Official Protocol Title:	A Phase 2B Randomized, Double-Blind, Placebo- and Active-Controlled Trial of the Efficacy and Safety of MK-8189 in Participants Experiencing an Acute Episode of Schizophrenia
NCT number:	NCT04624243
Document Date:	16-Mar-2023

TITLE PAGE

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Protocol Title: A Phase 2B Randomized, Double-Blind, Placebo- and Active-Controlled Trial of the Efficacy and Safety of MK-8189 in Participants Experiencing an Acute Episode of Schizophrenia

This protocol amendment is applicable only to Serbia

Protocol Number: 008-05

Compound Number: MK-8189

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	Not Applicable
EU CT	Not Applicable
EudraCT	2020-000094-24
JRCT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	118,986

Approval Date: 16 March 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	16-MAR-2023	Serbia-specific amendment to fulfill health authority request to correct minor discrepancies in Amendment 4.
Amendment 4	16-NOV-2022	Updates to remove MK-8189 8 mg treatment arm and Brief Assessment of Cognition (BAC) in response to enrollment and retention challenges.
Amendment 3	17-DEC-2021	Updates to increase flexibility in eligibility criteria in response to enrollment challenges.
Amendment 2	24-NOV-2020	Updated exclusion criterion and revised liver testing criteria to comply with FDA feedback.
Amendment 1	30-JUN-2020	Update number of capsules for risperidone due to change in dose strength and update with P007 data for Panel D.
Original Protocol	19-FEB-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 008-05

Overall Rationale for the Amendment:

Serbia-specific amendment to fulfill health authority request to correct minor discrepancies in Amendment 4.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
		These changes were made to address agency request to amend protocol to correct minor discrepancies (in protocol clarification letter) in Amendment 4.
1.1 Synopsis 3. Hypotheses, Objectives, and Endpoints	The phrase "in men and women aged 18-50 years who are experiencing an acute exacerbation of schizophrenia" was updated to refer to men and women aged 18-55 years	Typographical errors that do not align with the updated eligibility criteria in the protocol amendment.
1.1 Synopsis	Estimated Duration of Study that states, "The Sponsor estimates that the study will require approximately 2.5 years from the time the first participant (or their legally acceptable representative provides documented informed consent until the last participant's last study-related contact," should instead be approximately 4 years.	Typographical error that does not align with the updated study timeline.
5.2 Exclusion Criteria	Exclusion criterion #21 CCI [redacted].	Typographical/grammatical clarification to ensure intended interpretation of the text for translations.
10.2 Appendix 2: Clinical Laboratory Tests	In Screening/Baseline laboratory notes, reference to exclusionary criterion for screening eGFR of <60 mL/min/1.73m^2 should instead be <50 mL/min/1.73m^2. In Additional notes, references to discontinuation related to a persistent eGFR of <60 mL/min/1.73m^2 should instead be <40 mL/min/1.73m^2.	Typographical errors that do not align with the updated discontinuation criteria in the protocol amendment.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
1.1 Synopsis	Type of control changed to “placebo” from “placebo, active control”	Simplification of choices in drop-down menu.
1.1 Synopsis	Intervention table updated to sync with Table 1 in Section 6	To match study intervention table in Section 6.
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added text noting that a positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention	To provide clarity.
8.4.5 Pregnancy and Exposure During Breastfeeding	Added text regarding situations that qualify as an AE/SAE (eg, any pregnancy complication and medical reason for elective termination of a pregnancy)	To provide clarity and better align with regulations.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2B Randomized, Double-Blind, Placebo- and Active-Controlled Trial of the Efficacy and Safety of MK-8189 in Participants Experiencing an Acute Episode of Schizophrenia

Short Title: Phase 2B Study of MK-8189 in Participants with an Acute Episode of Schizophrenia

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

In men and women aged 18-55 years who are experiencing an acute exacerbation of schizophrenia:

Primary Objective	**Primary Endpoint**
To compare the efficacy of MK-8189 at 16 and 24 mg to placebo in reducing the PANSS total score at Week 6 • Hypothesis (H1): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS total score • Hypothesis (H2): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS total score	PANSS total score
To evaluate the safety and tolerability of MK-8189	Adverse events Study intervention discontinuations due to adverse events

Secondary Objectives	Secondary Endpoints
To compare the efficacy of MK-8189 at 16 and 24 mg to placebo in reducing the PANSS positive subscale at Week 6 • Hypothesis (H3): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS positive subscale • Hypothesis (H4): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS positive subscale	PANSS positive subscale score
To evaluate the efficacy of MK-8189 at 16 and 24 mg in reducing the CGI-S score at Week 6, as compared to placebo • Hypothesis (H5): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in CGI-S • Hypothesis (H6): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in CGI-S	CGI-S score
To evaluate the impact of MK-8189 on weight at Week 12, as compared to risperidone • Hypothesis (H7): MK-8189 24 mg is superior to risperidone in reducing the Week 12 mean change from baseline in weight • Hypothesis (H8): MK-8189 16 mg is superior to risperidone in reducing the Week 12 mean change from baseline in weight	Weight (kg)
To evaluate the impact of MK-8189 on weight at Week 6, as compared to placebo	Weight (kg)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Schizophrenia
Population	Adult participants experiencing an acute episode of schizophrenia, according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5™)
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Investigator Sponsor Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 500 participants will be randomized such that sufficient evaluable participants complete the study as described in Section 9.

Before Amendment 4, the total sample size was to be approximately N=576; on implementation of Amendment 4 the total sample size is predicted to be approximately N=500, noting that the exact number of participants to be ultimately enrolled is, in part, a function of the (unknown) number of participants randomized to the MK-8189 8 mg treatment arm before the implementation of Amendment 4. On implementation of Amendment 4, eligible participants will be randomized in a 2:2:1:2 ratio to 1 of the 4 following treatment sequences: MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, or placebo/MK-8189 24 mg.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
MK-8189 8 mg/ MK-8189 8 mg	MK-8189	4 mg + 0 mg	4 mg qd	Oral	Days 1-3 Day 8 to Week 12	Test Product
MK-8189 8 mg/ MK-8189 8 mg	MK-8189	4 mg + 4 mg	8 mg qd	Oral	Day 4 to Week 12	Test Product
MK-8189 8 mg/ MK-8189 8 mg	Placebo to risperidone	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo
MK-8189 16 mg/ MK-8189 16 mg	MK-8189	4 mg + 0 mg	4 mg qd	Oral	Days 1-3	Test Product
MK-8189 16 mg/ MK-8189 16 mg	MK-8189	4 mg + 4 mg	8 mg qd	Oral	Days 4-6	Test Product
MK-8189 16 mg/ MK-8189 16 mg	MK-8189	12 mg + 0 mg	12 mg qd	Oral	Day 8 to Week 12	Test Product
MK-8189 16 mg/ MK-8189 16 mg	MK-8189	4 mg + 12 mg	16 mg qd	Oral	Day 7 to Week 12	Test Product
MK-8189 16 mg/ MK-8189 16 mg	Placebo to risperidone	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo
MK-8189 24 mg/ MK-8189 24 mg	MK-8189	4 mg + 4 mg	8 mg qd	Oral	Days 1-3	Test Product
MK-8189 24 mg/ MK-8189 24 mg	MK-8189	4 mg + 12 mg	16 mg qd	Oral	Days 4-6 Day 8 to Week 12	Test Product
MK-8189 24 mg/ MK-8189 24 mg	MK-8189	12 mg + 12 mg	24 mg qd	Oral	Day 7 to Week 12	Test Product
MK-8189 24 mg/ MK-8189 24 mg	Placebo to risperidone	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo
Risperidone 6 mg/ Risperidone 6 mg	Placebo to MK-8189	0 mg + 0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Risperidone 6 mg/ Risperidone 6 mg	risperidone	2 mg	2 mg qd	Oral	Days 1-3	Test Product
Risperidone 6 mg/ Risperidone 6 mg	risperidone	2 mg	4 mg qd	Oral	Days 4-6 Day 8 to Week 12	Test Product
Risperidone 6 mg/ Risperidone 6 mg	risperidone	2 mg	6 mg qd	Oral	Day 7 to Week 12	Test Product
Placebo/MK-8189 24 mg	Placebo to MK-8189	0 mg + 0 mg	0 mg qd	Oral	Days 1-42	Placebo
Placebo/MK-8189 24 mg	MK-8189	4 mg + 4 mg	8 mg qd	Oral	Days 43-45	Test Product
Placebo/MK-8189 24 mg	MK-8189	4 mg + 12 mg	16 mg qd	Oral	Days 46-48 Day 50 to Week 12[a]	Test Product
Placebo/MK-8189 24 mg	MK-8189	12 mg + 12 mg	24 mg qd	Oral	Day 49 to Week 12	Test Product
Placebo/MK-8189 24 mg	Placebo to risperidone	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo

Total Number of Intervention Groups/Arms	5
Duration of Participation	Each participant will participate in the study for approximately 15 weeks from the time the participant provides documented informed consent through the final contact. After a screening period of 2 to 7 days (including, if needed, a tapering of prohibited medications), participants will be randomized to receive assigned intervention for approximately 12 weeks (6 weeks acute treatment, then 6 weeks extension treatment). After end of study intervention, each participant will be followed for 14 days.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

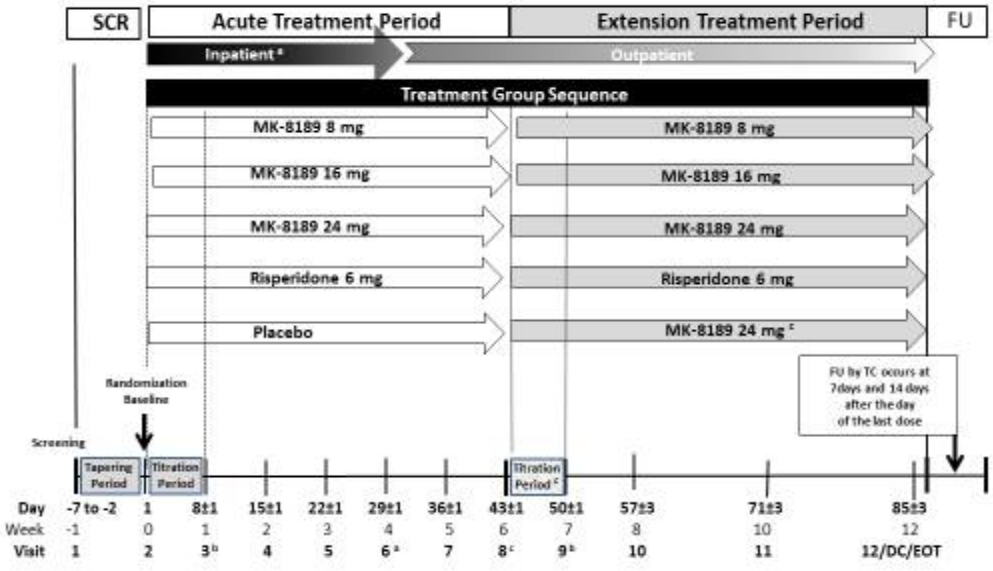
Study Accepts Healthy Participants: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



[a] Inpatient stay is required to V6 but may be longer if participant is not ready to be discharged
[b] Request for down-titration attempt through IRT is allowed after at least one dose of the target dose in the acute treatment period is reached. One re-challenge attempt request and one subsequent down-titration attempt request are allowed. No requests are allowed during either acute or extension titration periods
[c] At Visit 8, participant on placebo switches to MK-8189 24 mg treatment and follows dosing titration during the first week of the extension period. Note that MK-8189 8 mg/MK-8189 8 mg treatment arm will be removed as of Amendment 4, however there are participants enrolled prior to Amendment 4 who will remain on 8 mg MK-8189 and continue to receive study drug per protocol.

Abbreviations: DC=discontinuation; EOT=end of treatment; FU= follow-up period; IRT=interactive response technology; SCR=screening period; TC=telephone or virtual contact

1.3 Schedule of Activities (SoA)

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Administrative and General Procedures														
Informed Consent	X													
Informed Consent for Future Biomedical Research	X													Not required for participation in main study
Inclusion/Exclusion Criteria	X	X												
Participant Identification Card	X	X				X								ID card to be updated at V2 to include randomization information. At Visit 6 (or discharge day, if later), confirm card is in participant's possession.
Psychiatric History	X													
Psychiatric Intake Evaluation	X													

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Clinical Validation Inventory for Study Admission (C-VISA™)	X													Must be reviewed and approved by the external SDE before randomization. See Section 8.1.8.
MINI International Neuropsychiatric Interview	X													Must be recorded using Sponsor-provided recording technology. See Section 8.1.6.
Medical History	X													
Substance, Alcohol and Smoking History	X													
Social History	X													
Identification of External Contact Person	X													Participants must have an identified external contact person meeting all criteria as specified in Section 8.1.7
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	No prohibited psychotropic medications to be taken before V12 or EOT visit
IRT Visit Registration	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
IRT Randomization		X												
Study Intervention Dispensing		X	X	X	X	X	X	X	X	X	X			First dose to be taken PM on V2 and last dose to be taken PM before V12 or EOT visit
Study Intervention Compliance		X	X	X	X	X	X	X	X	X	X	X		Down-titration for tolerability not allowed during Weeks 1 or 7. After down-titration, 1 rechallenge attempt may be made during the study (see Section 6.6).

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Telephone or Virtual Contacts between visits (if Outpatient)						X	X	X	X	X	X	X		First TC within 3 days post discharge. Other TCs to occur approximately midway between visits. If participant is an outpatient for first dose in extension, then a TC is to occur on the day after first extension dose. Additional TCs may be conducted at investigator discretion (see Section 8.1.18).

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Efficacy Assessments														
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	X	X	X	X	X		As best practice PANSS interviews to be conducted early in visit and must be recorded using Sponsor-provided recording technology. Screening PANSS must be reviewed and approved by external SDE before randomization.
Personal and Social Performance Scale (PSP)		X						X				X		
Clinical Global Impression-Severity of Illness (CGI-S)	X	X	X	X	X	X	X	X	X	X	X	X		
Safety Assessments														
Physical Examination	X							X				X		
Height	X													

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Weight, Waist Circumference	X	X[a]		X		X		X		X		X		[a]Waist circumference is not collected at baseline (see Section 8.3.2)
Vital Signs (pulse, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X			X						X		X		At SCR, perform triplicate ECG. Otherwise, perform triplicate ONLY if QTc prolongation is suspected (see Section 8.3.4).
Columbia Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version	X													
C-SSRS Since Last Visit Version		X	X	X	X	X	X	X	X	X	X	X		
Abnormal Involuntary Movement Scale (AIMS)		X		X		X		X		X	X	X		
Barnes Akathisia Rating Scale (BARS)		X	X	X		X		X	X	X	X	X		
Simpson Angus Extrapyramidal Side Effects Scale (SAS)		X		X		X		X		X	X	X		

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
AE/SAE review	X==========X													
Chemistry/Hematology/Lipid Panel	X	X				X		X		X		X		Specific tests in Appendix 2. laboratory samples are collected in fasting state while inpatient. Outpatients will be instructed and encouraged to fast overnight, before sample collection.
Insulin	X	X						X						
Prolactin	X	X						X				X		
TSH	X													With free thyroxine (T4) if TSH is abnormal.
HbA1c	X							X				X		

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Serum β-Human Chorionic Gonadotropin(hCG)	X													WOCBP only Also required to confirm a positive urine pregnancy test; or may replace a urine test per local guidelines. May also be done at investigator discretion throughout study.
Serum Follicle-Stimulating Hormone (FSH) -	X													Only required if needed to evaluate for WOCBP status
HIV Screen	X													Per site SOP and at discretion of the investigator
Hepatitis Screen	X													Per site SOP and at the discretion of the investigator
Blood for Genetic Analysis		X												Refer to Biomarkers and FBR sections (Sections 8.8 and 8.9)

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
Urine Alcohol/Drug Screen	X							X		X		X		May also be done at investigator discretion throughout study
Urinalysis	X	X				X		X		X		X		Specific tests noted in Appendix 2
Urine Pregnancy Test	X			X		X		X		X		X		WOCBP only. If urine test is positive, it must be confirmed with a serum pregnancy test. May also be done at investigator discretion throughout study.
Pharmacokinetics														
Pharmacokinetics Blood Sample		X		X		X[b]		X		X		X[c]		[b]Robust PK sampling scheme on, and 1 day before V6 PANSS. [c]PK samples not collected after EOT. See Section 8.6 (Table 6).

Study Period	**Screening**		**Acute Treatment Period**						**Extension Treatment Period**				**Postdosing Follow-up Period**	**Notes**
Visit Number/Title	**1 SCR**	**2 Base-line**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/ DC/ EOT**	**Follow-up TC 7 &14 days post dose**	**Inpatient stay is required to V6 if on treatment, but may be longer if needed.**
Scheduled Visit Day and Window:	**-7 to -2**	**1**	**8±1**	**15±1**	**22±1**	**29±1**	**36±1**	**43±1**	**50±1**	**57±3**	**71±3**	**85±3**	**LD+7±3 LD+14+3**	
AE=adverse event(s); BL=baseline; DC=discontinuation; ECG=electrocardiogram; EOT=end of treatment; FBR=future biomedical research; HIV= human immunodeficiency virus; IRT=interactive response technology; LD=last dose; PANSS=positive and negative syndrome scale; PK=pharmacokinetic; SCR=screening; SDE=Sponsor-designated expert; SOP=standard operating procedure; TC=telephone or virtual contact; TSH= thyroid-stimulating hormone; V=visit; WOCBP=women of childbearing potential. Notes: See Section 8.10.4 for information for participants who discontinue study intervention before V12.													

2 INTRODUCTION

Schizophrenia is a chronic debilitating disorder consisting of 3 symptom domains: positive symptoms (eg, psychosis, hallucinations, and delusions); negative symptoms (eg, apathy, amotivation); and cognitive impairment (eg, impaired memory, planning). Schizophrenia affects about 1% of the population globally. It is believed that disruption of corticostriatal signaling, stemming from increased dopamine and decreased glutamate neurotransmission, results in the positive symptoms of schizophrenia, and may also contribute to cognitive impairment. Atypical antipsychotics are the current standard of care medications used for the treatment of schizophrenia and are frequently used in bipolar disorder. However, a substantial portion of patients with schizophrenia and bipolar disorder are not adequately treated by these medications. Approximately 65% of patients with schizophrenia switch medications within a year, either due to dissatisfaction with efficacy or due to intolerability arising from various AEs. The major AEs associated with these medications include weight gain/metabolic effects, extrapyramidal side effects, increased prolactin secretion and sedation [Conley, R. R. 2005].

MK-8189 is a potent and selective inhibitor of PDE10A that is being developed as a novel therapeutic for the treatment of schizophrenia. PDE10A is highly expressed in the striatum and functions to metabolically inactivate the second messengers cAMP and cGMP. Preclinical experiments show that PDE10A inhibition increases cAMP/cGMP signaling in pathways in the striatum that have been associated with underlying pathology (glutamate) and clinically validated therapeutics (D2 receptor antagonists) for schizophrenia. MK-8189 was shown to be fully efficacious in 3 well defined preclinical assays predictive of antipsychotic activity. Other preclinical findings suggest that PDE10A inhibitors may attenuate cognitive impairment, while preclinical and preliminary clinical data suggest that PDE10A inhibition may be associated with weight loss and without negative impacts on metabolic parameters or prolactin secretion. PDE10A inhibitors may therefore potentially be an alternative treatment as monotherapy or as adjunct treatment in patients with schizophrenia who have inadequate response to first-line AAP treatment.

2.1 Study Rationale

The purpose of this Phase 2b study is to evaluate the efficacy and safety of MK-8189 at a range of doses in adult participants who have an acute episode of schizophrenia according to DSM-5™ criteria.

This study will provide important dose-ranging information to appropriately evaluate the dose-response relationship for the compound and improve the understanding of the compound's benefit/risk profile. The 12-week treatment period also permits an evaluation of the time course for weight changes, effects on metabolic parameters, and exploratory investigations into negative symptom effects.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

MK-8189 is a potent and selective inhibitor of PDE10A that is being developed as a novel therapeutic for the treatment of schizophrenia. The PDE10A enzyme metabolically inactivates the ubiquitous second messengers cAMP and cGMP [Bender, A. T. and Beavo, J. A. 2006], and is highly expressed in the striatum, an integral part of the corticostriatal pathway that regulates and modulates motivation, cognition, and goal-directed motor function [Seeger, T. F., et al 2003]. Preclinical pharmacology studies show that PDE10A inhibition increases cAMP/cGMP signaling in pathways associated with underlying schizophrenia pathology (glutamate) as well as clinically validated therapeutics (dopamine D2 receptor antagonists). Enhanced signaling in these pathways is hypothesized to restore the behavioral inhibition that is disrupted in schizophrenia [Grauer, S. M., et al 2009] [Schmidt, C. J., et al 2008]. PDE10A inhibitors may potentially be an alternative treatment as monotherapy or as adjunct treatment in patients with schizophrenia who have inadequate response to first-line AAP treatment. Preclinical findings also suggest that PDE10A inhibitors such as MK-8189 may be efficacious in improving motivation and cognitive dysfunction in schizophrenia.

MK-8189 has been tested in a variety of preclinical and Phase 1 clinical CCI [redacted]. It has also been tested at the 12-mg dose level in 1 Phase 2a study of adult participants experiencing an acute exacerbation of schizophrenia. The Phase 2a study (P005) was a randomized, double-blind study with placebo and active control (risperidone). Study medication was titrated over a 1-week period to the target dose (12 mg for MK-8189 and 6 mg for risperidone). The primary endpoint was the change from baseline in PANSS total score at 4 weeks. While MK-8189 showed improvement in the PANSS total score of -14.6 points, improvement was not significant (placebo-subtracted difference -4.7, 95% CI (-9.8, 0.5), p=0.074). However, the observed effects of MK-8189 and risperidone overlapped (p=0.440), suggesting evidence of MK-8189 effect. Also, MK-8189 was superior to placebo on the PANSS positive subscale, as was risperidone. Overall, the results suggested evidence of activity for MK-8189's novel mechanism of action and supported further development.

Overall, the preclinical and clinical pharmacology findings suggest that MK-8189 may potentially have a therapeutic effect in the treatment of schizophrenia. Further details may be found in the IB.

2.2.2 Ongoing Clinical Studies

P014 is a Phase 1 study to evaluate the safety, tolerability, PK and the effect of MK-8189 on QTc in participants with schizophrenia.

P017 is a Phase 1 study to evaluate the safety and tolerability of MK-8189 in participants with Alzheimer's Disease with and without neuropsychiatric symptoms.

2.2.3 Information on Other Study-related Therapy

Risperidone is indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term studies in adults, 2 short-term studies in adolescents (ages 13 to 17 years), and 1

long-term maintenance study in adults. Risperidone will act as the active control in this study to aid interpretation of the study results.

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.

MK-8189, as a PDE10A inhibitor, represents a novel mechanism of action that may potentially address psychotic symptoms. Data from P005 suggest possible efficacy in improving psychosis at a tolerated dose and associated with modest decrease in weight. However, further investigation into safety and effectiveness are required.

Based on the mechanism of action of PDE10A inhibition, which modulates dopaminergic pathways, EPS may be expected after treatment with MK-8189. In this study, participants will be assessed for signs of EPS (dystonia, dyskinesia, akathisia and parkinsonism) using specific rating scales. Close medical supervision and monitoring should be provided if EPS occurs. Details on supportive medication for the treatment of EPS are provided in Section 8.3.7.

The safety monitoring practices used by this protocol (ie, physical examination, vital signs, 12-lead ECG, laboratory tests, C-SSRS assessments, EPS assessments, and adverse events monitoring) are considered to be adequate to protect the participants' safety and to detect adverse events. This study requires frequent observations including initial treatment in an inpatient setting, flexible discharge requirements based on clinical readiness, discontinuation criteria, and follow-up after treatment period. An external contact person, who has regular contact with the participant, is required as part of inclusion criteria for this study.

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.

In men and women aged 18-55 years who are experiencing an acute exacerbation of schizophrenia:

Primary Objective	**Primary Endpoint**
To compare the efficacy of MK-8189 at 16 and 24 mg to placebo in reducing the PANSS total score at Week 6 • Hypothesis (H1): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS total score • Hypothesis (H2): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS total score	PANSS total score
To evaluate the safety and tolerability of MK-8189	Adverse events Study intervention discontinuations due to adverse events
Secondary Objectives	**Secondary Endpoints**
To compare the efficacy of MK-8189 at 16 and 24 mg to placebo in reducing the PANSS positive subscale at Week 6 • Hypothesis (H3): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS positive subscale • Hypothesis (H4): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in PANSS positive subscale	PANSS positive subscale score

To evaluate the efficacy of MK-8189 at 16 and 24 mg in reducing the CGI-S score at Week 6, as compared to placebo • Hypothesis (H5): MK-8189 24 mg is superior to placebo in reducing the Week 6 mean change from baseline in CGI-S • Hypothesis (H6): MK-8189 16 mg is superior to placebo in reducing the Week 6 mean change from baseline in CGI-S	CGI-S score
To evaluate the impact of MK-8189 on weight at Week 12, as compared to risperidone • CCI [redacted] • Hypothesis (H8): MK-8189 16 mg is CCI [redacted]	Weight (kg)
To evaluate the impact of MK-8189 on weight at Week 6, as compared to placebo	Weight (kg)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

CCI	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study to evaluate the efficacy and safety of MK-8189 at 16 and 24 mg qd dosing using risperidone as an active control in adult participants who have a current acute episode of schizophrenia according to DSM-5™ criteria.

For each participant, this study will last approximately 15 weeks, with an initial screening period from 2 to 7 days, followed by a treatment period of 12 weeks. The 12-week treatment period consists of a 6-week acute treatment period inclusive of an initial 1-week titration period to reach target dose, followed by a 6-week extension treatment period. A follow-up period consists of 14 days after the last dose of study intervention.

The screening period will include a screening visit and a taper period. All participants must be safely tapered off psychotropic medications in a manner consistent with local medical practice with the last dose of all prohibited medications to be taken no later than the evening before the baseline visit.

Participants could be admitted to the hospital/inpatient unit as early as the day of signing consent, but no later than the evening of the screening (V1) visit after assessment completion. It is anticipated that participants will continue as inpatients in this study until at least Week 4 (V6) assessments are completed. Participants are not to be discharged from an inpatient setting unless they are clinically ready to be discharged: that is, deemed clinically stable, capable of self-administration of study intervention, and able to comply with the visit schedule as an outpatient, according to the investigator. Hospitalization beyond what is required for the protocol may apply if consistent with standard of care. Refer to Section 8.1.17 for details on hospitalization under this protocol.

At the baseline (V2) visit, participant eligibility will be reassessed for final eligibility per inclusion/exclusion criteria as described in Section 5. The participant must not be randomized into the study until after ensuring that they meet all criteria, including approval by the external SDEs where noted. Note: randomization and first dose must occur on the same day.

Before Amendment 4, eligible participants were randomly assigned to 1 of 5 treatment sequences, with each sequence detailing the treatments that the participants were to receive in the acute and extension treatment periods (acute treatment/extension treatment). Participants were randomized in a 2:2:2:1:2 ratio to one of the following treatment sequences: MK-8189 8 mg/MK-8189 8 mg, MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, or placebo/MK-8189 24 mg.

On implementation of Amendment 4, eligible participants will be randomized in a 2:2:1:2 ratio to 1 of the 4 following treatment sequences: MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, or placebo/MK-8189 24 mg.

Before Amendment 4 the total sample size was to be approximately N=576; on implementation of Amendment 4 the total sample size is predicted to be approximately N=500, noting that the exact number of participants to be ultimately enrolled is, in part, a function of the (unknown) number of participants randomized to the MK-8189 8 mg treatment arm before the implementation of Amendment 4.

Participants randomized to receive placebo in the acute treatment period will receive MK-8189 24 mg qd in the extension period. During the first week of the extension treatment period, participants in this treatment group sequence will be up-titrated to MK-8189 24 mg qd. Note that initial dosing and titration of study intervention to target dose is described in Section 6.6.

For participants who complete 12 weeks of study intervention treatment, the Week 12 visit is intended to take place the day after the participant's last dose of study intervention. Medication prohibitions in Table 3 and restrictions as listed in Table 4 do not end until after all assessments have been completed for the Week 12 visit.

If the participant discontinues study intervention treatment before the intended last visit at Week 12, then an EOT visit should be completed as soon as possible after the last dose. Medication prohibitions in Table 3 and restrictions as listed in Table 4 do not end until after all assessments have been completed for the EOT visit.

For participants who continue study visits after the EOT visit, refer to Section 8.10.4.

Participants will have follow-up TC (post treatment Days 7 and 14) after their last dose of study intervention, regardless of whether they complete the full treatment period or discontinue study intervention early.

An eDMC will evaluate the unblinded safety data on a regular basis. In addition, the eDMC will review unblinded efficacy data if the futility IA is conducted (Section 9.7), noting that the eDMC may also request unblinded efficacy data at any time to assess the benefit/risk profile.

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.

The primary endpoint and secondary endpoints are described in Section 3.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and will be used as the primary efficacy endpoint measure [Kay, S. R., et al 1987]. The PANSS has been used extensively as a primary endpoint in multiple global

pivotal studies of therapies for schizophrenia, is capable of detecting treatment effects, and captures clinically relevant aspects of the condition.

The CGI-S is a single-item, 7-point clinician-rated scale for assessing the global severity of the illness, taking all relevant clinical information into account [Haro, J. M., et al 2003]. Similar to the PANSS, the CGI-S has been extensively used in schizophrenia studies to detect treatment effects and has been well characterized in multiple populations.

The PSP scale is a clinician-rated scale that measures personal and social functioning in the domains of Socially useful activities, Personal and social relationships, Self-care, and Disturbing and aggressive behaviors. [Morosini, P. L., et al 2000]. The PSP scale is considered to be a reliable and valid instrument for assessing social functioning of patients with schizophrenia and is therefore a useful and patient-relevant measure of activities of daily living.

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for clinical adverse experiences. Physical examinations, vital signs, 12-lead ECGs and laboratory safety tests will be performed routinely to detect any clinically meaningful effects.

The AIMS, BARS, and SAS are clinician-rated scales that will be used to standardize the evaluation of EPS observed in the study.

The AIMS is a 12-item scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements), global severity, and participant's awareness and distress related to said movement disorders. [Department of Health, Education, and Welfare Public Health Servi 1976].

The BARS is a combined clinical observation and interview that evaluates for akathisia and consists of the following items: objective items for clinician rating of observable restless movements that are associated with akathisia, subjective items related to awareness of the restlessness and distress associated with akathisia, and a global severity item [Barnes, T. R. E. 1989].

The SAS is a structured clinical examination that measures drug-induced parkinsonism. The rater asks the participant to perform tasks and rates responses from normal to severe. Specific symptoms include muscle rigidity, tremor, akinesia, and salivation [Simpson, G. M. and Angus, J. W. S. 1970].

The C-SSRS will be administered to screen for the presence, and assess the severity, of possible suicidal ideation and behavior in all study participants (refer to Section 4.2.3).

4.2.1.3 Pharmacokinetic Endpoints

Blood will be drawn at time points specified in the SoA for MK-8189 PK measurements. The plasma samples will be used to evaluate the PK of MK-8189 in a patient population, and to enable the characterization of the PK/pharmacodynamics and PK/AE relationships.

Additional metabolites based on ongoing metabolites in safety testing analysis may also be evaluated. These data will be used in PK model development and analysis with results reported separately.

The final decision as to which plasma samples will be assayed will be made by the Sponsor's Department of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism and the Clinical Director. Information regarding the collection and shipping of plasma samples will be provided in the administrative binder.

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic endpoints are 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 absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples 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 multi-study 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 Comparator/Placebo

Despite the seriousness of the condition, a placebo treatment arm is necessary to evaluate both efficacy and safety. Without the use of placebo, false assumptions regarding the true efficacy of new drugs may be made. In the absence of a placebo control, it is nearly impossible to distinguish true drug effects from nonspecific effects in this study population.

Risperidone is an antipsychotic drug mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, and the mixed and manic states of bipolar disorder. Risperidone is a second-generation atypical antipsychotic. It is a dopamine antagonist possessing antiserotonergic, antiadrenergic and antihistaminergic properties. The recommended starting dose of risperidone approved by the FDA for schizophrenia in adults is 2 mg (qd). Further dosage adjustments in 1 to 2 mg qd increments are recommended if necessary, to the recommended target dose of 4 to 8 mg qd. Efficacy with risperidone in schizophrenia was shown in a dose range of 4 to 16 mg qd in clinical trials according to the US approved label. However, doses above 6 mg per day were not shown to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. The current study will use a target dose of risperidone 6 mg qd as the active control to aid interpretation of the study results.

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 biologics license application, as well as assessment in studies that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

4.3 Justification for Dose

The first-in-human SAD study (P001) identified that the immediate-release formulation would not be desirable for further development given the relatively high peak:trough ratio and the presence of mild dystonia in 3 participants receiving 3 mg and moderate dystonia in 1 participant at 6 mg. The controlled-release formulation was subsequently developed with improved peak:trough ratios and improved tolerability (see IB for details). The prior POC study (P005) tested a dose of 12mg as this was a well-tolerated dose in the MAD study (P004) and, based on PET EO, was predicted to achieve exposures that would reach or exceed the minimal efficacy threshold of 30% PDE10A inhibition at trough for >90% of the estimated population. The POC study supported the tolerability and efficacy of 12mg, and no dose-limiting adverse effects were identified.

In the current study (before Amendment 4), 8 mg, 16 mg, and 24 mg doses were selected. These 3 doses provide maximal spread across the dose-response range still predicted to be efficacious based on enzyme occupancy from the PET EO study (P002). Across these doses,

the range of median EO is approximately 52% to 77%, with the estimated fifth percentile exposures ranging from approximately 30% at 8 mg to 50% at 24 mg.

4.3.1 Maximum Dose Exposure for This Study

The maximum dose of MK-8189 in this study is 24 mg qd.

In the clinical pharmacology program to date, MK-8189 has been generally well tolerated at doses of up to 24 mg. Three single-dose and 1 multiple-dose clinical studies have been conducted in healthy subjects and subjects with schizophrenia (as both monotherapy and adjunctive) to evaluate safety, tolerability, and PK from 2 mg to 16 mg, with a total of 6 patients exposed to 16 mg. Dose-limiting toxicities have not been identified, and a maximum tolerated dose has not been established. Adverse events have been generally mild to moderate. There have generally been no clinically significant changes or group trends in laboratory, vital sign or ECG assessments.

The PK data from P005 were also included to update the population PK model of MK-8189 and an updated PK-EO relationship was produced. CCI [redacted]

4.3.2 Rationale for Dose Interval and Study Design

Based on the controlled-release formulation and estimated half-life of the compound, once daily dosing is predicted to be an appropriate dosing interval for the treatment of schizophrenia.

MK-8189 doses will be up-titrated (refer to Section 6.6) to the target dose per treatment sequence to improve tolerability and minimize EPS, and a matched placebo control will be included to reduce bias with regards to patient reporting and investigator assessment of AEs.

The 12-week treatment duration was selected to cover both the acute episode and the early residual period to evaluate early durability of efficacy. The selected treatment duration also permits exploratory evaluation of negative symptoms and cognitive performance, as well as an improved understanding of the trajectory for weight changes and effects on metabolic parameters.

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).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

The diagnosis will be confirmed using the MINI, Version 7.0.2. All psychiatric diagnoses specified in the inclusion and exclusion criteria will be made according to the DSM-5™ criteria by a qualified psychiatrist (MD) or psychologist (PhD) (or equivalent qualification). The investigator responsible for psychiatric diagnoses must also have at least 3 years of psychiatric clinical experience and be approved by the Sponsor.

All assessments of psychiatric symptoms that require an interview with the participant (ie, MINI, PANSS, PSP, C-SSRS and CGI-S) must be performed in a language in which both the assessor and the participant are fluent, ie, no interpreter is needed.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Meet the diagnostic criteria for schizophrenia according to the DSM-5™ (for further details, refer to Section 8.1.6).

2. Be currently experiencing active phase symptoms of schizophrenia (DSM-5™ Criterion A, for further details, refer to Section 8.1.6).

3. Have an illness duration for schizophrenia of at least 1 year (for further details, refer to Section 8.1.6).

4. Be confirmed to be experiencing an acute episode of schizophrenia, as evidenced by ALL of the following:

   a. Onset of the current acute episode CCI before screening

   b. Current symptoms represent a marked and substantial worsening compared with the participant's usual symptomatic state prior to the current acute episode, and are associated with diminished functional ability

   c. In need of increased psychiatric attention to treat worsening acute episode symptoms

      For further details, refer to Section 8.1.6. **Note:** this criterion will be reviewed and approved by the external SDE prior to randomization.

5. Have a minimum PANSS total score of ≥80 at screening.

   Note: the screening minimum PANSS total score will be independently verified by a SDE prior to randomization.

6. Have a score of ≥4 (moderate) in 2 or more of the following items in the positive subscale of the PANSS at screening: CCI [redacted]

   Note: these scores will be independently verified by the SDE prior to randomization.

7. Have a CGI-S score of ≥4 (moderately ill) at screening and baseline.

8. Be able to taper off psychotropic medications (including antipsychotics, antidepressants and mood stabilizers) without significant destabilization or increased suicidality in the opinion of the investigator (see Table 3) CCI [redacted] with the exception that the last dose of past MAO inhibitors cannot be within 30 days of the screening visit.

9. Have had a positive response to antipsychotic medication (other than clozapine) during at least 1 period of treatment for a prior psychotic episode (for further details, refer to Section 8.1.6).

Demographics

10. Be male or female, from 18 years to <56 years of age inclusive, at the time of signing the informed consent.

Female Participants

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

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  - Has a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) 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 10.5.3.

- Abstains from breastfeeding during the study intervention period and for at least 7 days after study intervention.

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

Informed Consent

12. Provide documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

13. Have a level of decision-making capacity needed to make a meaningful choice about whether to participate in the study.

Additional Categories

14. Be willing and considered able by the investigator to participate in protocol assessments, including recordings of interviews, adhere to dose and visit schedules, study procedures and restrictions; this includes the ability to participate in all study procedures without the use of a language interpreter.

15. Have an identified responsible person (eg, family member, social worker, case worker, case manager, or nurse), referred to as the "external contact person" in the protocol, who has agreed to provide information about the participant's location if needed during outpatient portion of the study. The site personnel must consider this identified responsible person a reliable contact person, and the contact person must have regular contact with the participant (defined at screening as direct contact no fewer than 3 times per week with the participant), and with the expectation that this frequency of contact would continue (either in person or via other contact method) throughout duration of study, including the follow-up period).

    Note: if the participant does not have a reliable external contact person, then the site may designate a site staff member who will take on the role of external contact person, with the same responsibilities as described above.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a primary current diagnosis other than schizophrenia or a comorbid diagnosis (for example, major depression) that is primarily responsible for the current symptoms and functional impairment.

2. Meets criteria for moderate to severe substance use disorder currently or within past 6 months prior to screening (excluding those related to caffeine or tobacco/nicotine).

3. Has a known history of the following:

    a. Borderline personality disorder, antisocial personality disorder, or bipolar disorder

    b. Traumatic brain injury causing ongoing cognitive difficulties, Alzheimer's Disease or another form of dementia, or any chronic organic disease of the central nervous system

    c. Intellectual disability of a severity that would impact the ability of the participant to participate in the study

4. Has a current diagnosis of a psychotic disorder (other than schizophrenia), or a behavioral disturbance thought to be substance-induced or due to substance abuse.

5. Has moderate or severe tardive dyskinesia according to the investigator.

6. Is or was under involuntary commitment for the current acute episode, because the participant is considered a danger to themselves or others.

7. Has committed an act of violence (assaultive behavior) ≤2 years prior to the screening visit.

8. Has a BMI <18.5 kg/m^2.

9. Has a risk factor for QTc prolongation as defined by:

    a. A known history or current evidence of QTc interval >450 msec for both men and women

b. A known history of risk factors for Torsades de Pointes (eg, heart failure, cardiomyopathy or family history of long QT syndrome)

Note: determination of QTc interval at screening as a pretreatment reference will be based on the average of 3 measurements, using the Fridericia formula (QTcF) for correction. The average will be calculated by the site based on the central read.

10. Has known renal disease or is experiencing renal insufficiency as defined by:

    eGFR of <50 mL/min/1.73m^2 (as measured by CKD-EPI formula)

11. Has known history of chronic convulsive disorder (eg, epilepsy or seizure disorder) except febrile seizures of childhood.

12. Has a history of neuroleptic malignant syndrome.

13. Has a history of malignancy ≤3 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

14. Is at imminent risk of self-harm or harm to others as assessed by the investigator, based on clinical interview, MINI, or responses provided on the C-SSRS.

    Note: participants must be excluded if they report suicidal ideation meeting the description of C-SSRS Type 4 or 5 (ie, suicidal ideation with intent, with or without a plan) within the past 2 months or suicidal behavior (as described by the C-SSRS) within the past 6 months at screening. Participants must be excluded at baseline if they report suicidal ideation of Type 4 or 5 or suicidal behavior between screening and baseline.

15. Has a history of 3 or more significant allergies (including latex allergy) to prescription or nonprescription drugs or food, according to the investigator.

16. Has a known allergy or intolerance to risperidone or any of its active or inert ingredients.

17. Has hypothyroidism, diabetes, high blood pressure, cardiovascular condition, respiratory condition or other chronic medical conditions unless the condition is stable according to the investigator; the prescribed dose and regimen of medication are stable for ≥ 3 months prior to screening; and there are no expected changes in comedication during the study.

    Note: the prescribed dose and regimen of medication are considered stable if dose adjustments reflect optimizing treatment rather than reacting to significant changes in the treated conditions.

Prior/Concomitant Therapy

18. Has a history of treatment resistance exhibited by any of the following:

    a. No or minimal response to at least 2 periods of treatment lasting 6 weeks or longer, with antipsychotic agents (from at least 2 different chemical classes) at the maximally

tolerated dose. Participants who have responded to antipsychotics only when paired with clozapine are considered treatment-resistant (for further details, refer to Section 8.1.6).

b. History of ECT treatment for treatment-resistant schizophrenia within the past 6 months.

c. Past or current use of clozapine as single or adjunctive therapy for schizophrenia within the past 3 months.

19. Is currently taking and benefiting from a moderate or strong CYP3A and/or CYP2C9 inhibitors and inducers and/or CYP2B6 sensitive substrates (see Section 8.1.9 and Table 3).

20. Is currently taking and benefiting from strong CYP2D6 inhibitors (see Section 8.1.9 and Table 3).

Prior/Concurrent Clinical Study Experience

21. CCI [redacted]

22. Has been previously participated in the MK-8189 program according to the following: previous screen failure in this study; was previously randomized (regardless of treatment) in any MK-8189 study.

Diagnostic Assessments

23. Is unwilling to allow the recording of the MINI and PANSS interview at screening and baseline.

24. Has laboratory or clinical evidence of clinically significant hepatic conditions such as one or more of the following:

a. ALT or AST >2X ULN and total bilirubin >1.5X ULN

b. ALT or AST >3X ULN

c. A history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the 6 months prior to screening

25. Has a prolactin laboratory value of ≥ 5X ULN at screening.

26. Has a positive urine alcohol/drug screen at the screening visit with the following exceptions:

    a. Participants with positive psychotropic medication results for drugs permitted at time of screening may be included, provided the finding(s) can be accounted for by documented prescription use, the participant is able and willing to comply with protocol requirements regarding excluded medications, and eligibility criteria pertaining to the use of concomitant medications and substance use disorder are met

    b. Participants with positive alcohol or cannabis results on the urine alcohol/drug screen may be included at the investigator's discretion, provided the investigator does not feel the participant is a compliance risk and the participant does not fulfill the criteria for moderate or severe substance use disorder

Other Exclusions

27. Is unwilling or unable to remain hospitalized for the duration of screening and at least the first 28 days of treatment period.

28. Has a severe, acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

29. Has adverse events or clinically significant abnormal laboratory, vital sign, or physical examination, or ECG finding during screening period indicative of emerging or unstable medical conditions that potentially interfere with the ability to evaluate the safety, tolerability and the efficacy of the study intervention, according to the judgment of the investigator.

30. Is known to be repeatedly medically noncompliant in the management of their schizophrenia as assessed by the investigator.

31. Is known to be noncompliant or who is assessed by the investigator to be potentially noncompliant with the management of a current severe, acute or chronic medical condition which requires strict adherence to treatment (eg, tuberculosis, HIV).

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

There are no caffeine and tobacco/nicotine restrictions.

See Table 3 and Appendix 2 regarding illicit drug use prohibitions.

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 is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Note that participants who are screen failures cannot repeat screening.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

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 of MK-8189 and risperidone will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Titration schedules to reach target dose strengths specified in Table 1, as well as rules pertaining to subsequent dose down-titration and rechallenge, are specified in Section 6.6.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
MK-8189 8 mg/ MK-8189 8 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 0 mg	4 mg qd	Oral	Days 1-3 Day 8 to Week 12	Test Product	IMP	Central
MK-8189 8 mg/ MK-8189 8 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 4 mg	8 mg qd	Oral	Day 4 to Week 12	Test Product	IMP	Central
MK-8189 8 mg/ MK-8189 8 mg	Experimental	Placebo to risperidone	Drug	Capsule	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo	IMP	Central
MK-8189 16 mg/ MK-8189 16 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 0 mg	4 mg qd	Oral	Days 1-3	Test Product	IMP	Central
MK-8189 16 mg/ MK-8189 16 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 4 mg	8 mg qd	Oral	Days 4-6	Test Product	IMP	Central
MK-8189 16 mg/ MK-8189 16 mg	Experimental	MK-8189	Drug	Tablet	12 mg + 0 mg	12 mg qd	Oral	Day 8 to Week 12	Test Product	IMP	Central
MK-8189 16 mg/ MK-8189 16 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 12 mg	16 mg qd	Oral	Day 7 to Week 12	Test Product	IMP	Central
MK-8189 16 mg/ MK-8189 16 mg	Experimental	Placebo to risperidone	Drug	Capsule	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo	IMP	Central
MK-8189 24 mg/ MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 4 mg	8 mg qd	Oral	Days 1-3	Test Product	IMP	Central
MK-8189 24 mg/ MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 12 mg	16 mg qd	Oral	Days 4-6 Day 8 to Week 12	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
MK-8189 24 mg/ MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	12 mg + 12 mg	24 mg qd	Oral	Day 7 to Week 12	Test Product	IMP	Central
MK-8189 24 mg/ MK-8189 24 mg	Experimental	Placebo to risperidone	Drug	Capsule	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo	IMP	Central
Risperidone 6 mg/ Risperidone 6 mg	Active Comparator	Placebo to MK-8189	Drug	Tablet	0 mg + 0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo	IMP	Central
Risperidone 6 mg/ Risperidone 6 mg	Active Comparator	risperidone	Drug	Capsule	2 mg	2 mg qd	Oral	Days 1-3	Test Product	IMP	Central
Risperidone 6 mg/ Risperidone 6 mg	Active Comparator	risperidone	Drug	Capsule	2 mg	4 mg qd	Oral	Days 4-6 Day 8 to Week 12	Test Product	IMP	Central
Risperidone 6 mg/ Risperidone 6 mg	Active Comparator	risperidone	Drug	Capsule	2 mg	6 mg qd	Oral	Day 7 to Week 12	Test Product	IMP	Central
Placebo/MK-8189 24 mg	Experimental	Placebo to MK-8189	Drug	Tablet	0 mg + 0 mg	0 mg qd	Oral	Days 1-42	Placebo	IMP	Central
Placebo/MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 4 mg	8 mg qd	Oral	Days 43-45	Test Product	IMP	Central
Placebo/MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	4 mg + 12 mg	16 mg qd	Oral	Days 46-48 Day 50 to Week 12[a]	Test Product	IMP	Central
Placebo/MK-8189 24 mg	Experimental	MK-8189	Drug	Tablet	12 mg + 12 mg	24 mg qd	Oral	Day 49 to Week 12	Test Product	IMP	Central
Placebo/MK-8189 24 mg	Experimental	Placebo to risperidone	Drug	Capsule	0 mg	0 mg qd	Oral	Day 1 to Week 12	Placebo	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/AxMP	Sourcing
EEA=European Economic Area; IMP=investigational medicinal product; mg= milligram; NIMP/AxMP=noninvestigational/auxiliary medicinal product, qd=once daily. 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. Note: MK-8189 8 mg/MK-8189 8-mg treatment arm will be removed as of Amendment 4; however there are participants enrolled before Amendment 4 who will remain on 8 mg MK-8189 and continue to receive study drug per protocol.											

Arm names are treatment sequences.

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

Refer to Section 8.1.13 for details regarding administration of the study intervention.

All placebos will be created by the Sponsor to match active product.

6.1.1 Medical Devices

Medical devices are not used in this study.

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

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. Prior to Amendment 4, there were 5 study intervention arms. Participants were assigned randomly in a 2:2:2:1:2 ratio to one of the following treatment sequences (acute treatment/extension treatment): MK-8189 8 mg /MK-8189 8 mg MK-8189, 16 mg /MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, and placebo/MK-8189 24 mg.

On implementation of Amendment 4, eligible participants will be randomized in a 2:2:1:2 ratio to 1 of the 4 following treatment sequences: MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, or placebo/MK-8189 24 mg.

6.3.2 Stratification

Intervention allocation will be stratified according to the following factors:

1. Region/race (US–Black, US–Non-Black, Japan, Rest of World)

This stratification was selected as recent US schizophrenia studies have shown changing demographics and conflicting evidence for possible subgroup effects on efficacy [Mahableshwarkar, A. R., et al 2017]. While there are no known intrinsic factors that could explain these potential differences, it is difficult to exclude extrinsic factors, including recruitment practices, ascertainment biases, variable socioeconomic factors, or variable access to mental health care.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-8189 and risperidone will be packaged identically relative to their matching placebos so that blind is maintained. 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 longer than [redacted] will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

A missed dose is defined as taking less study intervention than specified (ie, fewer tablets or capsules than required) per day.

Tablets and capsules are packaged in blister packs designed to electronically capture the time and date of blister openings.

Medication compliance during the study will be monitored and determined by study intervention counts for both tablets and capsules. The dispensed blister pack(s), including any remaining study intervention will be returned. The site will perform a tablet and capsule count and also review associated electronically captured dispensing data. The site will use both participant report and electronic dispensing data to help assess compliance.

The circumstances under which electronically captured dispensing data must be edited are captured in the AARDEX manual. When editing is necessary, the site will need to determine the most accurate representation of actual study intervention administration.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication. Specific prohibitions for concomitant therapy during the treatment period are listed in Table 3 and restricted permitted concomitant therapies during the treatment period are listed in Table 4.

If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and the participant's primary physician, if applicable. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

6.5.1 Rescue Medications and Supportive Care

Refer to Section 8.1.9 regarding the use of EPS medications and permitted medications for treating insomnia, agitation, and anxiety as supportive care during the study (Table 4).

Medication prohibitions in Table 3 and restrictions as listed in Table 4 do not end until after all assessments have been completed for the applicable study visit (either EOT or Week 12 visit as described in Section 4.1), which takes place after the last dose of study intervention treatment.

6.6 Dose Modification (Titration)

Eligible participants will receive treatment in a double-dummy fashion of 2 tablets (either which may contain MK-8189 or placebo matching MK-8189) and 3 capsules (risperidone or placebo matching risperidone) taken qd.

Participants randomized to the MK-8189 and the risperidone treatment sequence groups will be titrated to their target doses during the first week of the acute treatment period in a blinded

fashion. Participants randomized to the MK-8189 and the risperidone treatment sequence groups will start the extension period on the same treatment dose as received on the last day of the acute treatment period. Participants randomized to the placebo/MK-8189 24 mg treatment sequence group will start the extension period after the same titration schedule as that prescribed for the MK-8189 24-mg dose group in the acute period.

If a participant cannot tolerate being up-titrated to the target dose during the first 7 days of treatment in the acute or extension treatment periods, the participant will be discontinued from treatment.

Titration requests can be made on Days 8 to 42 of the acute treatment period or Days 50 to 84 of the extension treatment period. Titration requests to the IRT are blinded and limited with a maximum of 3 dose changes allowed during the entire 12-week period in this fixed order: down-titration, rechallenge, down-titration. Participants may be down-titrated based on lack of tolerability after at least 1 target dose is taken, as an alternative to discontinuing the participant from treatment. A subsequent rechallenge may occur. In the event of intolerability after the rechallenge, down-titration may occur after which no further titration steps are allowed.

Permitted dose adjustment scenarios for all the treatment sequence groups in the 2 treatment periods is shown in Table 2 below.

MK-8189 16 mg and 24 mg treatment sequence groups may down-titrate to 12 mg and 16 mg, respectively. Risperidone 6 mg treatment sequence group may down-titrate to 4 mg. Titration requests may also be made for participants in the Placebo/MK-8189 24 mg treatment sequence group during the acute treatment period to maintain the blind; however, these requests will not result in a dose change (ie, participant remains on placebo). Placebo/MK-8189 24 mg treatment sequence group may down-titrate to MK-8189 16 mg after extension target dose is reached if, during the acute treatment period, there was no initial down-titration request made or if a rechallenge request was made.

Decisions to change the dose are to be made at scheduled visits whenever possible. If intolerable adverse events prohibit a delay in dose reduction, then an unscheduled visit for drug dispensing may be conducted.

Table 2 Down-titration and Rechallenge Scenario Chart

Treatment Sequence	**Intolerability During Days 1-7 and Day 43-49**	**Down-titration #1: First Instance of Intolerability Day 8-Day 42 or Day 50 to Day 84**	**Rechallenge Dose Day 8-Day 42 or Day 50 to Day 84**	**Down-Titration #2: Day 8-Day 42 or Day 50 to Day 84**
MK-8189 8 mg/ MK-8189 8 mg[a]	Discontinue study intervention	Down-titrate to 4 mg MK-8189	8 mg MK-8189	Down-titrate to 4 mg MK-8189 for remainder of treatment period[b]
MK-8189 16 mg/ MK-8189 16 mg	Discontinue study intervention	Down-titrate to 12 mg MK-8189	16 mg MK-8189	Down-titrate to 12 mg MK-8189 for remainder of treatment period[b]
MK-8189 24 mg/ MK-8189 24 mg	Discontinue study intervention	Down-titrate to 16 mg MK-8189	24 mg MK-8189	Down-titrate to 16 mg MK-8189 for remainder of treatment period
Risperidone 6 mg/ Risperidone 6 mg	Discontinue study intervention	Down-titrate to 4 mg risperidone	6 mg risperidone	Down-titrate to 4 mg risperidone for remainder of treatment period[b]
Placebo/ MK-8189 24 mg acute treatment only	Discontinue study intervention	Down-titration leads to no dose change (ie, participant remains on placebo Day 8-Day 42)	Rechallenge leads to no dose change (Day 8-Day 42)	Down-titration leads to no dose change (Day 8-Day 42)
Placebo/ MK-8189 24 mg extension treatment only if participant not down-titrated in acute treatment	Discontinue study intervention	Down-titrate to 16 mg MK-8189 (Day 50-Day 84)	24 mg MK-8189 (Day 50-Day 84)	Down-titrate to 16 mg MK-8189 (Day 50-Day 84)
Placebo/ MK-8189 24 mg extension treatment only if participant was down-titrated in acute treatment with no subsequent	Discontinue study intervention	Down-titration not allowed Participant already down-titrated (Day 8-42)	No change in dose (Day 50-Day 84) ie, participant remains at 24 mg	Down-titrate to 16 mg MK-8189 (Day 50-Day 84)
Placebo/ MK-8189 24 mg extension treatment only if participant was down-titrated in acute treatment with subsequent	Discontinue study intervention	Down-titrate to 16 mg MK-8189 (Day 50-Day 84)	Rechallenge not allowed	Down-titration not allowed

[a] MK-8189 8 mg/MK-8189 8 mg treatment arm will be removed as of Amendment 4, however there are participants enrolled before Amendment 4 who will remain on 8 mg MK-8189 and continue to receive study drug per protocol

[b] If a participant is unable to tolerate the reduced dose, study intervention should be discontinued. For participants that wish to remain in the study after discontinuation of study intervention, refer to Section 8.10.4 for details.

6.7 Intervention After the End of the Study

After the last dose of study intervention, assessments for the EOT visit (for participants who discontinue study intervention treatment early) or for the Week 12 visit (for participants who complete 12 weeks of study intervention treatment) should be completed as soon as possible after the last dose, preferably on the day after the participant's last dose of study intervention. After the assessments have been completed, the participant may begin standard of care treatment for schizophrenia.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.15). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment regimen will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.4 unless the participant has withdrawn from the study Section 7.2.

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.

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 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 been confirmed pregnant by a positive serum pregnancy test.
    - A positive or ambiguous urine pregnancy test requires immediate interruption of study intervention until serum hCG can be performed. Participant must be permanently discontinued from study intervention and reported and followed per Section 8.4.5, if pregnancy is confirmed by a positive serum pregnancy test. If the serum pregnancy test is negative, blinded study intervention can be resumed and the participant should be counseled about appropriate contraceptive measures. Refer to Appendix 2 and Section 10.5 for pregnancy testing.
- The participant experiences a further increase of psychotic symptoms during the study intervention which, in the opinion of the investigator or Sponsor, places the participant at unnecessary risk or does not allow the participant to adhere to the requirements of the protocol.

- The participant experiences one of the following elevated liver enzyme conditions, which is confirmed by repeat testing. Repeat testing is to be conducted within 48-72 hours for the following:

    o ALT or AST ≥3X ULN

    Note: the appearance of jaundice, worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia need not be accompanied by an elevated liver enzyme condition of ALT or AST ≥3X ULN to consider the participant, in their medical judgment, as being in need of study intervention discontinuation to avoid unnecessary risk to the participant.

- The participant experiences an ECI consistent with meeting DILI criteria: ALT or AST ≥3X ULN with TBL ≥2X ULN and ALP <2X ULN. See Section 8.4.7. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

- The participant has an absolute neutrophil count of <1000 per mm^3, and after repeat testing within 48-72 hours, the values are not normalized or increased.

- The participant reports suicidal ideation with intent, with or without a plan or method through an AE or C-SSRS (ie, a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior. If the reported suicidal ideation is passive, and participant expressly denies any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the study, the participant may continue on study intervention. Refer to Section 8.3.6.1 for requirements pertaining to the evaluation of such events and Section 8.4.7.

- The participant has a persistent eGFR of <40 mL/min/1.73m^2 as measured by CKD-EPI formula (refer to Appendix 2 for definition and determination of persistent eGFR).

- The participant has a QTcF interval of ≥500 msec (the average of the 3 QTcFs will be used and the average will be calculated by the site based on the central read).

- The participant cannot tolerate being up-titrated before receiving 7 days of treatment in the acute period or before receiving 7 days of treatment in the extension period.

- The participant is determined to have previously participated in a MK-8189 study.

In the event of any reason for discontinuation from treatment, all procedures for the EOT visit should be performed.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed. Refer to Section 8.10.4 for details.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.14. 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.

Refer to Section 8.1.7 and Section 8.1.18 for protocol-specific procedures in place to avoid lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

For assessments that require review by a central reader or external SDE for eligibility qualification, the review must be completed before randomization. Refer to the rater manual for details.

8.1.3 Participant Identification Card

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

The participant ID 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.

Clinically significant findings in physical examination, laboratory tests, ECGs, and other physical evaluations during screening are to be noted in the medical history. Clinically significant changes from the screening evaluation during the study should be captured as adverse events.

Psychiatric conditions and symptoms that are not core symptoms of schizophrenia (eg, agitation, anxiety, insomnia, depression), including those captured in the MINI evaluation, are to be recorded in the medical history.

8.1.5 Substance/Alcohol/Smoking History/Social History

Personal and social history such as living/employment/arrest and substance/alcohol/smoking will be reviewed. CCI [redacted]

8.1.6 Psychiatric History, Intake Evaluation, and MINI

All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the relevant DSM-5™ criteria.

A psychiatric history and intake evaluation will be conducted by the investigator or qualified designee. The investigator may review and use multiple information sources CCI [redacted] to obtain relevant historical information.

The psychiatric intake evaluation of the participant will include:

- Participant's psychiatric and treatment history (including response to previous antipsychotics as described in the inclusion criteria), medical history, mental status and treatment plan, approximate number of psychiatric hospital admissions (lifetime), and illness duration. To determine illness duration, the PI will use their best estimate based on available resources (including medical charts, participant self-report, family member, health or paraprofessional report).
- A detailed description of the current acute episode (onset, duration, precipitants, evidence that symptoms and function have worsened vs. usual baseline).

- The aforementioned detailed description will be used to complete the C-VISA™, which is an instrument detailing the required elements for participant eligibility. As stated in Section 8.1.8 External SDE Review of Participant Eligibility Considerations, the C-VISA™ once completed is submitted for review by the SDE to ensure that protocol eligibility criteria pertaining to psychiatric history, diagnostic eligibility, and psychiatric assessments are met and that corroborative sources as specified in this section are adequate.
- The C-VISA™ notes must include a description of the nature and duration of the relationship between the participant and corroborative sources, for corroboration both of schizophrenia diagnosis and illness duration and of the current acute episode onset, as described here:

CCI [redacted]

- Sites are expected to perform due diligence to confirm, at a minimum, that the diagnosis and the duration of schizophrenia is based on site-independent, professional sources. Professional sources could include medical records, psychiatric records, discussion with the potential participant's treating psychiatrist, or information from other health care professionals/paraprofessionals.
- If the site is unable to acquire site-independent, professional corroboration during the screening window, please see SDE guidance document.

Corroborative sources of the current acute episode onset:

- Only if no professional sources are available, nonprofessional sources may be considered to corroborate the duration of the current acute episode, if those sources meet the criteria specified in the SDE guidance document. Participant self-report cannot be used as the sole corroborator of the duration of the current acute episode. Nonprofessional sources could include: family member, friend, roommate, etc.
- CCI [redacted]

8.1.7 Identification of External Contact Person

To be considered eligible for enrollment, the participant must have an identified responsible external contact person who agrees to aid the site in locating the participant if the participant cannot be reached during the outpatient phase. The external contact person may be a family member, social worker, case worker, case manager, nurse or other individual who has a significant relationship with the participant as evidenced by a broad range of assistance typically provided to the participant by the external contact person. The participant must provide the name and contact information of this person. Site personnel must confirm that this person has agreed to be available to locate the participant if the participant cannot be contacted. The site must interview the potential external contact person and consider this

person reliable and that this person confirmed that they anticipate having contact no less than 3 times per week with the participant as an outpatient during the study; either in person or via other contact method. The source documents must record the external contact person's agreement to act as the participant's contact person. If the participant does not have an external contact person that is considered reliable by the site, the site may designate a site representative to act as the participant's external contact person, with the same responsibilities as described above. The investigator may not act as the external contact person. In the event the external contact person cannot participate for the entire study duration, a new external contact will need to be identified with the same requirements as above.

The investigator is responsible for documenting in the source that the external contact person will have sufficient time to meet their responsibilities as defined by the protocol requirements.

8.1.8 External SDE Review of Participant Eligibility Considerations

Participants cannot be randomized without the approval of the external SDE, which will be based on the review of screening PANSS and MINI interview, the scores of PANSS, CGI-S and C-SSRS, and the completed C-VISA™. The C-VISA™ will be used to provide the relevant elements of the psychiatric history, diagnostic eligibility, and psychiatric assessments to the SDE for independent review. Refer to the rater manual for details. To ensure a timely review, the above-mentioned screening assessments, which include the completed C-VISA™, should be transmitted immediately (within 2 calendar days of the screening visit).

In the event of unforeseen circumstances that may delay the submission of the C-VISA™ and screening rating scales data, the investigator or pertinent site staff must contact the external SDE immediately to ensure speedy remediation.

In those circumstances where C-VISA™ and screening rating scales data cannot be transmitted on time to ensure V2 can be completed within 7 days of V1, the external SDE and PI will agree on an acceptable alternative, which may include telephone review of critical elements.

8.1.9 Prior and Concomitant Medications Review

8.1.9.1 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 V2. One-year history of antipsychotics will also be recorded.

8.1.9.2 Concomitant Medications

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

The following therapies are prohibited or restricted during the course of the study:

1. Medications specifically prohibited in the exclusion criteria are also prohibited during the treatment period.

2. Medications with a moderate or strong inhibiting or inducing effect on cytochrome P450 CYP3A or CYP2C9, or the use of medications that are sensitive substrates of CYP2B6, are prohibited during the treatment period.

3. All psychotropic medications (including antipsychotics, antidepressants, mood stabilizers, other psychotropics) are prohibited during the treatment period, except as described in Table 4.

4. Medications that are strong CYP2D6 inhibitors are prohibited during the treatment period.

5. Medications for the treatment of agitation, anxiety, and insomnia are prohibited during the screening and treatment periods, except for those stated in Table 4.

The participant must be able to discontinue or, in the opinion of the investigator, safely taper off, of any prohibited treatment listed under "Medications Supplements, Other Substances and Procedures" in Table 3 during the taper period CCI [redacted] without significant destabilization or increased suicidality. See footnotes in Table 3 for exceptions.

The following list of prohibited medications in Table 3 is not comprehensive. The investigator should use their medical judgment when a participant presents with a medication that meets a prohibited category, but is not on the list or call the Sponsor for clarification.

Prohibitions and restrictions are not lifted until after the completion of V12/EOT visit (see Section 8.10).

Table 3 Prohibited Medications During the Treatment Period

CYP Inducers, Inhibitors And Sensitive Substrates[a]	
CYP3A strong or moderate inhibitors:	amprenavir, aprepitant, atazanavir, boceprevir, casopitant, ceritinib, cimetidine, ciprofloxacin, clarithromycin, cobicistat, conivaptan, crizotinib, cyclosporine, danoprevir, darunavir, diltiazem, dronedarone, duvelisib, elvitegravir, erythromycin, faldaprevir, fedratinib, fluconazole, idelalisib, imatinib, indinavir, isavuconazole, istradefylline, itraconazole, ketoconazole, letermovir, lopinavir, mibefradil, mifepristone, nefazodone, nelfinavir, netupitant, nilotinib, posaconazole, ravuconazole, ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, tofisopam, troleandomycin, verapamil, voriconazole
CYP3A strong or moderate inducers	apalutamide, asunaprevir, avasimibe, beclabuvir, bosentan, carbamazepine, dabrafenib, daclatasvir, efavirenz, enzalutamide, etravirine, ivosidenib, lersivirine, lesinurad, lopinavir, lorlatinib, lumacaftor, mitotane, modafinil, nafcillin, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's Wort extract, talviraline, telotristat ethyl, thioridazine
CYP2C9 strong or moderate inhibitors	amiodarone, ataciguat, azapropazone, benzbromarone, bucolome, fluconazole, miconazole, oxandrolone, piperine, phenylbutazone, sulfaphenazole, tasisulam, tienilic acid, voriconazole
CYP2C9 strong or moderate inducers	carbamazepine, enzalutamide, rifampin, ritonavir
CYP2B6 known substrates with sensitive therapeutic range	bupropion, efavirenz
CYP2D6 strong inhibitors	bupropion, dacomitinib, fluoxetine, paroxetine, pridopidine, quinidine
Medications Supplements, Other Substances and Procedures	
Antipsychotics (other than study intervention)	
Antidepressants	
Mood stabilizers	
Stimulants such as methylphenidate and amphetamines	
MAO inhibitors[b]	
Herbal drugs/dietary supplements, including and not limited to St John's Wort, ginkgo, goldenseal[c]	
Antiemetics with dopamine antagonist activity	
Illicit drugs[d]	
Benzodiazepines are prohibited during the screening and treatment period for any indication, except as stated in Table 4	
ECT	

CYP=Cytochrome P450; ECT=electroconvulsive therapy; MAO=monoamine oxidase; UDS=urine drug screen

a Sources include the FDA website http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency. Note the prohibitive list is not exhaustive. Applies to agents with significant systemic absorption (eg, oral, subcutaneous).

b The last dose of a MAO inhibitor must be ≥30 days before screening.

c Dietary supplements that are specifically marketed for psychiatric symptoms (eg, valerian, Bach's flower remedies) are prohibited. Supplements with broader applications for general health (such as omega-3-fatty acids, magnesium) are not prohibited.

d In the event of positive UDS, the investigator should interview the participant and ensure that the participant understands to refrain from using cannabinoid drugs and prohibited psychotropic medications throughout their participation in the study. Alcohol use during the study should also be discouraged. This discussion must be noted in the source documents or on the laboratory report.

Table 4 Medications and Procedures Permitted During the Treatment Period

Permitted medications post baseline[a]	
As needed use nonpsychotropic medications	Aspirin, NSAIDs, acetaminophens
Chronic use medication	Chronic use of certain medications are allowed if the history of its use and participant's condition meets specifications of the eligibility criteria.
Approved extrapyramidal symptoms medications	Anticholinergic or any other medications to treat EPS ongoing at the time of screening can be maintained as needed through the treatment period, and doses adjusted as needed. If EPS begins at any time during the study, then the use of anticholinergic or any other medications to treat EPS may be considered for use by the investigator.
Lorazepam up to 6 mg/day during the taper period and the first 14 days of active treatment or the equivalent dose of approved benzodiazepines for the treatment of agitation, anxiety. Remainder of days on active treatment: lorazepam up to 4 mg/day or an equivalent dose of approved benzodiazepine on a daily basis.[b,c]	To be used only on as needed basis. For recording in the CRF, enter total daily dose for each day when recording benzodiazepine use. If a daily dose is the same over consecutive days, recording of the consecutive date range for the same daily dose is acceptable.
Partial benzodiazepine agonists for the treatment of insomnia at recommended dose ranges[c,d] Suvorexant[e]	Zolpidem (2.5 to 10 mg/day), zaleplon (5 to 20 mg/day), zopiclone (7.5 to 15 mg/day), or any equivalent short half-life nonbenzodiazepine hypnotic may also be used for insomnia/sleep disturbance if zolpidem, zaleplon, or zopiclone are not available in specific countries. To be used only on an as needed basis: suvorexant (10 mg to 20 mg).

CRF=case report form; EPS=extrapyramidal symptoms; NSAIDs=nonsteroidal anti-inflammatory drugs

a Chronic use of certain medications are allowed if the participant's condition is stable, and the dose was stabilized before the first dose on Day 1 and they are not strong or moderate CYP3A known inhibitors and inducers, strong or moderate CYP2C9 known inhibitors and inducers, and CYP2B6 known substrates with sensitive therapeutic range.

b To be used on as needed basis. CCI [redacted]

c The use of drugs to treat agitation, anxiety, or insomnia or with known sedative effects have the potential to impact efficacy assessments. The sites should consider avoiding their use within the 4 to 8 hours before efficacy assessments.

d Any equivalent short half-life nonbenzodiazepine hypnotic may also be used for insomnia/sleep disturbance if zolpidem, zaleplon, or zopiclone are not available in specific countries.

e In countries where approved (USA, Japan).

8.1.10 Assignment of Screening Number

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

8.1.11 Assignment of Treatment/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.

8.1.12 IRT

The investigator or designee will call/log into IRT as specified in the SoA. On confirmation of a participant's eligibility at V2, the investigator or designee will call/log into IRT to randomize the participant. Participants who do not meet eligibility criteria will be screen-failed in IRT. IRT will also be used for drug dispensing in the event of a down-titration or rechallenge. For completed participants or participants who discontinue study intervention, the investigator or designee will make the call/log into IRT at their last treatment visit (EOT or Week 12 visit). Refer to IRT user manual for actions performed through IRT.

8.1.13 Study Intervention Administration

Study intervention is administered by the study or inpatient staff during the inpatient phase. All personnel responsible for overseeing/managing study intervention administration must receive training 1) at the investigator meeting, or 2) on site from a Sponsor representative.

All individuals who dispense study intervention to the participant should monitor the participant to ensure doses are ingested as directed and record relevant dosing information which includes number of tablets and capsules and time taken in source documents.

Study intervention will be self-administered after hospital discharge.

Before discharge, participant will be educated by a trained member of the study staff on dosing requirements, package opening, the requirement to return all drug package(s) at each outpatient visit, and compliance. Documentation of participant training must be filed with the participant's source documents.

8.1.13.1 Timing of Dose Administration

The first dose will be administered after all baseline visit safety assessments and efficacy assessments are completed (including the collection of blood samples and predose PK sample) and after subsequent randomization. The first dose will be taken in the evening on the day of the baseline visit only after all baseline assessments have been completed. Thereafter, participants should be administered their study intervention at approximately the same time each evening. If a dose is delayed into the next calendar day (eg, 1:00 am), then the dose may be taken provided it is at least 12 hours before the next scheduled dose. Participants should not take double or extra doses to attempt to make up for a missed dose.

Before being discharged to an outpatient setting, participants will be instructed to endeavor to take their doses in the evening, at the same time each evening, and review what steps to take if a dose is late or missed.

Study intervention can be taken without regard to food intake.

8.1.14 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.4.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT/DC visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.14.1 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.

8.1.15 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency

unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a 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 may be allowed to continue study intervention with Sponsor consultation and should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

8.1.16 Calibration of Equipment

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

8.1.17 Hospitalization During the Study

For those participants who were already hospitalized when approached for recruitment into this study, the start of hospitalization for the study must be no earlier than the day of the signing of the consent form.

For participants who are outpatients when approached for recruitment into this study, participants could be admitted to the hospital as early as the day of start of consenting, but no later than the evening of the screening visit.

Participants will continue as inpatients in this study throughout at least the first 29 ±1 days of the active treatment period. Participants may be considered for discharge after completing V6 (Week 4) assessments if the following minimum conditions are met:

- According to investigator's judgment, the participant's clinical symptoms and functioning are sufficiently improved that continued treatment can occur safely in a less restrictive environment (eg, participant is not at risk to self or others);
- The participant can self-administer the study intervention correctly;
- The participant can abide by all study procedures as an outpatient as described in this protocol.

On the day of discharge, the participant will be given the visit schedule, dosing instructions, and a dosing notebook. The site will ensure that the participant has their participant ID card.

CCI [redacted]

Standard local practice that includes exceptions to the typical inpatient/outpatient model (eg, intensive observaton period as an outpatient before confirming they meet criteria for formal discharge) may apply after V6 (Week 4) and should be documented for review and approval by Sponsor before the execution of that practice for this study.

CCI [redacted]

The Sponsor is to be contacted if it is anticipated that the participant will not be ready to be discharged from the hospital after screen fail, treatment discontinuation, or after V6 assessments are completed on Day 28.

8.1.18 Telephone or Virtual Contacts

TCs will be performed as specified in the SoA in between outpatient visits by a trained site representative to check compliance and ability to manage self-administration of study intervention, review adverse events, and remind participants of the visit schedule. TCs during the follow-up period will be used to review adverse events and concomitant medications. Where applicable, TCs will also be used to instruct and encourage participants to fast overnight before scheduled outpatient clinical laboratory sample collection (refer to Appendix 2 for definition of fasting). Additional TCs/visits may be scheduled at the investigator's discretion.

The principal investigator is responsible for ensuring that all TCs are performed by a site staff member who is a health care professional qualified to elicit a discussion with the

participant that will lead to a clinically meaningful disclosure on the participant's well - being. TCs are to be documented in a contact log, and the investigator must review the updated log within 2 days of the new log entry. In the event of worsening symptoms reported by either the participant or the external contact person, the ensuing action steps taken by the site must be recorded. The site must follow-up on any report of worsening symptoms by contacting the participant to schedule an immediate visit.

If the participant cannot be reached by TC at the regularly scheduled time or misses a visit, the site should make at least 3 attempts (in addition to the initial TC) to contact the participant within 48 hours of the missed scheduled time. The last contact attempt should represent stronger action by the site to contact the participant (ie, a visit to the participant's residence, an attempt to reach the external contact person identified at the time of screening) if the participant cannot be reached on the third attempt. All TCs, attempted contacts, and home visits should be recorded in source documents.

8.2 Efficacy Assessments

Efficacy assessments are performed at each site by raters who meet the qualification and training requirements per scale. Rater qualifications, training and applicable certification process are established in a separate document. Each efficacy assessment may require different raters, but it is strongly encouraged that the same rater evaluates the same participant for the duration of the study.

As a best practice, a back-up PANSS rater should be prospectively identified for each participant at screening to improve continuity and reliability of the ratings. Recommendations for preparing the prospective back-up rater to rate the participant's behavior is provided in the rater manual.

To avoid the influence of participant fatigue on the diagnostic and primary outcome data, the recommended order of assessments is to perform the PANSS interview as the first clinical assessment conducted at each applicable visit. The CGI-S is recommended as the last clinical efficacy assessment so that all relevant information can be reviewed when completing the CGI-S.

All PANSS interviews are to be recorded and submitted for review to the SDE. Some or all of the PANSS recorded interviews will be reviewed and scored by an SDE. All screening PANSS interviews will be reviewed and must be approved by the external SDE before randomization. The external SDE will provide feedback to the site raters on the quality of the site rater interviews and ratings to help develop and maintain good interrater reliability. Additionally, the external SDE feedback may be used to refine the PANSS scores entered by the site for an individual rating, at the discretion of the site rater.

The PANSS rating includes collection of information from an informant. Ideally, all PANSS informant interviews will be recorded when performed in person. Informants must provide consent before any audio recordings of their interview. It is acknowledged that PANSS informants may change over time.

While concerns have been raised that recording assessments via audiotaping or videotaping could theoretically compromise participant privacy, this issue must be balanced with the need to conduct methodologically adequate and scientifically rigorous trials that are capable of testing key hypotheses. Given that the key endpoints in this study involve subjective clinical judgments, monitoring the adequacy of participant interviews and ratings is essential and part of strong research methodology. Prior studies suggest that the failure to adequately monitor such ratings can substantially increase the risk of failed trials [Khan, A., et al 2013]. Recorded interviews will be encrypted using state-of-the-art methods to ensure privacy. Additional steps will be taken to ensure anonymity of specific private health information. Recordings will be reviewed only by approved study personnel for quality control purposes and will be destroyed in accordance with current retention requirements.

8.2.1 PANSS

The PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and will be used as the primary efficacy endpoint measure. The PANSS is comprised of 3 subscales that measure positive symptoms, negative symptoms, and general psychopathology [Kay, S. R., et al 1987]. The PANSS Positive subscale consists of 7 items that measure delusions, conceptual disorganization, hallucinations, excitement, grandiosity, hostility, and suspiciousness/persecution. The PANSS Negative subscale consists of 7 items that measure blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The General Psychopathology subscale consists of 16 items that measure somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, unusual thought content, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

8.2.2 PSP

The PSP scale is a clinician-rated 100-point (1-100) scale that measures personal and social functioning in 4 domains: Socially Useful Activities, Personal and Social Relationships, Self Care, and Disturbing and Aggressive Behaviors [Morosini, P. L., et al 2000]. The rater evaluates the participant's level of impairment in each domain, ranging from absent, mild, manifest, or marked to severe or very severe; however, different descriptive anchors are used for disturbing and aggressive behaviors.

8.2.3 CGI-S

The CGI-S is a single-item, 7-point clinician-rated scale for assessing the global severity of the illness [Haro, J. M., et al 2003]. It is recommended that the CGI-S be performed as the last efficacy assessment.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted, per institutional standard. The investigator or medically qualified designee (consistent with local requirements) will perform a physical examination that includes the following organ systems:

- Head, eyes, ears, nose, and throat
- Neck
- Respiratory system
- Cardiovascular system
- Abdomen
- Skin and extremities
- General appearance
- Neurological system, including mental status, motor strength, muscle tone, and reflexes

Height, weight, and waist circumference will also be measured and recorded (Section 8.3.2).

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any medical conditions found during the full physical examination will be recorded in the Sponsor database.

8.3.2 Height/Weight/Waist Circumference

Height (inches/centimeter) and waist circumference (inches/centimeter) will be collected and recorded at time points specified in the SoA. Measurements should be recorded to the nearest inch/centimeter.

Abdominal waist circumference should be measured by encircling the participant's body at the navel with a cloth measuring tape or similar pliable measuring device. It is important that the position of the participant while measuring circumference, be consistent throughout the study. If circumference is measured with the participant lying down, it is important to be performed on a firm surface (eg, an examination table or bed with minimal padding).

Body weight will be measured using a standardized scale provided by Sponsor and should be reported to 1 decimal place (eg, 0.1 kg). The procedure will be conducted as follows:

- Weight will be taken in duplicate throughout the study at approximately the same time of day, after voiding and while wearing only light clothing (no coats, shoes or socks)

- The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb then:

    - Check the participant to ensure proper positioning

    - Collect a new set of duplicate measurements that should be recorded in the source documents

8.3.3 Vital Signs

Pulse and BP will be assessed.

Vital signs will be measured in a semisupine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse.

For blood pressure readings, the correct size of the blood pressure cuff and the correct positioning on the participant's arm is essential to increase the accuracy of blood pressure measurements. The same method for measuring pulse and blood pressure (eg, manual or automated) is recommended for all measurements for each individual participant and should be the same for all participants throughout the study.

8.3.4 Electrocardiograms

12-lead ECG will be obtained using central ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals according to the instructions in a separate ECG Instruction Manual. Cardiologist overread will be provided by central ECG vendor.

For the purposes of determining baseline QTcF, the central read will be used.

Triplicate measurements of ECG will be required at the screening visit.

When triplicate ECG measurements are required, the 3 individual ECG tracings should be obtained as close in succession as possible, but no more than 2 minutes apart, with the full set of triplicates to be completed in less than 4 minutes.

A single ECG is required at postscreening visits unless there is an observation of a QTc prolongation (QTcF interval of ≥500 msec) according to the ECG printout. An additional 2 ECGs will be required, and an average taken to determine the QTc interval for that visit based on central over read QTc interval values.

If a postbaseline single ECG has a printout of QTcF interval<500 msec (ie, there is no requirement to do a triplicate ECG), but subsequent central over read finds a QTcF interval of ≥500 msec, then an additional 3 ECGs will be required soon as practical, but no later than

next scheduled visit, and average taken to determine the QTc interval will be based on central over read QTc interval values.

See exclusion criterion 9 regarding exclusions for QTc prolongation as measured by ECG.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Suicidal Ideation and Behavior Monitoring

8.3.6.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

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, the assessor should also inquire and document if this is also present at the time of the screening visit.

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 specified time points, as indicated in the SoA, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness.

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

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. CCI [redacted] 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 Monitoring of Extrapyramidal Symptoms

Extrapyramidal symptoms (including dystonia, dyskinesia, akathisia, and parkinsonism) will be evaluated via routine AE evaluation and reporting. Also, dyskinesia, akathisia, and parkinsonism will be assessed using the AIMS, BARS and SAS, which are described in Section 4.2.1.2.

It is strongly encouraged that the same rater evaluates the same participant throughout their participation in the study.

EPS present at screening must be recorded in the medical history.

During the study, EPS must be recorded as an AE when:

- Clinically significant movement disorder side effects are observed by study staff or volunteered by the participant
- A clinically significant movement disorder already present at screening increases in severity
- Concomitant therapy for increasing or emerging EPS symptoms is initiated, increased, or reinstated while the participant is in the study

CCI [redacted]

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator 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, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Events resulting in or prolonging an existing inpatient hospitalization will not be considered an SAE if:

- The admission or prolongation is solely for social reasons
- Extended hospitalization for subjects not clinically ready to be discharged is not in itself an SAE. The PI instead should consider whether the events associated with extended hospitalization meet the definition of an SAE. Extended hospitalization beyond standard of care must be discussed with the Sponsor and the reasons for extended hospitalizations must be documented in the medical record daily until discharge.

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. 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).
2. CCI [redacted]
3. EPS resulting in study intervention discontinuation
4. Treatment-emergent adverse event of new or worsening tardive dyskinesia
5. CCI [redacted]

Note that the above AEs are classified as ECIs only after treatment allocation.

8.5 Treatment of Overdose

In this study, an overdose is a dose that is >2X higher than the intended number of either tablets or capsules in 1 dosing interval (refer to Section 8.1.13.1 for definition of dosing interval and Appendix 3 for reporting of overdose).

No guidance can be given at this stage on recognition of potential signs and symptoms of overdose. There is no specific antidote for overdose with MK-8189. If overdose is suspected, treatment should consist of general supportive measures.

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

Table 6 PK Sampling Schedule

Acute Treatment Period			
PK Sample	**PK Collection Day**	**PK Collection Time Window**	**Notes**
1	Baseline (Day 1)	Any time before first dose	Blood for PK sampling is collected at the baseline visit laboratory blood draw
2	V4	Within 24 hours before dose on day of visit	Collect date/time of dose on day before V4
3	Day before V6	-3 to 0 hr Predose	Suggested dose window (6-10pm) Sample 0-3 hr before dose on day before V6
4	Day before V6	2 to 4 hr Postdose	Suggested dose window (6-10pm) Sample 2-4 hr after dose on day before V6
5	V6	10 to 12 hr Postdose	Relative to dose taken on day before V6
6	V6	16 to 18 hr Postdose	Relative to dose taken on day before V6
7	V8	Anytime during visit	Collect date/time of dose on day before V8
Extension Treatment Period			
8	V10	Anytime during visit	Collect date/time of dose on day before V10
9	V12	Anytime during visit	Collect date/time of dose on day before V12
hr=hour; PK=pharmacokinetic; V=visit.			

Note that PK collection is not required once the participant discontinues study intervention treatment. If a participant discontinues before V12, then the last PK sample is collected at any time during the EOT visit.

An exposure-response analysis of PANSS total score data will be explored to determine the efficacious dose range of MK-8189 for the treatment of schizophrenia and to assess the impact of factors such as exposure, patient population characteristics and drop-out on outcomes with MK-8189.

8.6.1 Blood Collection for Plasma MK-8189

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

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research 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 drawn 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 blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA from the planned genetic analysis sample

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8. It is important that the site carefully schedule visit assessments to avoid unnecessary burden to the participant: assessments should be scheduled at the participant's convenience so that participant is not forced to wait between assessments. Refer to Section 8.1 for recommended order of assessments.

8.10.1 Screening

The screening period will include a screening (V1) visit and a taper period. All participants must be safely tapered off psychotropic medications with the CCI [redacted]

Informed consent is provided before the start of any study-specific procedures. The first day of the screening/tapering period starts on the day the consent form is signed. Note that the intended screening period is a maximum of 7 days, and that the baseline visit (V2) is the day after the last day of the screening period (maximum of 8 days from screening visit). Screening periods beyond this interval require Sponsor consultation before randomization.

During the screening visit, potential participants will be evaluated to determine if they fulfill the entry requirements as described in Section 5.1 and Section 5.2. A psychiatric diagnostic assessment will be performed and recorded using the MINI, Version 7.0.2. The participant's medical history, prior and current medications, and demographic information will be obtained. Additional assessments of psychiatric symptoms and safety evaluations will be performed (see SoA). If the participant meets the screening eligibility criteria for which results are available, the participant will begin the tapering period. Participants could be admitted to the hospital/inpatient unit as early as the day of signing consent, but no later than the evening of the screening (V1) visit after assessment completion.

Note that central laboratory results, final central ECG interpretation and external review and subsequent documented approval of MINI, PANSS scores and corroboration of acuity by the SDE may be pending at the start of the tapering period. If the participant is deemed ineligible based on review and corroboration of the screening eligibility criteria, the participant will be considered a screen failure before the baseline visit (V2).

The tapering period will begin after the screening visit is completed. All participants must be safely tapered off prohibited medications (antipsychotics, antidepressants and mood stabilizers, see Table 3) and abide by medication allowances (see Table 4) in a manner consistent with local practices. The duration of the taper period should balance the need to taper medication safely with the need to limit the duration of time the acutely ill participant remains in screening. CCI [redacted]

Note that if exclusion criteria are met pertaining to laboratory values (ie, prolactin, eGFR and LFT values), those results are final, ie, assessments are not to be repeated to challenge those results. Other screening laboratory and ECG procedures may be repeated only after Sponsor consultation and subsequent approval.

CCI [redacted]

Note that participants who are screen failures cannot repeat screening.

8.10.2 Treatment Period

Each visit should be performed as noted in the SoA. For visits that require additional explanations, please see those specific visits below.

A visit must occur within the scheduling window around the actual scheduled day (relative to Day 1, the day on which study intervention is first taken), regardless of the actual day the previous visit occurred. For example, V8 must occur on Day 43 ± 1 day, regardless of how many days early or late any of the previous visits actually occurred. If visits deviate from the schedule, an attempt should be made to follow the original visit schedule for subsequent visits.

It is anticipated that participants will continue as inpatients in this study until at least Week 4 (V6) assessments are completed. Refer to Section 8.1.17 for details on hospitalization under this protocol.

Visit 2

Participants will be assessed for final eligibility per inclusion/exclusion criteria as described in Section 5.1 and Section 5.2. The participant may be randomized into the study and will be assigned a randomization number (via IRT) only after ensuring that the participant meets all criteria. For study intervention titration and timing of first dose, refer to Section 6.6 and Section 8.1.13.1.

Visit 12

Prohibited medications (Table 3) must not be initiated until after all visit assessments are completed. Restrictions on medications (see Table 4) are lifted the same day as the Week 12 (V12) visit, but only after all visit assessments are completed.

Study Intervention Discontinuation (End of Treatment)

EOT visit procedures as outlined in the SoA will be performed for participants who discontinue study intervention. The visit should occur as soon as possible after the decision is made, and must be before the initiation of prohibited medication and lifting of medication restrictions (see Table 3 and Table 4). All participants who discontinue study intervention before completion of the protocol-specified treatment period will be encouraged to continue their participation in the study off study intervention and be followed for all remaining study visits as outlined in the SoA (Section 8.10.4). For participants who discontinue study participation on the same date as they discontinue study intervention, their last visit will be the EOT visit. If the participant discontinues treatment during the first 28 days of study, and after completion of the EOT visit, the protocol-specified inpatient period is no longer required for those who wish to continue participating in study visits. On the day of discharge, the participant will be given the visit schedule, and the site will ensure that the participant has their ID card. Approximately midweek after discharge, the participant should be telephoned by study staff to assess AEs, and to remind the participant of the visit schedule.

Study Discontinuation Visit (DC)

DC visit procedures as outlined in the SoA will be performed for participants who discontinue the study after the EOT visit (see Section 8.10.4). The DC visit should occur as soon as possible once the decision is made.

8.10.3 Follow-up Period

Participants will be followed after the last dose of study intervention according to the SoA. Note that more frequent contact may be performed if necessary. The 14-day follow-up period consists of a schedule of TCs. Safety follow-up occurs unless participant explicitly withdraws consent from being followed up for safety.

Refer to Section 8.1.18 regarding telephone or virtual contact procedures.

If the follow-up period occurs before the participant being discharged, it is anticipated that these specified contacts will still take place, but may be conducted between the site personnel and participant in person.

Scheduling of follow-up TCs are based on day of last dose, not last visit in the treatment period. Requirements for follow-up visits may then run concurrently with routine scheduled visits if participants continue to participate in study visits of the treatment period after last dose. A routine scheduled visit will replace a follow-up TC if both are scheduled on same day or within the same window.

Once participants have discontinued study medication (whether at DC visit or end of treatment), they will typically require a transition to treatment with approved medications. Investigators should manage this transition for participants based on local norms and standard of care.

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

If the participant chooses to continue in the study after discontinuation of treatment (after completion of EOT visit), they will be encouraged to continue their participation in the study off study intervention and be followed for all remaining study visits as outlined in the SoA. Exception: PK samples will not be collected after the EOT visit.

If the participant continues with study visits off study intervention, but discontinues before the Week 12 (V12) visit, a DC visit will be conducted with the same procedures as the EOT visit.

8.10.5 Poststudy

Participants will not be followed after their completion of the study.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but before any unblinding/final database lock, changes are made to primary or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before unblinding/final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analysis of PK data, participant-reported outcomes, and FBR) will be documented in separate analysis plans.

Treatment sequences (MK-8189 8 mg/MK-8189 8 mg, MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, placebo/MK-8189 24 mg and risperidone/risperidone) will be used for analyses of extension period data as well as for analyses of data that span the acute treatment and extension periods. Treatment groups (MK-8189 8 mg, MK-8189 16 mg, MK-8189 24 mg, placebo, and risperidone) will be used for analyses of data solely collected in the acute treatment period. Within this section, the terms “treatment” or “treatment arm” will be used generally to refer to either “treatment group” or “treatment sequence” depending on the period(s) to which the analyses refer.

9.1 Statistical Analysis Plan Summary

Study Design Overview	A Phase 2B Randomized, Double-Blind Trial of the Efficacy and Safety of MK-8189 Compared with Placebo Using Risperidone as an Active Comparator in Participants Experiencing an Acute Episode of Schizophrenia
Treatment Assignment	Before Amendment 4, eligible participants were randomly assigned to 1 of 5 treatment sequences in a 2:2:2:1:2 ratio in a double-blind fashion via IRT, with each sequence detailing the treatments that the participants are to receive in the acute and extension treatment periods. The treatment sequences were MK-8189 8 mg/MK-8189 8 mg, MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, and placebo/MK-8189 24 mg. Specifically, participants randomized to receive either MK-8189 or risperidone in the acute treatment period continued to receive that same treatment in the extension period. Participants randomized to receive placebo in the acute treatment period received MK-8189 24 mg in the extension period. A mix of region and race (US-Black, US–Non-Black, Japan, Rest of World) will be the lone stratification factor. On implementation of Amendment 4, eligible participants will be randomized in a 2:2:1:2 ratio to 1 of the 4 following treatment sequences: MK-8189 16 mg/MK-8189 16 mg, MK-8189 24 mg/MK-8189 24 mg, risperidone 6 mg/risperidone 6 mg, or placebo/MK-8189 24 mg.
Analysis Populations	Efficacy: FAS Safety: APaT PK: PP

Primary Efficacy Estimand	The primary efficacy estimand follows the guidance in ICH E9 (R1) and has the following 4 attributes: 1. The population targeted by the scientific question: individuals diagnosed with schizophrenia experiencing an acute episode of schizophrenia. 2. The endpoint: Week 6 CFB score in PANSS Total Score. 3. The specification of how to account for intercurrent events to reflect the scientific question of interest: any assessments either obtained after initiation of prohibited psychotropic medication or obtained more than 5 days after study intervention discontinuation will be excluded. 4. The population-level summary for the endpoint which provides the basis for a comparison between-treatment conditions: difference (MK-8189 - placebo) in mean CFB at 6 weeks, as computed using the primary longitudinal ANCOVA model.
Primary Endpoint	CFB in PANSS Total Score at Week 6 (MK-8189 16 and 24 mg compared to placebo)
Key Secondary Endpoints	CFB in PANSS-PSS at Week 6 (MK-8189 16 and 24 mg compared to placebo) CFB in CGI-S at Week 6 (MK-8189 16 and 24 mg compared to placebo) CCI [redacted]
Statistical Methods for Key Efficacy Analyses	The primary efficacy hypotheses will be evaluated by comparing MK-8189 to placebo with respect to the mean change from baseline in PANSS total score at Week 6 using a longitudinal ANCOVA model. Both primary hypotheses (1 each for 16 mg and 24 mg) will be assessed using the p-values corresponding to the mean CFB treatment comparisons, in conjunction with a Bonferroni approach. The overall study will be considered as successful if at least 1 of the 2 primary hypotheses is supported.
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method.
Interim Analyses	Two types of interim analyses may be performed in this study. Results will be reviewed by an eDMC. These interim analyses are summarized below. Additional details are provided in Section 9.7. The first type of interim analysis will be for safety only and will be conducted approximately every 4 to 6 months, with the frequency subject to change per eDMC recommendation. The second type of interim analysis pertains to futility. This futility IA may be conducted at the behest of the Sponsor, and if conducted will occur only once (though it is noted that the eDMC may request efficacy analyses at any time to assess the benefit-risk profile). If conducted, the futility IA will be conducted when ~50% of the randomized participants in the MK-8189 16 mg, MK-8189 24 mg, and placebo treatment arms (N=~64/arm) are estimated to have had the opportunity to treat for 6 weeks. Futility may be declared if the conditional power for both primary hypotheses is less than 10%.

Multiplicity	The Type-I error rate over the multiple treatment comparisons will be controlled using a Bonferroni procedure (across doses), in conjunction with sequential testing over the multiple endpoints (see Section 9.8).
Sample Size and Power	The planned sample size is ~500 participants (128/arm for MK-8189 16 mg, MK-8189 24 mg, and placebo; 64 for risperidone 6 mg, and ~52 for MK-8189 8 mg). It is noted that the number of participants that will ultimately be randomized to the MK-8189 8 mg treatment arm is unknown before final database lock and unblinding. There is CCI probability that at least 1 of MK-8189 16 mg or MK-8189 24 mg will be superior to placebo as measured by the change in PANSS total score at Week 6 under the primary assumptions as provided in Table 11 with 128 participants randomized per arm.

9.2 Responsibility for Analyses/In-house Blinding

The final statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The official, final database will not be unblinded until after the final Week 12 visit has occurred.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

Primary Endpoint

The PANSS is a 30-item clinical-rated instrument for assessing the symptoms of schizophrenia. The CFB in the PANSS total score at Week 6 is the primary efficacy endpoint.

Key Secondary Endpoints

The 30-items within the PANSS may be categorized into 3 domains. One of these domains is the Positive Symptom Domain, with the sum of these items defined as the PANSS-PSS. The CFB in the PANSS-PSS score at Week 6 is a key secondary efficacy endpoint.

The CGI-S is a 7-point clinician-rated scale for assessing the global illness severity. The CFB in the CGI-S at Week 6 is a key secondary efficacy endpoint.

CFB for weight at Week 12 is considered as a key secondary endpoint.

Other Secondary Endpoints

CFB for weight at Week 6 is considered as a secondary endpoint.

Exploratory Endpoints

Analyses of the PANSS total score, PANSS-PSS, and CGI-S will also be conducted in an exploratory fashion at all other scheduled time points (with Week 6 already denoted as primary/ key secondary). Model-based analyses of weight will also be conducted in an exploratory fashion at all other scheduled time points (with Weeks 6 and 12 already denoted as secondary).

Unless otherwise noted, all other exploratory measures will be analyzed at all scheduled time points, including:

- The other domains from the PANSS, namely the PANSS-NSS and the PANSS-GSS and the PANSS Marder factor scores (positive symptom score, negative symptom score, disorganized thought symptom score, hostility/excitement symptom score, and anxiety/depression symptom score).

- The PSP is a clinician-rated scale that measures personal and social functioning in the domains of Socially useful activities, Personal and social relationships, Self-care, and Disturbing and aggressive behaviors. The change from baseline in PSP at Week 6 compared to placebo and at Weeks 6 and 12 compared to risperidone are tertiary efficacy endpoints.

Table 7 describes the directionality of improvement in efficacy measures.

Table 7 Directionality of Improvement in Efficacy Measures

Measurement	Direction of Improvement	Direction of Treatment Difference (vs. pbo) Indicating Favorable Efficacy
PANSS (and all subscales)	Decrease	Negative
CGI-S	Decrease	Negative
PSP	Increase	Positive

Measurement	Direction of Improvement	Direction of Treatment Difference (vs. pbo) Indicating Favorable Efficacy
CGI-S=Clinical Global Impression-Severity; PANSS=Positive and Negative Syndrome Scale; pbo=placebo; PSP=Personal and Social Performance Scale; vs=versus		

Most efficacy endpoints are derived as a function of subquestions/items (eg, the PANSS total score is calculated as the sum of 30 items). Details pertaining to the imputation and calculation of these total scores when one or more of the subquestions/items is missing are discussed in the sSAP.

The number and percent of participants showing a 30% response in PANSS total score %-response = ([postdose – baseline]/baseline) will be summarized by treatment group and time point.

It is noted that participants enrolled before Amendment 4 were administered the BAC, and that the BAC was defined as an exploratory endpoint. However, given the limited amount of data collected on the BAC before its removal at Amendment 4, no analyses will be presented for the BAC in the CSR.

9.4.2 Safety Endpoints

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

Responses on the C-SSRS are classified according to 11 prespecified categories (Ideation: Passive, Active-nonspecific, Active-method, Active-method and intent, and Active-method, intent and plan; Behavior: Preparatory actions or behaviors, Aborted attempt, Interrupted attempt, Suicide attempt, and Completed suicide; Nonsuicidal Self-Injurious Behavior). The most severe treatment-emergent event within each of 3 broad categories (suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior) reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it is either newly emerged or is more severe than the most severe event reported to have occurred in the study-defined pretreatment reference period.

The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements), global severity, and participant's awareness and distress related to said movements. Most items are scored on a 0 (none) to 4 (severe) basis.

The BARS rates objective and subjective components of akathisia (restlessness) using 3 items scored on 4-point scale (0 to 3): objective akathisia, subjective awareness of restlessness, and subjective distress related to restlessness. These 3 items may be summed to obtain a total score (ranging from 0-9). In addition, a global clinical assessment of akathisia assessment item is also present and is rated on a 0 to 5 scale. For all components, higher scores represent higher degrees of impairment.

The SAS evaluates symptoms of parkinsonism or parkinsonian side effects (including rigidity, tremor, akinesia, and salivation) using 10 items each on a 5-point scale (0 [normal] to 4 [most severe, according to description]). A total score will then be computed as the average of these 10 items.

In addition, composite AEs for dystonia, dyskinesia, akathisia, parkinsonism, and EPS will be analyzed.

9.4.3 Pharmacokinetic Endpoints

Descriptive statistics of PK parameters including AUC_{0-24}, C_{max}, and C_{24} will be derived. Plasma concentration values from P008 will also be added to historical MK-8189 data in ongoing efforts to build the population PK modeling for MK-8189 and may also be used in describing exposure-response relationships for efficacy and safety. The modeling results of MK-8189 will be reported separately from the clinical study report.

9.4.4 CCI

[redacted]

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population will be defined separately for each efficacy measure and consists of all randomized participants who:

- Receive at least 1 dose of study intervention
- Have a baseline measurement and at least 1 valid postrandomization observation for the analysis measurement after at least 1 dose of study intervention
    - for analyses-by-time point, a valid postrandomization observation is an observation which: 1) is within an analysis window 2) is in the treatment period corresponding to the analysis window (eg, observations in the Week 6 analysis window occurring after the first dose of extension study intervention will be excluded and thus do not grant inclusion into the analyses population) and 3) does not occur after the relevant window pertaining to either cessation of study intervention or initiation of prohibited medication (for those analyses in which such observations are to be excluded).

Participants will be included in the treatment arm to which they were randomized for the analysis of efficacy data using the FAS population.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention.

- For analyses conducted by time point, participants must have a baseline measurement and at least 1 valid posttreatment observation for the analysis measurement.
    - For analyses-by-time point, a valid posttreatment observation is an observation which is: 1) within the analysis window 2) in the treatment period corresponding to the analysis window, 3) does not occur after the relevant window pertaining to either cessation of study intervention or initiation of prohibited medication (for those analyses in which such observations are to be excluded).

Participants will be included in the treatment arm corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment arm to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment arm corresponding to the study intervention actually received.

9.5.3 Pharmacokinetic Analysis Populations

The PP Population will be used for the PK analyses. The PP 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 show 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 before 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 1 treatment (dose level) will be included in the PP dataset.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8. Nominal *p*-values and 95% CIs may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

The primary analysis for all efficacy endpoints will exclude any assessments obtained

- After initiation of prohibited psychotropic medication (eg, selected antipsychotics; see sSAP for complete handling)
- More than 5 days after study intervention discontinuation
- After premature unblinding of either the investigator or participant

Unless otherwise noted:

- The term “MK-8189” refers to the treatment arms “MK-8189 8 mg”, “MK-8189 16 mg”, and “MK-8189 24 mg” in the acute period and to the treatment sequences “MK-8189 8 mg/MK-8189 8 mg”, “MK-8189 16 mg/MK-8189 16 mg”, and “MK-8189 24 mg/MK-8189 24mg” in the extension period. It does not include the “Placebo/MK-8189 24 mg” arm.
- Tables in which only summary statistics are presented will include analyses for all 3 “MK-8189” doses (8 mg, 16 mg, and 24 mg), in addition to the risperidone and placebo treatment arms.
- Tables which include model-based analyses will exclude the MK-8189 8 mg treatment arm.

- Analyses involving baseline are with respect to the baseline assessment collected before the first dose of study intervention for the acute period. This is the case even when the analysis being conducted pertains to the extension period.

Basic summary statistics will be computed for all efficacy endpoints over time. This minimally includes means and standard deviations for continuous-type endpoints and counts and percents for categorical endpoints.

For the analysis of all continuous measures (including PANSS total score), a longitudinal ANCOVA model will be used to generate confidence intervals and p-values for change-from-baseline means within treatment as well as for change-from-baseline means between treatments. This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. CCI [redacted] In addition, the model will also include the interaction terms of week-by-treatment and week-by-baseline. The treatment difference in terms of the mean change from baseline at a given time point will be estimated, and as appropriate, tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger approximation will be used to compute the degrees of freedom [Kenward, M. G. and Roger, J. H. 1997].

Treatment comparisons, via confidence intervals and p-values, for each active treatment arm (MK-8189 16 mg, MK-8189 24 mg, risperidone) will be performed against placebo at Week 6. These statistics will also be separately provided for the comparison of each MK-8189 dose against risperidone for PANSS total score, PANSS-PSS, PANSS-NSS, CGI-S, and Weight at Week 6 and Week 12.

Model-based analyses pertaining to the acute period will only include data from the acute period, whereas model-based analyses pertaining to the extension period will use data from both the acute period and the extension period. This approach will reduce the potential for nonconvergence as a function of sparse data in the acute period analyses, which would require the removal of covariates. If the model does not converge for a given analysis, covariates will be removed one-by-one in the following order until convergence is achieved: cohort, stratum, gender, age, and duration of illness.

CCI [redacted]

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint	Approach[a]	Statistical Method[b]	Analysis Population	Missing Data Approach
Primary Hypothesis				
PANSS Total Score – CFB at Week 6	P	Longitudinal ANCOVA	FAS	Model-Based
	S	Longitudinal ANCOVA, assessments after prohibited medication initiation or SM cessation included	FAS	Model-Based
	S	Longitudinal ANCOVA, with Control-Based Mean Imputation	FAS	Model-Based
Key Secondary Endpoints				
PANSS-PSS Score – CFB at Week 6	P	Longitudinal ANCOVA	FAS	Model-Based
	S	Longitudinal ANCOVA, assessments after prohibited medication initiation or SM cessation included	FAS	Model-Based
	S	Longitudinal ANCOVA, with Control-Based Mean Imputation	FAS	Model-Based
CGI-S – CFB at Week 6	P	Longitudinal ANCOVA	FAS	Model-Based
	S	Longitudinal ANCOVA, assessments after prohibited medication initiation or SM cessation included	FAS	Model-Based
	S	Longitudinal ANCOVA, with Control-Based Mean Imputation	FAS	Model-Based
Weight at Week 12	P	Longitudinal ANCOVA	FAS	Model-Based
	S	Longitudinal ANCOVA, assessments after prohibited medication initiation or SM cessation included	FAS	Model-Based
	S	Longitudinal ANCOVA, with Control-Based Mean Imputation	FAS	Model-Based

ANCOVA=analysis of covariance; CFB=change from baseline; CGI-S=Clinical Global Impression-Severity; FAS=full analysis set; PANSS=Positive and Negative Syndrome Scale; PANSS-PSS= PANSS Positive subscale; SM=study medication.

[a] P=Primary; S=Supportive

[b] CCI [redacted]. In addition, the model will also include the interaction terms of week-by-treatment and week-by-baseline.

Two sensitivity analyses will be conducted for the primary and key secondary endpoints. These sensitivity analyses will not be conducted for any other endpoints.

CCI [redacted]

CCI [redacted]

The strategy to address multiplicity issues regarding multiple treatment comparisons, multiple efficacy endpoints and interim analyses is described in Section 9.7 and in Section 9.8.

Weight

For weight, 95% confidence intervals for the mean treatment difference (MK-8189 vs. placebo and MK-8189 vs. risperidone in the acute period and MK-8189 vs. risperidone in the extension period) in percent-change from baseline will be constructed using the primary efficacy ANCOVA model. CCI [redacted] It is noted that confidence intervals will only be produced for a given comparison if both treatment arms have at least 25 participants (~20% of the total sample size per arm).

9.6.2 Statistical Methods for Safety Analyses

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

Analyses will be conducted separately for the acute period and the extension period. Unless otherwise noted, all assessments and events within 14 days of the last dose of study medication from a given period will be included in the analyses for that period, noting that any assessments or events taking place after the first dose of extension study medication are precluded from being phased to the acute period.

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet PDLCs in laboratory, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

There are no Tier 1 events for this protocol as no inferential testing is planned.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (via the Miettinen and Nurminen method) [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 3% of participants (corresponding to 2 participants in the risperidone arm and 4 participants in the MK-8189 and placebo arms) in any treatment arm show the event. The threshold of at least 3% was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment arms of equal size each have less than 4 events (and when a treatment arm of half-allocation has less than 2 events) and thus would add little to the interpretation of potentially meaningful differences. To avoid overreporting, and since the final number of subjects that will ultimately be randomized to the curtailed MK-8189 8 mg arm is unknown (but is known to be smaller than all other arms), membership in Tier 2 for the MK-8189 8 mg arm requires at least 2 participants.

Because many 95% confidence intervals for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 3% or more of participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE that is both drug-related and serious, and discontinuation due to an AE will also be considered Tier 2 endpoints.

As mentioned in Section 9.4.2, composite AEs for dystonia, dyskinesia, akathisia, parkinsonism, and EPS will also be constructed. These composite AEs will be analyzed as Tier 2 AEs.

Since all CIs generated for safety analyses will be constructed as comparisons against placebo, and since the extension period does not have a placebo arm, no CIs will be provided for the extension period.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment arm are provided for Tier 3 safety parameters.

Categorical Safety Measures

C-SSRS

The percentage of participants with any treatment-emergent suicidal ideation or with any treatment-emergent suicidal behavior will be analyzed per the tiered analysis strategy outlined above, and will be considered as either Tier 2 or Tier 3 events, depending on the

number of participants with an event observed within each treatment group. Additionally, the 11 prespecified categories of suicidal ideation and behavior will be summarized. Participant counts (and cumulative counts) for each category will be based on the most severe treatment-emergent event observed during the assessment period.

In constructing the treatment-emergent C-SSRS analyses, a pretreatment reference period is required, from which a baseline score for each of the 3 categories (ideation, behavior, nonsuicidal self-injury) is derived. For this study, the baseline score for each of the 3 categories will be taken as the maximum score arising from the 2 predose C-SSRS administrations. The first predose administration references lifetime history. The second predose administration references the timeframe between the first and second predose administrations.

It is noted that the first predose administration is actually comprised of 2 separate administrations; one using lifetime as the reference period and another using fixed-time intervals (6 months for behavior and 2 months for ideation). The fixed-time administration is solely included for inclusion/exclusion purposes (noting that the contemporaneous maximum lifetime baseline score may not be less than the maximum fixed-time baseline score by definition).

BARS

The number and percent of participants with at least 2-point worsening on the BARS total score will be summarized by treatment group and time point.

In addition, the number and percent of participants transitioning from a baseline global score to a postdose global score will be summarized by treatment and time for the following transitions: (0 or 1) to (2 or 3), (0 or 1) to (4 or 5), and (2 or 3) to (4 or 5).

AIMS

Basic summary statistics for both the raw values and the change-from-baseline values will be provided by treatment and time point for the AIMS composite score (sum of Items 1-7; ranging from 0-28). Also, the number and percent of participants with at least a 2-point worsening on the AIMS composite score will be summarized by treatment group and time point.

In addition, the number and percent of participants transitioning from a baseline global score to a postdose global score will be summarized by treatment and time for the following transitions: (0 or 1) to 2, (0 or 1) to (3 or 4), and 2 to (3 or 4).

SAS

Basic summary statistics for both the raw values and the change-from-baseline values will be provided by treatment and time point for the total score (0 to 4).

In addition, the number and percent of participants with a total score ≥0.7 will be summarized by treatment group and time point.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment arm.

Though model-based analyses pertaining to weight are considered as efficacy analyses, the standard analyses for weight (change-from-baseline summary statistics and predetermined limits of change) will be considered as safety analyses. Of note, the predetermined limits of change are as follows: Increase of ≥7% and Decrease of ≥7%.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any serious AE	X	X
	Any drug-related AE	X	X
	Any serious and drug-related AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs and SOCs (incidence ≥3% participants in at least 1 treatment group)	X	X
	Composite AE of dyskinesia	X	X
	Composite AE of dystonia	X	X
	Composite AE of akathisia	X	X
	Composite AE of parkinsonism	X	X
	Composite AE of extrapyramidal symptoms	X	X
Tier 3	Specific AEs and SOCs (incidence <3% participants in all treatment groups)		X
	Change from baseline results (labs, ECGs, vital signs)		X
	BARS		X
	AIMS		X
	SAS		X
	C-SSRS		X

AE=adverse experience; AIMS=Abnormal Involuntary Movement Scale BARS=Barnes Akathisia Rating Scale; C-SSRS=Columbia Suicide Severity Rating Scale; CI=confidence interval; ECG=electrocardiogram; SAS=Simpson Angus Extrapyramidal Side Effects Scale; SOC=System Organ Class; X=results will be provided

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics.

The number and percent of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Baseline characteristics and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The number and percentage of participants transitioned from inpatient to outpatient will be summarized by week and treatment.

9.7 Interim Analyses

Two types of interim analyses may be performed in this study. Results will be reviewed by an eDMC.

The first type of interim analysis will be for safety only and will be conducted approximately every 4 to 6 months, with the frequency subject to change per eDMC recommendation.

The second type of interim analysis pertains to futility. This futility IA may be conducted at the discretion of the Sponsor, and, if conducted, will occur only once (though it is noted that the eDMC has the ability to request efficacy analyses at any time to assess the benefit-risk profile). If conducted, this IA will be conducted when ~50% of the randomized participants in the MK-8189 16 mg, MK-8189 24 mg, and placebo treatment arms (N~=64/arm) are estimated to have had the opportunity to treat for 6 weeks. Futility may be declared if the BPCP for both primary hypotheses is less than 10%.

The endpoints, timing, and purpose of the interim analyses are summarized in Table 10.

Table 10 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Safety Endpoints as requested by eDMC	Interim safety analyses will be reviewed initially every 4-6 months (approximately) by the eDMC. The eDMC may change the frequency of these analyses based on the results of these analyses.	Safety
Week 6 CFB in PANSS Total Score	If conducted, the futility IA will be conducted when ~50% of the randomized participants in the MK-8189 16 mg, MK-8189 24 mg, and placebo treatment arms (N=~64/arm) are estimated to have had the opportunity to treat for 6 weeks.	Assess futility

CFB=change from baseline; eDMC=external Data Monitoring Committee; IA=interim analysis; PANSS=Positive and Negative Syndrome Scale

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators before the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no responsibilities associated with the conduct or design of the study.

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Treatment-level results from the interim analysis will be provided to the eDMC by the unblinded statistician. Before final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits. This approach to include all available information is in line with the ICH-E9 guideline, the ITT principle and the CHMP guideline on adaptive designs.

Should the futility IA be conducted, then the decision of whether to terminate the study for futility will be based on the BPCP, ie, the likelihood of correctly detecting a treatment difference at the end of the study given the results at the interim, corresponding to the primary hypotheses. The BPCPs will be computed assuming that the observed trend at the interim will continue to the end of the study. Details pertaining to the computation of the BPCPs are included in the sSAP.

Consideration may be given to terminate the study for futility if the BPCP for the primary endpoint for both doses is less than 10%. The probability of incorrectly stopping the study, β, at the IA would be approximately 1% under the primary set of assumptions.

The usefulness of the futility criterion may be assessed by examining the probability of terminating the study in the presence of a no or a nonmeaningful drug effect. Assuming no treatment effect for both doses results in a 40.2% probability of terminating the study at the futility IA and assuming a 1-point treatment effect for both doses (thought to not be clinically meaningful), results in a 29.2% probability of terminating the study at the futility IA.

9.8 Multiplicity

Since there are 2 active doses (MK-8189 16 mg and MK-8189 24 mg) and 4 endpoints (PANSS vs. Placebo at Week 6, PANSS-PSS vs. Placebo at Week 6, CGI-S vs. Placebo at Week 6, Weight vs. Risperidone at Week 12) on which strong control is desired, there are 8 total hypotheses on which strong Type 1 error control must be maintained at a familywise

α=0.05 level. This control will be achieved by utilizing a Bonferroni approach in conjunction with a closed testing sequential approach. Specifically, a separate hypothesis family will be created for each of MK-8189 16 mg and MK-8189 24 mg. Each family will be comprised of 4 hypotheses corresponding to the primary endpoint and the 3 key secondary endpoints. Using a Bonferroni approach, each family will be tested independently at the α=0.025 level (two-sided).

Within each of the 2 dose families, the primary hypothesis will be tested at a two-sided

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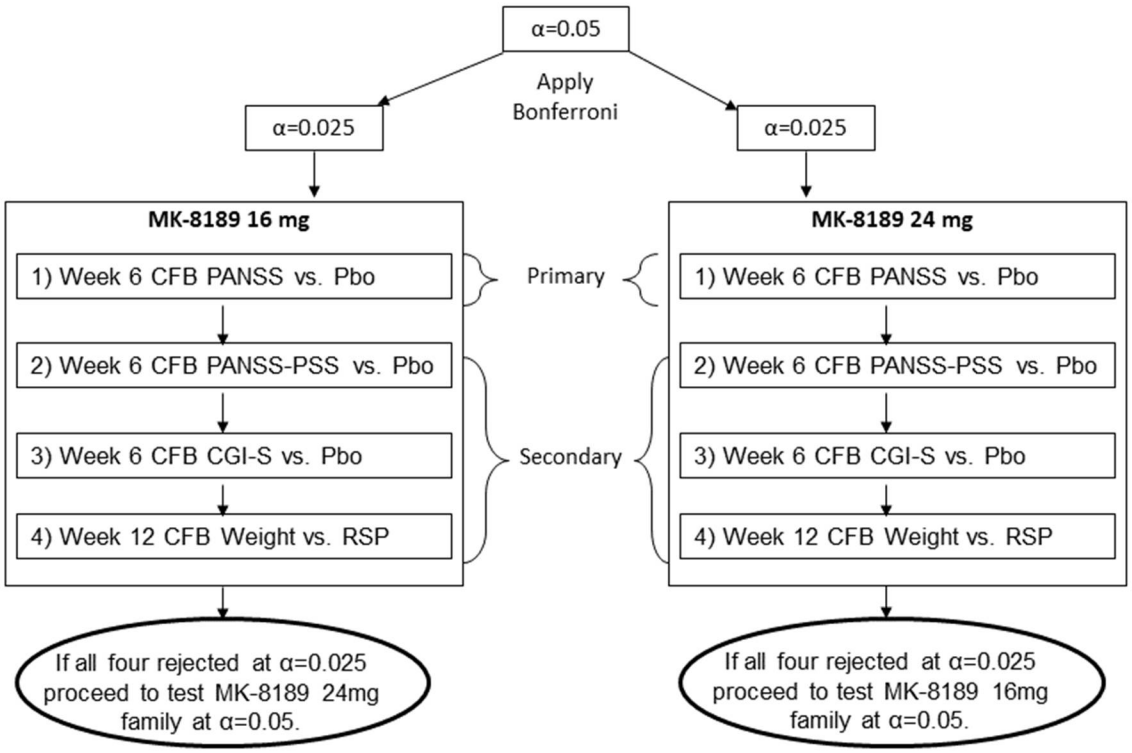
[redacted]

Figure 2 Testing Strategy to Address Multiplicity



CFB=change from baseline; CGI-S=Clinical Global Impression-Severity; PANSS=Positive and Negative Syndrome Scale; PANSS-PSS= PANSS Positive subscale; Pbo=placebo; RSP=risperidone

9.9 Sample Size and Power Calculations

9.9.1 Efficacy Parameter Estimates

Parameter estimates and other required assumptions were primarily based on data from MK-8189 P005, which featured a 4-week acute period and a 12-mg dose of MK-8189. Since the primary endpoints for the current study pertain to the 16-mg and 24-mg doses (at which efficacy higher than 12 mg is assumed) at Week 6 (at which efficacy higher than Week 4 is assumed), assumptions about the effect of dose and time were required. Details pertaining to the derivation of the parameter assumptions are in the sSAP. Table 11 displays the assumed Week 6 CFB treatment differences (MK-8189 – Placebo). This table also displays the assumed Week 6 CFB standard deviations.

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9.9.2 Efficacy Sample Size and Power Calculations

Sample size was determined based on the PANSS total score. Power was estimated via simulations which took the 1 planned futility IA into account, using a futility bound of 10%. Sample size was computed using the multiplicity approach outlined in Section 9.8 to have at least 90% power to reject the null hypothesis for at least 1 dose (MK-8189 16 mg or MK-8189 24 mg).

Table 12 provides the probability of declaring success on at least 1 dose (16 mg and/or 24 mg) and at each dose separately for a variety of underlying assumptions with 128 randomized participants per arm. With 128 randomized participants per arm, there is approximately a 91% probability of declaring success on PANSS total score for at least 1 dose under the primary assumptions.

All sample size and power calculations have been conducted assuming that 65% of randomized participants will have a Week 6 efficacy measurement.

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Using the assumptions provided in Table 11, marginal power calculations for the PANSS-PSS and CGI-S were computed (not simulated) and are presented in Table 13. These marginal calculations do not incorporate the sequential nature of the multiplicity approach over the endpoints nor do they incorporate the potential futility analysis.

In a similar fashion, marginal power calculations for weight were computed (not simulated) and are presented in Table 14. It is noted that power calculations are provided assuming 2 different completer rates (65% and 50%), meant to approximate the percentage of completers at Week 6 and Week 12 respectively. It is also noted that the power calculation corresponding to the Week 12 completion rate was computed using a 2:1 sample size ratio (since risperidone is the comparator).

As noted in Figure 2, testing will only proceed to the respective key secondary hypotheses if all null hypotheses preceding the given hypotheses are successfully rejected. Therefore, the actual probabilities corresponding to the key secondary hypotheses are lower than the corresponding presented marginal probabilities.

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9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the primary endpoint (PANSS total score) and key secondary endpoints (PANSS-PS, CGI-S, and Weight) will be estimated and plotted within each category of each subgroup. The primary model will be used for all subgroup analyses, applied to the given subset of participants. It is noted that some of the covariates in the primary model may need to be removed either of necessity (eg, removing gender from the model when analyzing the male subgroup) or to facilitate convergence (in which case terms will be removed in the same order as that specified for the primary analysis). Confidence intervals will only be produced if both treatment arms have at least 25 participants (~ 20% of the total sample size per arm).

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In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

9.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study intervention taken by each participant, the number tablets/capsules remaining in study packaging will be counted, reviewed, and recorded at regular intervals. Study intervention records will be used to calculate participant compliance.

A day within the study will be considered an "On-Therapy" day if the participant takes the required number of tablets/capsules of each type as noted in Section 6.6. It is noted that a participant will be considered as "On Therapy" for a given day if they took the correct number of tablets/capsules, even if the tablets/capsules taken were intended for a different study day (eg, during 1 of the titration weeks). Therefore, it is possible for a participant to be considered as "On Therapy" for a given day, even if the participant mistakenly took incorrect study intervention on that day.

For a participant who is followed for the entire study period, the "Number of Days Should be On Therapy" is the total number of days from randomization to the last day of treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be On Therapy" is the total number of days from randomization to the date of the last dose of study intervention.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the APaT population.

9.12 Extent of Exposure

The extent of exposure to study intervention will be evaluated by summary and cumulative frequencies by treatment group or treatment sequence.

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)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 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.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 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.

10.1.9 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.

10.1.10 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 15 will be performed by the central laboratory.

Use of local vs. central laboratory test results:

- If a local sample is required for timely decision-making, then a sample for central analysis should be obtained at the same time. Local laboratory results should be entered into the relevant CRF if a central result is not available.

- In the event of unforeseen issues leading to delayed or missing screening laboratory samples, duplicate laboratory specimens may be collected, with 1 specimen being sent to the local laboratory for immediate analysis of all screening parameters and the other processed at the central laboratory. The local laboratory results will be used as a guide to determine participant eligibility.

- At any time during the study, if the investigator determines that immediate local laboratory results for protocol-specified parameters are needed to further evaluate the participant's condition, a duplicate set of sample(s) should be collected and sent to the central laboratory.

Screening/Baseline laboratory notes:

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.

- Screening laboratory tests are not to be repeated if the initial tests results meet the exclusionary criteria. For example, if the screening eGFR is <50 mL/min/1.73m^2 (CKD-EPI formula), the laboratory test is not repeated, and participant is a screen failure.

- If screening insulin values are still pending at time of the planned baseline visit, and the investigator considers the pending insulin value unnecessary to judge participant eligibility, the investigator may go forward with the baseline visit and potential randomization with insulin values pending.

- Fasting blood draws at screening are encouraged.

Additional notes:

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- It is anticipated that laboratory blood samples should be obtained fasting while the participant is an inpatient. For outpatients, they will be instructed and encouraged to fast overnight before clinical laboratory sample collection. Note that it is recognized that samples may be collected in a nonfasting state. The self-reported

fasting/nonfasting state of the participant will be noted on the laboratory requisition form (ie, no food or drink other than water ≥10 hours is considered fasting).

- In the event of a positive or ambiguous urine test for pregnancy, refer to Sections 10.5 and 7.1.

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- A participant must be discontinued if the participant has a persistent eGFR of <40 mL/min/1.73m^2 as measured by CKD-EPI formula (see Section 7.1). eGFR of <40 mL/min/1.73m^2 is considered persistent if the values are met for 2 consecutive blood draws at 2-week intervals. If an eGFR of <40 mL/min/1.73m^2 is met at the baseline visit (V2), an unscheduled blood sample should be collected at Visit 4 and sent to central laboratory for analysis.

- Prolactin values are masked post baseline. The investigator will be alerted by the central laboratory if a postbaseline value is >10X ULN. If the investigator finds it necessary to unmask a prolactin value to understand an AE (ie, those potentially associated with prolactin dysregulation), the investigator may contact central laboratory to be provided with prolactin value. Requests for actual prolactin values are to be recorded in the source documents.

- Prolactin levels are not to be determined by local laboratory testing. The prohibition in local prolactin level testing is in place until the follow-up period is completed.

- Note: follow-up visits will run concurrently with routine scheduled visits if participants continue with study visits after last dose (see Section 8.10.3). The prohibition in local prolactin level testing is lifted after the participant completes the follow-up period.

Table 15 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	White blood cell (WBC) count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
	Red blood cell (RBC) Count		
	Hemoglobin		
	Hematocrit		
Chemistry	Blood Urea Nitrogen (BUN) Potassium Sodium Chloride Bicarbonate Creatinine eGFR (CKD-EPI formula) Phosphorous Magnesium Calcium Creatine Phosphokinase (CK)	AST/SGOT ALT/SGPT Albumin Total protein Alkaline phosphatase Lactate Dehydrogenase Total bilirubin Direct bilirubin, if total bilirubin is elevated above the upper limit of normal	Glucose (fasting) • Lipid Panel: • Total cholesterol • High Density Lipoproteins • (HDL) • Low Density Lipoproteins • (LDL) • Triglycerides • Insulin Prolactin (postbaseline results to be masked)
Urinalysis	• Specific gravity • pH, glucose, protein, blood (RBC count), ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if macroscopic examination is abnormal, i.e., blood or protein is abnormal), includes casts, crystals, epithelial cells, RBC, WBC • Albumin to creatinine ratio		
Other Screening Tests	• FSH (as needed in women of nonchildbearing potential only) • Highly sensitive serum or urine β-human chorionic gonadotropin • (hCG) pregnancy test (as needed for WOCBP) • HbA1c • TSH • Free Thyroxine (T4) (if reflex Thyroid-stimulating hormone [TSH] is abnormal) • Urine alcohol and drug screen includes: • Amphetamines • Barbiturates • Benzodiazepines (Urine) • Cannabinoids		

Laboratory Assessments	Parameters
	• Cocaine Metabolites • Methadone • Opiates • Phencyclidine • Propoxyphene • Separate test for ETG/alcohol run centrally. • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus [HCV] antibody) • Serologies are at the discretion of the investigator

10.2.1 Alcohol and Drug Screen

Provided there is no exclusionary evidence of moderate to severe substance use disorder (Section 5.2), a positive finding of alcohol, cannabinoid drugs, or prohibited psychotropic medications at screening will not necessarily exclude the participant from the study. However, the investigator should interview the participant and ensure that the participant understands that they must refrain from using cannabinoid drugs and prohibited psychotropic medications throughout the study. Alcohol use during the study should also be discouraged. This discussion must be noted in the source documents or on the laboratory report. The investigator may enroll the participant if they feel confident that the participant will comply with instructions. Additional tests may be scheduled postscreening at the discretion of the investigator. If a participant is considered to be under the influence of illegal drugs or is believed to have taken a prohibited psychoactive drug, or if they meet the DSM-5™ criteria for substance use disorder (excluding nicotine) within a 1-week period, the investigator may consider the participant for discontinuation.

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

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

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

10.3.4 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity

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

Assessment of causality

- Did the 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.

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[c,d] IUS[c,e] Non-hormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormonal contraception[c,d] - Oral - Injectable
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - abstinence (any method), withdrawal (coitus interruptus), Periodic spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

After the initiation of treatment, additional pregnancy testing will be performed according to the SoA, and as required locally.

Additional pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

(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.

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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/
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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AAPs	atypical antipsychotics
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BPCP	Bayesian predictive conditional probability
C24	plasma concentration at 24 hours
CAC	Clinical Adjudication Committee
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CGI-S	Clinical Global Impression-Severity of Illness
cGMP	cyclic guanosine monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum plasma concentration
CNS	central nervous system
CRF	Case Report Form
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
C-VISA™	Clinical Validation Inventory for Study Admission
CYP	Cytochrome P450

Abbreviation	Expanded Term
DC	discontinuation; visit when participant discontinues from the study after end of treatment
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECT	electroconvulsive therapy
EDC	electronic data collection
eDMC	external Data Monitoring Committee
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EO	enzyme occupancy
EOC	Executive Oversight Committee
EOT	end of treatment; visit when participant discontinues from study intervention
EPS	extrapyramidal symptoms
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1C
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure

Abbreviation	Expanded Term
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	Lactational Amenorrhea Method
LDL	low density lipoprotein
LFT	liver function test
LOCF	Last Observation Carried Forward
MAD	multiple ascending dose
MAO	monoamine oxidase
MINI	Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders
NDA	New Drug Application
PANSS	Positive and Negative Syndrome Scale
PANSS-GSS	PANSS General Psychopathology subscale
PANSS-NSS	PANSS Negative subscale
PANSS-PSS	PANSS Positive subscale
PCL	Protocol Clarification Letter
PDE10A	phosphodiesterase 10A
PDLC	predefined limits of change
PET	positron emission tomography
PI	primary investigator
PK	pharmacokinetic
POC	proof of concept

Abbreviation	Expanded Term
PP	per protocol
PR	pulse rate
PSP	Personal and Social Performance Scale
qd	once a day
QRS	QRS complex
QTc	Heart rate-corrected QT interval
QTcF	Fridericia formula
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAD	single ascending dose
SAE	serious adverse event
SAS	Simpson Angus Extrapyramidal Side Effects Scale, Statistical Analysis System
SDE	Sponsor-designated expert; medically qualified Sponsor representative who consults with sites on protocol-specific activities, such as the review of the screening C-VISA™ and PANSS to verify participant eligibility. An “external” SDE refers to a vendor SDE.
SLAB	Supplemental laboratory case report form
SoA	schedule of activities
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TC	telephone or virtual contact
TM	trademark
TSH	thyroid-stimulating hormone
UDS	urine drug screen
ULN	upper limit of normal
US	United States
V	visit
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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