to reduce bias with regards to the patient reporting and investigator assessment of AEs.

Dose regimen decisions will be based on AEs as acute tolerability (eg EPS and vomiting) is the concern.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Not Applicable.

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical AEs as well as through the conduct of neurological exams, physical exams, ECGs, VS, and laboratory safety tests. The C-SSRS will be administered to monitor mood and suicidal ideation and behavior in all trial participants (see Section 4.2.3.). In addition, scales will be included to evaluate EPS and general well-being. As EPS are associated with antipsychotics and have been observed in the MK-8189 clinical program, the BARS, AIMS and SAS will be used to quantify any EPS observed in the study. The BARS is an akathisia rating scale with objective and subjective measures and an overall rating from 0 to 5. A score of 0 presents no evidence for akathisia, a score of 3 is moderate akathisia and a score of 5 is severe akathisia. The AIMS evaluates 12 items and uses a 5-point scale to assess abnormal movement in 3 areas (orofacial, extremities, trunk). The SAS evaluates 10 items and uses a 5-point scale to measure symptoms of parkinsonism or parkinsonian side effects (including rigidity, tremor, akinesia, and salivation). Participants with severe EPS symptoms will be discontinued if not attenuated with dose reduction, dose titration and/or medical management.

The CGI-S scale is a rating system commonly used in clinical research and practice to evaluate the overall severity of illness and impairment in individuals with psychiatric conditions. The CGI-BP-S is a modified version of the CGI-S to be used specifically in patients with bipolar disorder. The CGI-BP-S scale consists of a range of severity ratings from 1 (normal, not ill) to 7 (very severely ill). The scale includes a severity assessment of mania, depression and overall bipolar illness.

The YMRS is an 11-item scale that assesses manic symptoms based on the patient's clinical observation during the interview. The 11 items are elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, rate and amount of speech, language-thought disorder, content, disruptive-aggressive behavior, appearance, and insight. The severity of the abnormality is rated on a 5-point (0 to 4) or 9-point (0-8) scale; scoring between listed points is encouraged. Possible scores range from 0-60.

The Hamilton Depression Rating Scale (HAM-D) is a widely used clinical assessment tool to measure the severity of depression. The HAM-D17 consists of 17 items or questions that assess various symptoms associated with depression. These items cover a range of symptoms including depressed mood, guilt feelings, suicidal ideation, insomnia, agitation, and so on. Each item is scored based on the severity and frequency of the symptom. The scoring is typically done on a 3- or 5-point scale, with higher scores indicating more severe symptoms.

4.2.1.3 Pharmacokinetic Endpoints

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

4.2.1.4 Pharmacodynamic Endpoints

Not Applicable.

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.

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 Placebo

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

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

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

4.3 Justification for Dose

As this is a Phase 1 assessment of MK-8189 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.6.

4.3.1 Starting Dose for This Study

Doses of 16 mg and 24 mg dose of MK-8189 are currently being evaluated in a Phase 2B trial in participants with schizophrenia. In Phase 2B doses are currently titrated to the target dose. For the treatment of a manic episode of bipolar, it is important to reach the target clinical dose as soon as possible, thus, the starting dose in this trial will be 24 mg. This starting dose has been previously evaluated in participants with schizophrenia and found to be well tolerated (P011). No participants discontinued due to treatment-related AEs. The

majority of AEs were mild and no AEs were severe. AEs considered related to treatment included somnolence (n=2), hypertonia (n=1), decreased appetite (n=1), musculoskeletal stiffness (n=1) and increased ALT (n=1). No AEs of akathisia or dystonia were reported. Furthermore, in another study (P014), participants received starting doses of 48 mg MK-8189 and escalated to 60 mg or 80 mg MK-8189 and these doses were found to be generally well tolerated. Based on these data, titration does not appear to be required for good tolerability, however, this will be confirmed in the bipolar I population.

4.3.2 Maximum Dose Exposure for This Study

The current trial will evaluate doses up to and including 24 mg and there is significant clinical experience at or above this dose in the Phase 1 program and the 24 mg dose is currently being evaluated in the Phase 2b study.

As described in Section 2.2.2 and 2.2.3, previous and ongoing clinical studies have demonstrated that MK-8189 has been generally well tolerated following 48 mg QD for 3 days in participants with schizophrenia (P007, Panel D following titration from 8 mg to 48 mg over 12 days) and up to 80 mg in participants with schizophrenia (P014, Panel C following titration from 48 mg to 80 mg over 2 days). In P007, the observed steady-state Cmax and AUC0-24hr following the 48 mg dose on Day 15 was [redacted]*hr. Based on data from the chronic toxicology studies, the exposure multiple at the 48 mg dose for AUC0-24hr would be [redacted] based on the 6-month rat study and [redacted] fold based on the 9-month monkey study. Brief summaries of the chronic toxicology studies supporting dose escalation are provided below: In the 6-month rat study, doses of 0, 25, 100 and 750 mg/kg/day were evaluated. Two high-dose (750 mg/kg/day) female rats were found dead (Week 13 and Week 24) with acute tubular necrosis (with and without tubular mineralization). Therefore, the 100 mg/kg/day dose was considered the no observed adverse effect level (NOAEL) for this study (AUC0- 24hr = [redacted] at the 48 mg dose. In the 9-month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK-8189 were administered. Renal tubular degeneration was observed in the high-dose group (600/300 mg/kg/day). The NOAEL for target organ toxicity is 150 mg/kg/day [redacted], providing [redacted] over the supratherapeutic exposure of [redacted] at the 48 mg dose.

The effects of MK-8189 on measures of cardiac conduction and repolarization were assessed in both in vitro (hERG current [Ikr] evaluation) and in vivo (anesthetized guinea pigs and conscious telemetered monkey models). MK-8189 inhibited hERG current with an IC50 value of [redacted] providing a margin of [redacted] fold to the steady-state unbound Cmax in humans at 48 mg [redacted] In an anesthetized guinea pig study, MK-8189 had no effects on HR and ECG parameters. Average peak plasma concentrations of MK-8189 measured during the 20-min infusions of 10, 30 and 60 mg/kg were [redacted] and [redacted], respectively. Thus, the NOEL/NOAEL in this study was [redacted], providing an exposure margin of [redacted] fold relative to the observed steady-state supratherapeutic Cmax of [redacted] µM. In a telemetry study in monkeys, single oral doses of 2, 5, and 20 mg/kg were evaluated and test article-related dose-independent increases in HR, blood pressure (BP) and the rate-corrected QT interval were observed. In a second study at lower oral doses of 0.03, 0.1 and 0.3 mg/kg, there were

no test article-related effects. Thus, the no-observed effect level was a single-oral dose of 0.3 mg/kg providing exposure margins of CCI fold of the observed steady-state supratherapeutic Cmax. A number of studies were conducted to determine the underlying cause (see MK-8189 IB for additional details). The general conclusion from these studies was that increases in HR, BP and QT interval likely occur due to a stress induced release of epinephrine subsequent to PDE10A target engagement in conscious rhesus monkeys and therefore, these changes in QT, HR and BP are not relevant to humans. Therefore, clinical and preclinical data support dose escalation to 24 mg in the current study and provide margins up to exposures associated with a supratherapeutic steady-state dose of 48 mg.

Furthermore, a concentration-QTc analysis was conducted in P007 and as shown in CCI there is no evidence for a relationship between concentration and QTc at MK 8189 exposures achieved with the 48 mg dose. Though healthy participants only received doses up to 24 mg in P007, a concentration-QT effect would be driven by inhibition of hERG and independent of disease state.

CCI

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. Participants must meet diagnostic criteria for bipolar I disorder, manic or mixed features according to the Diagnostic and statistical manual of Mental Disorders TR (DSM-5 TR) and considered to be in a non-acute phase of their illness based on the following:
    - Clinical interview
    - No psychiatric hospitalization with the previous 90 days
    - No changes in psychotropic medication within the last 60 days
    - No increase in level of psychiatric care due to worsening of symptoms of bipolar I disorder for 90 days prior to screening.
    - CGI-BP-S Overall Illness Score of ≤ 3 at Screening
    - YMRS ≤10
    - HAM-D17 ≤10
2. Has a history of receiving and tolerating antipsychotic medication within the usual dose range employed for bipolar I disorder.
3. Be in good health based on medical history, physical examination, VS measurements, and ECGs performed before randomization. Note: The mean QTcF-duration must be ≤450 msec. Repeat 12-lead safety ECGs may be performed in participants whose parameters are, per investigator discretion, minimally outside the designated range.
4. Be in good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.
5. Participants BMI is between 18 and 40 kg/m2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)2.

6. If currently taking an antipsychotic, participant is able to discontinue the use of all antipsychotic medication at least 5 days or 3 half-lives (whichever is longer) prior to Day 1 and the duration of the study.
7. Able to swallow tablets and comply with the dosage regimen.
8. Has a stable living situation in which the participant or a contact person can be reached by the investigator if there is a need for follow up.

Demographics

9. Is an individual of any sex/gender, from 18 years to 60 years of age inclusive, at the time of providing the informed consent.
10. 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.
  - 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

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

Additional Categories

12. 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. Based on clinical interview and responses on the C-SSRS, is at imminent risk of self-harm or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.
2. Has any clinically significant abnormal laboratory, VS, physical examination, or 12-lead safety ECG findings at screening or changes from baseline that may interfere with the interpretation of PK or safety parameters or, in the opinion of the investigator, would make the participant inappropriate for entry into this study.
3. Has untreated or uncompensated endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases.
4. Has evidence or history of a primary DSM-5 axis I psychiatric diagnosis other than those specified in Inclusion Criterion No. 1
5. History of cancer (malignancy). Participants with definitively treated disease who, in the opinion of the study investigator, are highly unlikely to have a recurrence for the duration of the study may be enrolled at the discretion of the investigator.
6. Has evidence or history of mental retardation, borderline personality disorder, or organic brain syndrome.
7. Has a history of neuroleptic malignant syndrome or moderate to severe tardive dyskinesia
8. Has a substance-induced psychotic disorder or behavioral disturbance thought to be due to substance abuse.
9. Has a DSM-5 TR defined substance use disorder (excluding nicotine and caffeine) within 3 months of screening.
10. Has a history of seizure disorder beyond childhood or is receiving treatment with any anticonvulsant to prevent seizures.
11. 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.
12. Positive test(s) for HbsAg, hepatitis C antibodies or HIV. Note: Participants with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included upon consultation with the Sponsor.

13. Had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.
14. Does not tolerate venipuncture or have difficulty for collecting blood samples.
15. Inability to tolerate oral medication or swallow tablets.

Prior/Concomitant Therapy

16. Has received or is currently receiving treatment with clozapine for any length of time.
17. Has received treatment with monoamine oxidase inhibitors within 3 months of screening or cariprazine within 2 months of screening.
18. Subjects who have had a dose of depot antipsychotics within 12 months of screening.
19. Is unable to refrain from the use of co-medication that is a moderate or strong inhibitor or inducer of CYP3A or moderate or strong inducer of CYP2C9 beginning approximately 2 weeks or 5 half-lives, whichever is longer, prior to administration of the initial dose of trial drug and throughout the trial. (see Section 6.5).
20. Has received any vaccine starting from 30 days prior to study intervention or is scheduled to receive any vaccine through 30 days following study intervention. There may be certain vaccines that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

21. 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.

Other Exclusions

22. Is a smoker that does not agree to follow the smoking restrictions as defined by the CRU
23. 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.
24. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
25. A regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative drug screen (with the exception of cannabis and/or prescribed concomitant medications permitted at the discretion of the PI and Sponsor) prior to randomization.
26. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
27. Has been in incarceration or imprisonment within 3 months prior to screening.

28. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

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

On Full PK Sampling Days (Days 1, 8 and 14)

Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration until 1-hour postdose. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the Schedule of Activities. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each full PK sampling day in each panel (for this study the meal content should be consistent within a given clinical site). After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

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

On All Other Days

Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Water will be unrestricted in timing. Meals and snacks will be unrestricted in caloric content, composition and timing.

5.3.1.2 Fruit Juice Restrictions

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

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

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the prestudy and poststudy visits.

On full PK sampling days, participants will be permitted to consume approximately 2 units of caffeinated beverages or xanthine-containing products only between 1 hour and 2 hours postdose. Otherwise, participants will refrain from consumption of such products 8 hours prior to study drug administration until the last PK assessment is complete.

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

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits. 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 CRU.

5.3.3 Activity Restrictions

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

5.4 Screen Failures

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

Participants may be rescreened as appropriate, per Section 8.10.1.

5.5 Participant Replacement Strategy

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

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

6 STUDY INTERVENTION

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

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

Global clinical supply complaints and/or temperature excursions are to be reported to the Clinical Complaints Intake mailbox, via email to clinical.complaints.intake@MSD.com, within 1 business day of awareness.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 1.

Country-specific requirements are noted in Appendix 7.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Active	Experimental	MK-8189	Drug	Tablet	4 mg 12 mg	All dose levels	Oral	Dose Regimens 1, 2 and 3	Test Product	IMP	Provided centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Tablet	0 mg	All dose levels	Oral	Dose Regimens 1, 2 and 3	Placebo	IMP	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 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

A sample allocation table is provided below in Table 2.

Table 2 Allocation of Participants to Treatment

Panel A		**Days 1 to 14**		
MK-8189	n=12	24 mg QD		
Placebo	n=4	Placebo QD		
Panel B		**Days 1 to 3**	**Days 4 to 14**	
MK-8189	n=12	16 mg QD	24 mg QD	
Placebo	n=4	Placebo QD	Placebo QD	
Panel C		**Day 1**	**Day 2**	**Days 3 to 14**
MK-8189	n=12	8 mg QD	16 mg QD	24 mg QD
Placebo	n=4	Placebo QD	Placebo QD	Placebo QD
The suggested doses may be adjusted downward based on evaluation of safety, tolerability and/or pharmacokinetic data observed in previous treatment periods/panels.				

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant 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 perform a mouth check to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

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

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

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

- With the exception of antipsychotics, upon agreement with the sponsor, participants may continue treatment with their prescribed therapy for bipolar I disorder (See inclusion criteria no. 1) as well as comorbid conditions related to their primary diagnosis, including but not limited to depression, anxiety, insomnia. During the trial, the prescribed dose and regimen of medication must be stable for at least 3 months prior to screening and there are no expected changes in co-medication during the study.
- In addition, medications to treat mild chronic conditions such as hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other medical conditions are allowed during the study. For permitted medications, the prescribed dose and regimen of medication must be stable for at least 2 months prior to screening and there are no expected changes in co-medication during the study. See also Section 6.5.1 on rescue medication.
- Vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 30 days) of study intervention start.

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

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

6.5.1 Rescue Medications and Supportive Care

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

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

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

If a participant's symptoms of bipolar disorder worsen to the extent such that addition (or, if applicable, increase in dose) of a mood stabilizer, antipsychotic or antidepressant is required, they will discontinue treatment per stopping rules in Section 6.6.1.

6.6 Dose Modification (Dose Regimen Decisions)

All dose-regimen decisions (i.e. initiation of a Panel with a lower starting dose or continuation of enrollment within a dose regimen) will be made jointly by the investigator and the Sponsor. Members of the Sponsor safety review team will include: the trial clinical director, trial clinical scientist, Translational Medicine Therapeutic Area Lead or designee. The Sponsor safety review team will obtain input from the investigator regarding his/her evaluation of safety and tolerability from the previous dosing period and his/her recommendation to initiate the next panel as described in Figure 2.

Dose regimen decisions will be based on AEs as acute tolerability (e.g. EPS and vomiting) after 14 days of dosing.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify moving to a dose regimen with a higher starting dose or continuation with the current dose regimen, the next planned dose regimen may be followed per section 4.1 or altered such that participants:

- Receive the same dose level to further explore safety and tolerability at that level,
- Receive a lower dose of the study intervention (with or without food),
- Receive the same or lower dose as a divided dose, or
- Dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

6.6.1 Stopping Rules

6.6.1.1 Study Stopping Rules

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

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

- Three or more MK-8189 treated participants per Panel (Dosing Regimen) meet any of the criteria listed under 6.6.1.2 and the clinical investigator judges the event to be related to MK-8189.

6.6.1.2 Individual Stopping Rules

Administration of study intervention will be stopped for a participant if they meet any of the following criteria for exacerbation of symptoms:

- Requires, per clinical judgement of the investigator, the addition (or, if applicable, increase in dose) of a mood stabilizer, antipsychotic or antidepressant
- YMRS total score of ≥15
- HAM-D17 total score ≥15
- CGI-BP-S total score ≥4
- Hospitalization for worsening of symptoms
- Active suicidal ideation or homicidal ideation or suicidal behavior

Note: all events listed above are considered as Event of Clinical Interest and require reporting to the Sponsor within 24 hours (see Section 8.4.7).

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation 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.

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

6.9 Standard Policies

Not Applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

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 interrupts study intervention administration for more than 2 consecutive days or has 4 cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has severe EPS symptoms which are not attenuated with medical management or dose modification.
- The participant has a positive 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.

7.2 Participant Withdrawal From the Study

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

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

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

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

8.1.1.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

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 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 or assent (as applicable). At the time of intervention allocation site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 3 months before first dose of study intervention.

Use of any prescription or nonprescription medication during the washout period should first be discussed between the investigator and Sponsor unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. Note: medications permitted under Section 6.5 of the protocol do not need to be discussed prior to use.

Washout from Antipsychotics:

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

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

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication (start/stop time and reason for therapy), 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 allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff. All doses of study drug administration will be taken with approximately 240 mL of water. Site staff will ensure the participant has swallowed study treatment. Details on water and dietary restrictions are outlined in Section 5.3.1.

8.1.8.1 Timing of Dose Administration

Participants will be dosed according to the SoA (Section 1.3). MK-8189 study administration will be in the AM at approximately the same time each day (within a 30 minute window) and after an 8-hour overnight fast.

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 (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used

as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, they will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. The emergency unblinding call center will provide the investigator or medically qualified designee the requested information 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 mediations will be domiciled in the CRU from Day -5 prior to Day 1of the treatment period (to start the washout of current antipsychotic mediation) and will remain in the CRU until 72 hours post the last dose of study intervention on Day 14. Participants not currently being treated with antipsychotic medication may be domiciled starting on Day -1. 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 urgent or 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/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

BMI

BMI equals a person's weight in kilograms divided by height in meters squared (BMI = kg/m2). 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).

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

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

Triplicate HR and BP will be obtained at least 1 to 2 minutes apart at all timepoints. Day 1 predose triplicate measurements will be within 3 hours prior to dosing. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

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 at a given study site.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained per the SoA (Section 1.3). 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 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, RR, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.
- At each time point, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.
- Day 1 predose ECG triplicate measurements will be within 3 hours prior to dosing. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

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. 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.

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 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 interval 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 interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If at any time the QRS interval 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, the participant should be immediately transferred to an acute care setting for definitive therapy.

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Operations 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 Assessments

For this study, potential raters of clinical and psychiatric assessments (BARS [Section 8.3.8], SAS [Section 8.3.8], AIMS [Section 8.3.8] and CGI-BP-S [8.3.9], YMRS [8.3.9] and HAM-D17 [8.3.9]), will be identified based on review of their reported credentials against target minimum credentials for education, prior experience with the study 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.

8.3.9 Assessment of Neurological and Psychiatric Effects

A general (full) Neurological Exam will be conducted by a medically quailed investigator at the Screening and Baseline visits. A targeted Neurological Exam will be conducted by a medically quailed investigator at times specified in the SoA.

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

CGI-BP-S, YMRS and HAM-D17 will be performed only at times specified in the SoA.

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, must be reported by the investigator under any of the following circumstances:

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

From the time of intervention allocation 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

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
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. SAEs and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). The investigator will also make every attempt to follow nonserious AEs that occur in allocated 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.

3. Severe EPS or EPS leading to study intervention discontinuation
4. Treatment-emergent adverse event of new or worsening tardive dyskinesia
5. QTcF interval >500 msec
6. Suicidal or homicidal ideation, suicidal behavior.
7. Requires, per clinical judgement of the investigator, the addition (or, if applicable, increase in dose) of a mood stabilizer, antipsychotic or antidepressant to treat worsening of bipolar symptoms
8. YMRS total score ≥15
9. HAM-D17 total score ≥15
10. CGI-BP-S total score ≥4
11. Hospitalization for worsening of symptoms

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any study intervention administered that exceeds the dose prescribed by the protocol.

It is up to the investigator or the reporting physician to decide whether a non-study intervention dose (eg, rescue or concomitant medication) is to be considered an overdose, with notification of the Sponsor.

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

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189

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

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research 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 should be collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled visit, 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

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Leftover samples 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

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

Rescreening is defined as a separate screening period and can be initiated as appropriate, including for screen failures (Section 5.4). Rescreening is to include all screening procedures listed in the SoA (Section 1.3), including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period Visit

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 -5 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 -1.

On treatment days, participants will be dosed once daily with MK-8189 or placebo and have procedures completed per the SoA. Participants will remain in the unit through 72 hours post the 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 (72 hr postdose).

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 an official memo.

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 Procedures Based on Study Objectives: Timing of Procedure

At any postdose time point, the blood sample for MK-8189 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time. All Vital Signs assessments should be prior to or at least 10 minutes after a PK draw.

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.

- PK Collection as outlined in Table 4.

Table 4 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
0 to <1 h	+/- 5 min
1 to ≤24 h	+/- 15 min
24 to 72h	+/- 2 hr

- Study Intervention Administration: +/- 30 minutes.

Predose and Postdose Procedures

- Predose standard safety evaluations should be prior to the scheduled timepoint:
  - VS and ECG within 3 hours
  - laboratory safety tests within 72 hours,
  - physical examination within 24 hours
  - EPS scales, CSSR-S and CGI-BP-S, YMRS and HAM-D17 within 24 hours.
- Postdose standard safety evaluations: VS and ECG:
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical time

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 a panel to further understand tolerability of a Dose Regimen.
- Repeat of a panel with a more conservative dose titration than the prespecified Dose Regimens.
- Repeat of or decrease in the dose of the study intervention administered in any given period/panel.
- Entire period(s) or panel(s) may be omitted.
- Decrease in the duration of study intervention administration (eg, number of days).
- Adjustment of the dosing interval (eg, divided doses <bid to qd, qd to bid, tid, or vice versa>).
- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose.
- Addition of PK pause.
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data.
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data.

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

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

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

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

9 KEY STATISTICAL CONSIDERATIONS

9.1 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.

9.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol.

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Safety:

Clinical assessment of AEs and participant discontinuation due to AEs.

9.3.2 Exploratory Endpoints

Safety:

12-lead ECGs, vital signs, laboratory safety tests.

EPS assessments (AIMS, BARS, SAS), CSSRS, CGI-BP-S, YMRS, and HAM D17.

Pharmacokinetics:

MK-8189 AUC24, Cmax, C24, CL/F, Vz/F, Tmax and half life.

9.4 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.

9.4.1 All Participants As Treated Population

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

9.4.2 Per-Protocol (PP) Population

The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of

important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in pharmacokinetics analyses.

9.5 Statistical Methods

9.5.1 Statistical Methods for Pharmacokinetic Analyses

Model-based PK summary

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

A sample code for each panel is as follows:

```
proc mixed data=adpp; by panel parameter;

class subjid day;

model lnpk= day/ddfm=kr;

random subjid;

lsmeans day/alpha=0.05 cl; run;
```

Descriptive Statistics

For each panel, individual values will be listed for each PK parameter (AUC24, Cmax, C24, CL/F, Vz/F, and halflife), and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV, calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as $100 \times \text{sqrt}(\exp(s^2) - 1)$, where s^2 is the observed variance on the natural log-scale). Median, maximum and minimum will be provided for Tmax.

9.5.2 Statistical Methods for Safety Analyses

Primary:

Safety and tolerability will be assessed by clinical review of AEs.

The overall safety endpoints include the number of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, who discontinue from study intervention due to an AE, or with an AE resulting in death.

The safety evaluation will include a summary by treatment group of the number and percentage of participants with each type of AE.

Exploratory:

Safety and tolerability will also be assessed by clinical review of other relevant parameters, including laboratory test results, vital signs, and ECG measurements.

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

To explore changes in extrapyramidal symptomology, summary statistics will be generated for BARS, AIMS, SAS as well as for change from baseline. The difference from baseline will be computed on the original scale (raw change from baseline). Responses to the C-SSRS will be listed. The C-SSRS will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (i.e., ideation and behavior). Summary statistics for changes in baseline for CGI-BP-S will be provided.

Changes from baseline in YMRS total scores, HAM D17 total scores, and HAM D6 will be summarized. The 6-item HAM D6 is a subset of the HAM D17. It consists of 6 items (depressed mood, work and activities, somatic symptoms general, feelings of guilt, anxiety psychic, and retardation); these items are summed to obtain the HAM-D6 total score.

9.6 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (safety (labs, VS, ECGs)) may be prepared as needed to support decision-making meetings such as dose escalation meetings. The aggregate summaries will be presented in an unblinded manner. There are no planned interim analyses to test any formal hypotheses.

9.7 Multiplicity

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

9.8 Sample Size and Power Calculations

A study with sample size of 12 on active and 4 on placebo in each panel is considered adequate to address the study objectives around safety and pharmacokinetics.

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 their 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 their 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 their 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.

Pursuant to Union law (Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation 536/2014), the Investigator is responsible for pseudonymizing and assigning a key-code/patient ID to each study subject. In addition, the Investigator is required by Union law to store the Key (linking the Patient ID to the full name of the study subject) at the site in the EU/EEA throughout the course of the study and for a designated period of time thereafter. Finally, the study site is only permitted to share pseudonymized study subject personal data with the Sponsor.

The European Data Protection Board, in its Recommendations 01/2020 on measures that supplement transfer tools to ensure compliance with the EU level of protection of personal data ("Recommendations"), states in Paragraph 85 that pseudonymization (of study subject) personal data under the conditions described above constitutes an effective supplemental measure.

Organizational measures are contractually imposed on third party vendors wherever possible, to ensure that Personal Data are protected by industry-best practices against accidental destruction or loss (physical/logical) which include regular backup procedures, Firewalls, and disaster recovery plans.

In support of Corporate Policy 1 Information Risk Management, on a Sponsor-wide basis all supplier relationships, both IT and non-IT related, are strongly encouraged to meet the Sponsor's Supplier Information Risk Management Standard. To protect the confidentiality, availability and integrity of Sponsor information, conformity to information risk requirements by supplier personnel, hardware and software may be measured, analyzed and appropriate corrective/preventive actions taken as necessary. Based on the supplier criticality, additional activities (e.g., on-site reviews, integrated business continuity exercises) may be required to ensure the cyber-resiliency of the supplier on an on-going basis.

The Sponsor has implemented (Corporate Policy 13.1 Information Security Standards Handbook) an organization-wide process to assign user access rights based on the whether the employee/contractor has a legitimate need to utilize a database in order to carry out

his/her job; manager approval is required when granting user access rights (beyond those sites or databases intended for all employees/contractors); and a process is in place for an annual review by each manager of the user access rights currently in place. Organizational measures, also contractually imposed on third party vendors, to prevent data processing systems from being used by unauthorized persons include i) user identification and authentication procedures (e.g., special characters, minimum length, regular change of password), and ii) automatic blocking (e.g., password or timeout).

The Sponsor utilizes a database called "InForm", operated by Oracle, for the storage of its study subject clinical trial data. InForm is a role-based system and only authorized users can see the data. Sites may only see the data they have entered. Access by Sponsor users is restricted to only those associated with a specific clinical trial.

Study sites are provided with a password to access the database. Access to InForm requires https (Secure Socket Layer) with a FIPS 140-2 compliant algorithm to connect to the application via the study site's web browser. Once logged into the system, the connection between the database, located in Ashburn, Virginia, USA, and the site, is encrypted. The Sponsor also stores the name and access credentials of the Investigators and other site staff (Study Coordinators) who record patient data into InForm. Such study staff personal data is not pseudonymized. Note, such encryption during transmission may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Data, whether concerning a study subject or site staff, stored in the InForm database is encrypted. Note, such encryption may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Whenever possible, organization wide measures are imposed on third party vendors to prevent unauthorized persons from gaining access to the data processing systems available on premises and in facilities (including databases, application servers and related hardware), where Personal Data are processed, include i) Access control system (ID reader, chip), ii) key management, card-keys procedures, and iii) on-site security personnel and alarm system.

InForm is a HIPAA Part 11 capable system. Any data entered/changed or deleted will be associated with a viewable audit trail.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20). Pursuant to organization-wide requirements, the Sponsor periodically conducts audits of the vendors providing IT services, including Oracle, the vendor supporting the InForm database. The most recent audit of Oracle and its operations of InForm occurred in May 2020. Finally, Oracle has obtained ISO 27001 certification for the various databases it offers to third parties as a service, including the InForm database.

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 5 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.
- Participants should fast approximately 8 hours prior to all chemistry laboratory collections. If the individual comes to the screening visit and is not fasting, a recheck may be needed at the discretion of the investigator. The participant will be asked to return at a later time for the safety laboratory collection.

Table 5 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/blood 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; RBC=red blood cell; 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.

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/toxicity

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

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

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 *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant [a] • IUS [a] • 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 *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception [b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception [b] - 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 and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[c] • 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] IUS is a progestin releasing IUD [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] 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) [c]

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 their designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

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

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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 Tables

Panels A, B, C	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/Test
Laboratory Safety Tests (including FSH/hCG and drug screen)	1	4	1	6	12	72
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	4.5	4.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-8189		23		23	4	92
					Total Blood Volume per Participant[a]	**177 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	All	All
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc >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

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Nonspecific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	**All**	**All**

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1.

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

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

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

B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including repeats 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:

- The participant may be excluded from the study.
- 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).
- 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.
- The abnormal test may be repeated (refer to items below for continuation of algorithm for repeated values).
    - If the repeat test value is within the normal range, the participant may enter the study.
    - 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
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
bid	twice daily
BMI	body mass index
BP	blood pressure
CCU	Cardiac care unit
CI	confidence interval
CGI-BP-S	Clinical Global Impression-Bipolar Version-Severity of Illness
Cmax	maximum plasma concentration
CNS	central nervous system
CL/F	Apparent clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
CVD	cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Expanded Term
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HAM-D17	Hamilton Depression Rating Scale
HbsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board

Abbreviation	Expanded Term
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
LAM	lactational amenorrhea method
MOA	Mechanism of Action
mRNA	messenger RNA
NCS	not clinically significant
NDA	New Drug Application
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OR	objective response
PANSS	Positive and Negative Syndrome Scale
PCL	Protocol Clarification Letter
PDE10A	phosphodiesterase 10A
PK	pharmacokinetic
po	orally
POC	Proof of Concept
POCBP	Person of childbearing potential
PONCBP	Person of nonchildbearing potential
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
QD	once daily
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAS	Simpson Angus Scale
SD	standard deviation

Abbreviation	Expanded Term
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
Tmax	time to maximum plasma concentration
t½	half life
UDS	urine drug screen
ULN	upper limit of normal
UTN	Universal Trial Number
Vz/F	Apparent volume of distribution
VS	vital signs
WBC	white blood cell
YMRS	Young Mania Rating Scale

11 REFERENCES

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