Official Protocol Title:	A 2-Part Randomized Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Alternate MK-8189 Titration Regimens in Young Adult Participants With Schizophrenia and to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Elderly Participants With Schizophrenia and Healthy Elderly
NCT number:	NCT04506905
Document Date:	20-May-2021

Title Page

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This protocol amendment is applicable only to United States.

Protocol Title: A 2-Part Randomized Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Alternate MK-8189 Titration Regimens in Young Adult Participants With Schizophrenia and to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Elderly Participants With Schizophrenia and Healthy Elderly

Protocol Number: 011-05

Compound Number: MK-8189

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

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

Regulatory Agency Identifying Number(s):

IND	118,986

Approval Date: 20 May 2021

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
Protocol Amendment 05	20-MAY-2021	Inclusion of healthy elderly participants in additional panels (Panel F and Panel G) to support future development of MK-8189.
Protocol Amendment 04	08-MAR-2021	The rationale for the Amendment is to add flexibility to dose a smaller cohort (n=8) of participants in Panel D to assess initial tolerability in elderly participants and inform titration regimen in Panel E.
Protocol Amendment 03	10-FEB-2021	The rationale for the Amendment is to modify contraceptive language to align with an FDA request.
Protocol Amendment 02	21-JAN-2021	The rationale for the Amendment is to modify maximum blood volume collected per participant to account for potential additional volume needed to be drawn and discarded prior to collection of sample when a catheter is used.
Protocol Amendment 01	09-SEP-2020	The rationale for the Amendment is to address health authority feedback to modify screening QTc interval criteria such that only participants with a QTc interval of ≤450 msec be included in the current protocol.
Original Protocol	05-MAY-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Addition of healthy elderly panels (Panel F and Panel G) to support future development of MK-8189.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 3 Hypotheses, Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 5 Study Population 6.1 Study Intervention Administered 6.3.1 Intervention Assignment 8.10.2 Treatment Period	Details for the addition of Panel F and Panel G in this amendment were added to applicable sections of the protocol. Panel F and G will be conducted in the same manner as Panel D and Panel E, respectively.	Panel F and Panel G will enroll healthy elderly participants to evaluate the safety, tolerability and pharmacokinetics of MK-8189 in healthy elderly participants.

Section # and Name	Description of Change	Brief Rationale
9.3 Hypotheses/Estimation 9.4 Analysis Endpoints 9.6 Statistical Methods 10.8 Appendix 8: Blood Volume Table		
2.2.2 Preclinical and Clinical Studies	Added final, unblinded data from P007.	PN 007 is complete.
2.2.3 Ongoing Clinical Studies	Added preliminary blinded safety data from ongoing P011.	Part 1 of PN 011 is clinically complete. Preliminary blinded safety data from adult patients with schizophrenia provides information to support the evaluation of titration regimens in elderly participants
4.1 Overall Design	Randomization ratio has been deleted from this section.	The randomization ratio has been deleted to minimize treatment allocation information provided to trial site.

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LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 2-Part Randomized Clinical Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Alternate MK-8189 Titration Regimens in Young Adult Participants With Schizophrenia and to Evaluate the Safety, Tolerability and Pharmacokinetics of MK-8189 in Elderly Participants With Schizophrenia and Healthy Elderly

Short Title: Evaluation of MK-8189 Alternate Titration Regimens and Elderly Pharmacokinetic Study

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

In male or female participants with schizophrenia (young adults and elderly) and healthy elderly participants:

Primary Objectives	Primary Endpoints
Part 1 - To evaluate the safety and tolerability of MK-8189 oral, once-daily titration regimens in young adult participants with schizophrenia Part 2 - To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in elderly participants with schizophrenia and healthy elderly participants	Part 1 and Part 2 - Adverse experiences, laboratory safety tests, electrocardiograms and vital signs
Secondary Objectives	Secondary Endpoints
Part 1 - To characterize MK-8189 pharmacokinetics following different titration regimens in young adult participants with schizophrenia Part 2 - To characterize the pharmacokinetics of MK-8189 following multiple once-daily oral doses in elderly participants with schizophrenia and healthy elderly participants	Part 1 and Part 2 - AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd and apparent t1/2

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of schizophrenia
Population	Young adult and elderly participants with schizophrenia and healthy elderly participants
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 13 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 100 total participants may be allocated/randomized in Part 1 (n=28, actual sample size as Part 1 is clinically complete) and Part 2 (n ~72). In Part 1, approximately 16 evaluable participants with schizophrenia will complete a generally well-tolerated dose titration.

In Part 2, the intent is to evaluate up to 2 panels of elderly participants with schizophrenia (Panel D and Panel E) and up to 2 panels of healthy elderly participants (Panel F and Panel G).

Up to approximately 16 participants may be enrolled in Panel D and up to approximately 24 participants may be enrolled in Panel E to ensure approximately 16 elderly participants with schizophrenia complete a generally well-tolerated dose titration. Up to approximately 12 participants will be enrolled in Panel F and up to approximately 20 participants will be enrolled in Panel G to ensure approximately 12 healthy elderly participants complete a generally well-tolerated dose titration as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Adminis-tration	Panel/ Regimen	Use
Part 1 Active[a]	MK-8189	4 mg and 12 mg	QD	Oral	**Panel A** **Titration Regimen 1**: 12 mg x 1 tablet & 4 mg x 1 tablet Days 1-3; 12 mg x 2 tablets Days 4-7 AND **Panel B** **Titration Regimen 2**: 12 mg x 2 tablets Days 1-7 OR **Panel C** **Titration Regimen 3**: 4 mg x 2 tablets Day 1; 12 mg x 1 tablet & 4 mg x 1 tablet Day 2; 12 mg x 2 tablets Days 3-7	Experi-mental
Part 1 Placebo[a]	Placebo	N/A	QD	Oral	**Panel A** **Titration Regimen 1**: 12 mg x 1 tablet & 4 mg x 1 tablet Days 1-3; 12 mg x 2 tablets Days 4-7 AND **Panel B** **Titration Regimen 2**: 12 mg x 2 tablets Days 1-7 OR **Panel C** **Titration Regimen 3**: 4 mg x 2 tablets Day 1; 12 mg x 1 tablet & 4 mg x 1 tablet Day 2; 12 mg x 2 tablets Days 3-7	Control
Part 2[b] Active	MK-8189	4 mg and 12 mg	QD	Oral	**Panel D and Panel F** 4 mg x 2 tablets Days 1-3; 12 mg x 1 tablet & 4 mg x 1 tablet Days 4-6; 12 mg x 2 tablets Days 7-13	Experi-mental

						<u>Panel E and Panel G</u> **Titration Regimen 1**: 12 mg x 1 tablet & 4 mg x 1 tablet Days 1-3; 12 mg x 2 tablets Days 4-10 OR **<u>Panel E and Panel G</u>** **Titration Regimen 2**: 12 mg x 2 tablets Days 1-7 OR **<u>Panel E and Panel G</u>** **Titration Regimen 3**: 4 mg x 2 tablets Day 1; 12 mg x 1 tablet & 4 mg x 1 tablet Day 2; 12 mg x 2 tablets Days 3-9	
	Part 2[b] Placebo	Placebo	N/A	QD	Oral	**<u>Panel D and Panel F</u>** 4 mg x 2 tablets Days 1-3; 12 mg x 1 tablet & 4 mg x 1 tablet Days 4-6; 12 mg x 2 tablets Days 7-13 **<u>Panel E and Panel G</u>** **Titration Regimen 1**: 12 mg x 1 tablet & 4 mg x 1 tablet Days 1-3; 12 mg x 2 tablets Days 4-10 OR **<u>Panel E and Panel G</u>** **Titration Regimen 2**: 12 mg x 2 tablets Days 1-7 OR **<u>Panel E and Panel G</u>** **Titration Regimen 3**: 4 mg x 2 tablets Day 1; 12 mg x 1 tablet& 4 mg x 1 tablet Day 2; 12 mg x 2 tablets Days 3-9	Control

Abbreviations:

QD = Once a day

a Following completion and review of safety and tolerability data of Panel A, only Panel B or C will be conducted.

b The titration regimen selected for Panel E and Panel G will be based on safety and tolerability data from Part 2 Panel D and Panel F, respectively, as well as Part 1 safety and tolerability data.

Total Number of Intervention Groups/ Arms	2 intervention groups
Duration of Participation	Part 1 Each participant in Panel A and Panel B or C will participate in the study for approximately 7 weeks from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of approximately 4 weeks, including a washout period of approximately 1 week, each participant will receive assigned intervention for 1 week. After the end of treatment, each participant will be followed for 2 weeks. Part 2 **Panel D/Panel F**: Each participant will participate in the study for approximately 8 weeks from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of approximately 4 weeks, including a washout period of approximately 1 week, each participant will receive assigned intervention for 2 weeks. After the end of treatment each participant will be followed for 2 weeks. **Panel E/Panel G**: Each participant will participate in the study for approximately 7 weeks (Titration Regimen 2) or 7.5 weeks (Titration Regimens 1 and 3) from the time the participant signs the Informed Consent Form through the final contact. After a screening phase of approximately 4 weeks, including a washout period of approximately 1 week, each participant will receive assigned intervention for 1 week (Titration Regimen 2) or 1.5 weeks (Titration Regimens 1 and 3). After the end of treatment each participant will be followed for 2 weeks.

Study Governance Committees:

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

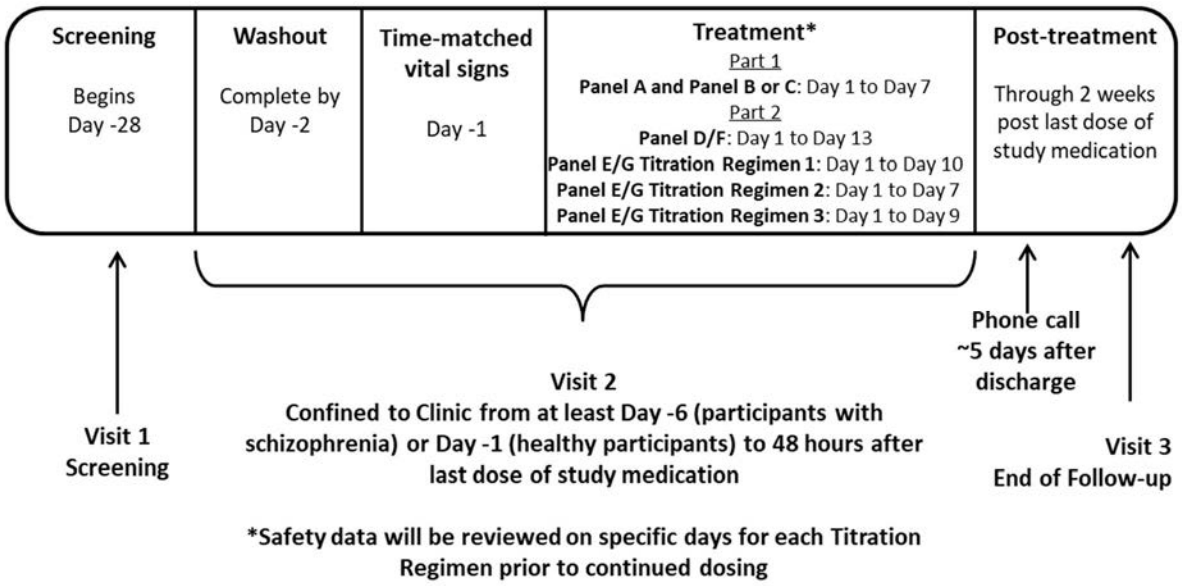
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 12.

1.2 Schema

The study design is depicted in [Figure 1].

Figure 1 Study Schema for Part 1 and Part 2



1.3 Schedule of Activities

1.3.1 Schedule of Activities: Part 1 (Panel A and Panel B or C)

Part 1 (Panel A and Panel B or C)																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~ 14		
Administrative Procedures																
Informed Consent	X															Section 8.1.1
Informed Consent for Future Biomedical Research	X															Section 8.1.1.2
Inclusion/Exclusion Criteria	X			X												Only specific criteria will be reviewed prior to randomization. Section 5
Participant Identification Card	X															Section 8.1.3
Medical History (includes psychiatric history and substance usage)	X															Substances: drugs, alcohol, and caffeine Section 8.1.4
Prior/Concomitant Medication Review	X----------														----------X	Section 8.1.5
Washout from Antipsychotics		X	X													Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. Section 8.1.5.1
Assignment of Allocation Number (Randomization)					X											Section 8.1.7
MK-8189/Placebo Administration					X	X	X	X	X	X	X					Sections 6.3.1 and 8.1.8
Standard Meals[a]				X	X	X	X	X	X	X	X	X				Section 5.3.1
Domiciling in Clinic[b]		X----------											----------X			Section 8.1.11
Follow-up Phone Call														X		
Safety Procedures																
Full physical examination	X			X									X		X	Section 8.3.1
Height	X															Section 8.3.1

Part 1 (Panel A and Panel B or C)																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~ 14		
Weight	X				X								X		X	Section 8.3.1
Full Neurological Exam	X			X												Section 8.3.7 and Appendix 11
Targeted Neurological Exam						X			X				X		X	Section 8.3.7 and Appendix 11
Vital Signs (heart rate, blood pressure)[c]	X			X	X	X	X	X			X		X		X	Section 8.3.2 and Section 8.3.2.1
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X	X	X	X	X			X		X		X	Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X				X			X					X		X	Section 8.3.2 and Section 8.3.2.1
12-lead Electrocardiogram[f]	X				X			X					X		X	Section 8.3.3
Serum β-hCG (WOCBP only)	X															Appendix 2
Urine Pregnancy Test (WOCBP only)[g]				X												Section 5.1
Serum FSH (WONCBP only)	X															Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X															Appendix 2
UDS/BDS (per site SOP)[h]	X			X												Appendix 2
Laboratory Safety Test (hematology, chemistry, urinalysis)[e]	X			X							X		X		X	Appendix 2
Columbia Suicide Severity Rating Scale (C-SSRS)-Baseline Version	X															Section 4.2.3
Columbia Suicide Severity Rating Scale (C-SSRS)-Since Last Assessment Version[e]				X		X			X				X		X	Section 4.2.3
Barnes Akathisia Rating Scale (BARS)[e, i]				X		X			X				X		X	Section 4.2.1.1

Part 1 (Panel A and Panel B or C)																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~ 14		
Abnormal Involuntary Movement Scale (AIMS)[e, i]				X		X			X				X		X	Section 4.2.1.1
Simpson Angus Scale (SAS)[e, i]				X		X			X				X		X	Section 4.2.1.1
Bond and Lader Visual Analog Scale (VAS)[e]				X		X			X				X		X	Section 4.2.1.1
Brief Psychiatric Rating Scale (BPRS)[e]	X			X		X			X				X		X	Section 4.2.1.1
AE/SAE review	X----------														----X	Section 8.4
Pharmacokinetics																
Blood for Plasma MK-8189 and/or Metabolites Assay[j]					X	X	X	X			X	X	X			Section 8.6.1
Biomarkers																
Blood for Genetic Analysis[k]					X											Collect predose from enrolled participants only. Section 8.8

AE=adverse event; BDS=blood draw screen; FSH=follicle stimulating hormone; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Meals should be given at approximately the same time every day starting on Day -1 through Day 8. Day -1 will be time-matched to Day 1. Breakfast will be given at ~ 1-hour postdose, lunch given at ~ 4-hours postdose, a snack given at ~ 8-hours postdose and dinner at ~ 12-hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

b. Participants will be confined minimally from Day -6 until Day 9 procedures are complete.

c. Single HR and BP measurements will be obtained at all timepoints unless otherwise noted. On the following days, specific timepoints are noted:

- Panel A and Panel B:
  - Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs.
  - Day 1, Day 4 and Day 7: 8, 16 and 24 hours postdose
  - Day 9: Time-matched to 24-hour postdose vital signs
- Panel C
  - Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs.
  - Day 1, Day 2, Day 3 and Day 7: 8, 16 and 24 hours postdose
  - Day 9: Time-matched to 24-hour post dose vital signs

d. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Participants should be standing for approximately 2 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:

- Panel A and Panel B:

Part 1 (Panel A and Panel B or C)																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~ 14		

- Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs.
- Day 1, Day 4 and Day 7: 8, 16 and 24 hours postdose
- Day 9: Time-matched to 24-hour post dose orthostatic vital signs

- Panel C
  - Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs.
  - Day 1, Day 2, Day 3 and Day 7: 8, 16 and 24 hours postdose
  - Day 9: Time-matched to 24-hour post dose orthostatic vital signs

e. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.
f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:
- Day 1: Triplicate measurements within 2 hours prior to dosing
- Day 1 and Day 4: 8, 16 and 24 hours post-dose

g. In the event the urine pregnancy test is positive or cannot be confirmed negative, a serum pregnancy test will be required.
h. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
i. Additional BARS, AIMS and SAS assessments will be conducted as soon as possible when there are observed or reported complaints of dystonia and/or akathisia (See Section 8.3.6).
j. MK-8189 plasma PK sample collection:
- Panel A:
  - Day 1 and Day 4: predose, 2, 6, 8, 10, 12, 16 and 24 hours postdose
  - Day 7: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
- Panel B:
  - Day1: predose, 2, 6, 8, 10, 12 and 16 hours postdose
  - Day 2 and Day 3: predose, 2, 6 and 8 hours postdose
  - Day 7: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
- Panel C:
  - Day 1 and Day 2: predose, 2, 6, 8, 10, 12 and 16 hours postdose
  - Day 3: predose, 2, 6, 8, 10, 12, 16 and 24 hours postdose
  - Day 7: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
- Optional sample when signs of dystonia and/or akathisia occur.
- Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.

k. This sample will be drawn for CYP2C9 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research.

1.3.2 Schedule of Activities: Part 2 (Panel D/Panel F)

Part 2 Panel D/Panel F																					
	Screening	Washout		Intervention																Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	~20		
Administrative Procedures																						
Informed Consent	X																					Section 8.1.1
Informed Consent for Future Biomedical Research	X																					Section 8.1.1.2
Inclusion/Exclusion Criteria	X			X																		Only specific criteria will be reviewed prior to randomization. Section 5
Participant Identification Card	X																					Section 8.1.3
Medical History (includes psychiatric history and substance usage)	X																					Substances: drugs, alcohol and caffeine Section 8.1.4
Prior/ Concomitant Medication Review	X----------X																					Section 8.1.5
Washout from Antipsychotics (Panel D only)		X	X																			Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. Section 8.1.5.1

Part 2 Panel D/Panel F																					
	Screening	Washout		Intervention																Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	~20		
Assignment of Allocation Number (Randomization)					X																	Section 8.1.7
MK-8189/ Placebo Administration					X	X	X	X	X	X	X	X	X	X	X	X	X					Sections 8.1.8 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 5.3.1
Domiciling in Clinic[b]		X----------X																				Section 8.1.11
Follow-up Phone Call																				X		
Safety Procedures																						
Full physical examination	X			X															X		X	Section 8.3.1
Height	X																					Section 8.3.1
Weight	X			X															X		X	Section 8.3.1
Full Neurological Exam	X			X																		Section 8.3.7 and Appendix 11
Targeted Neurological Exam						X			X			X				X			X		X	Section 8.3.7 and Appendix 11
Vital Signs (heart rate, blood pressure)[c]	X			X	X			X			X						X		X			Section 8.3.2 and Section 8.3.2.1
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X	X			X			X						X		X			Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X				X						X						X		X		X	Section 8.3.2 and Section 8.3.2.1
12-lead ECG[f]	X				X			X			X						X		X		X	Section 8.3.3

Part 2 Panel D/Panel F																					
	Screening	Washout		Intervention																Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	~20	
Serum β-hCG (WOCBP only)	X																				
Urine Pregnancy Test (WOCBP only)				X																	
Serum FSH (WONCBP only)	X																				Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X																				Appendix 2
UDS/BDS (per site SOP)[g]	X			X																	Appendix 2
Laboratory Safety Test (hematology, chemistry, urinalysis)[e]	X			X				X											X	X	Appendix 2
Columbia Suicide Severity Rating Scale(C-SSRS)-Baseline Version	X																				Section 4.2.3
Columbia Suicide Severity Rating Scale (C-SSRS)-Since Last Assessment Version[e]				X						X					X				X	X	Section 4.2.3
Barnes Akathisia Rating Scale(BARS)[e, h]				X					X			X				X			X	X	Section 4.2.1.1
Abnormal Involuntary Movement Scale (AIMS)[e, h]				X					X			X				X			X	X	Section 4.2.1.1

Part 2 Panel D/Panel F																					
	Screening	Washout		Intervention																Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	~20		
Simpson Angus Scale (SAS)[e, h]				X					X			X				X			X		X	Section 4.2.1.1
Bond and Lader Visual Analog Scale (VAS)[e]				X					X			X				X			X		X	Section 4.2.1.1
Brief Psychiatric Rating Scale (BPRS) (Panel D only)[e]	X			X					X			X				X			X		X	Section 4.2.1.1
AE/SAE review	X----------																			-----X		Section 8.4
Pharmacokinetics																						
Blood for Plasma MK-8189 and/or Metabolites Assay[i]					X			X			X						X					Section 8.6.1
Biomarkers																						
Blood for Genetic Analysis[j]					X																	Collect predose from enrolled participants only. Section 8.8

AE=adverse event; BDS=blood draw screen; ECG=electrocardiogram; FSH=follicle stimulating hormone; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Meals should be given at approximately the same time every day starting on Day -1 through Day 14. Day -1 will be time-matched to Day 1. Breakfast will be given at ~1-hour postdose, lunch given at ~4 hours postdose, a snack given at ~8 hours postdose and dinner at ~12 hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

b. Participants will be confined minimally from Day -6 until Day 15 procedures are complete.

c. Single HR and BP measurements will be obtained at all timepoints unless otherwise specified. On the following days, specific timepoints are noted:
- Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs
- Day 1, Day 4, Day 7 and Day 13: 8, 16 and 24 hours postdose
- Day 15: Time-matched to 24-hour postdose vital signs.

d. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Participants should be standing for approximately 2 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:
- Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs
- Day 1, Day 4, Day 7 and Day 13: 8, 16 and 24 hours postdose

Part 2 Panel D/Panel F																					
	Screening	Washout		Intervention																Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	~20	

- Day 15: Time-matched to 24-hour postdose orthostatic vital signs

e. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.
f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:
   - Day 1: Triplicate measurements within 2 hours prior to dosing
   - Day 1, Day 4, Day 7 and Day 13: 8, 16 and 24 hours post-dose
g. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
h. Additional BARS, AIMS and SAS assessments will be conducted as soon as possible when there are observed or reported complaints of dystonia and/or akathisia (See Section 8.3.6).
i. MK-8189 plasma PK sample collection:
   - Day 1, Day 4, and Day 7: predose, 2, 6, 8, 10, 12, 16 and 24 hours postdose.
   - Day 13: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
   - Optional sample when signs of dystonia and/or akathisia occur.
   - Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.
j. This sample will be drawn for CYP2C9 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research.

1.3.3 Schedule of Activities: Part 2 (Panel E/G Titration Regimen 1)

Part 2 Panel E/G Titration Regimen 1 MK-8189/matching placebo 16 mg x 3 days and 24 mg x 7 days																			
	Screening	Washout		Intervention														Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	~17		
Administrative Procedures																			
Informed Consent	X																		Section 8.1.1
Informed Consent for Future Biomedical Research	X																		Section 8.1.1.2
Inclusion/Exclusion Criteria	X			X															Only specific criteria will be reviewed prior to random-ization.
Participant Identification Card	X																		Section 8.1.3
Medical History (includes psychiatric history and substance usage)	X																		Substances: drugs, alcohol, and caffeine Section 8.1.4
Prior/Concomitant Medication Review	X----------X																		Section 8.1.5
Washout from Antipsychotics (Panel E only)		X	X																Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1. Section 8.1.5.1

Part 2 Panel E/G Titration Regimen 1 MK-8189/matching placebo 16 mg x 3 days and 24 mg x 7 days																			
	Screening	Washout		Intervention														Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	~17		
Assignment of Allocation Number (Randomization)					X														Section 8.1.7
MK-8189/Placebo Administration					X	X	X	X	X	X	X	X	X	X					Sections 8.1.8 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X	X	X	X				Section 5.3.1
Domiciling in Clinic[b]		X----------X																	Section 8.1.11
Follow-up Phone Call																	X		
Safety Procedures																			
Full physical examination	X			X												X		X	Section 8.3.1
Height	X																		Section 8.3.1
Weight	X				X											X		X	Section 8.3.1
Full Neurological Exam	X			X															Section 8.3.7 and Appendix 11
Targeted Neurological Exam						X			X			X				X		X	Section 8.3.7 and Appendix 11
Vital Signs (heart rate, blood pressure)[c]	X			X	X			X						X		X		X	Section 8.3.2 and Section 8.3.2.1
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X	X			X						X		X		X	Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X				X			X						X		X		X	Section 8.3.2 and Section 8.3.2.1
12-lead ECG[f]	X				X			X						X		X		X	Section 8.3.3

Part 2 Panel E/G Titration Regimen 1 MK-8189/matching placebo 16 mg x 3 days and 24 mg x 7 days																			
	Screening	Washout		Intervention														Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	~17		
Serum β-hCG (WOCBP only)	X																		
Urine Pregnancy Test (WOCBP only)				X															
Serum FSH (WONCBP only)	X																		Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X																		Appendix 2
UDS/BDS (per site SOP)[g]	X			X															Appendix 2
Laboratory Safety Test (hematology, chemistry, urinalysis)[e]	X			X		X			X					X		X		X	Appendix 2
Columbia Suicide Severity Rating Scale (C-SSRS)- Baseline Version	X																		Section 4.2.3
Columbia Suicide Severity Rating Scale (C-SSRS)- Since Last Assessment Version[e]				X		X			X			X				X		X	Section 4.2.3
Barnes Akathisia Rating Scale (BARS)[e, h]				X		X			X			X				X		X	Section 4.2.1.1
Abnormal Involuntary Movement Scale (AIMS)[e, h]				X		X			X			X				X		X	Section 4.2.1.1
Simpson Angus Scale (SAS)[e, h]				X		X			X			X				X		X	Section 4.2.1.1
Bond and Lader Visual Analog Scale (VAS)[e]				X		X			X			X				X		X	Section 4.2.1.1
Brief Psychiatric Rating Scale (BPRS) (Panel E only)[e]	X			X		X			X			X				X		X	Section 4.2.1.1

Part 2 Panel E/G Titration Regimen 1 MK-8189/matching placebo 16 mg x 3 days and 24 mg x 7 days																			
	Screening	Washout		Intervention														Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	~17		
AE/SAE review	X----------																----------X		Section 8.4
Pharmacokinetics																			
Blood for Plasma MK-8189 and/or Metabolites Assay[i]					X			X						X	X	X			Section 8.6.1
Biomarkers																			
Blood for Genetic Analysis[j]					X														Collect predose from enrolled participants only. Section 8.8

AE=adverse event; BDS=blood draw screen; FSH=follicle stimulating hormone; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Meals should be given at approximately the same time every day starting on Day -1 through Day 11. Day -1 will be time-matched to Day 1. Breakfast will be given at ~1-hour postdose, lunch given at ~4 hours postdose, a snack given at ~8 hours postdose and dinner at ~12 hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

b. Participants will be confined minimally from Day -6 until Day 12 procedures are complete.

c. Single HR and BP measurements will be obtained at all timepoints unless otherwise noted. On the following days, specific timepoints are noted:

- Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs.
- Day 1, Day 4 and Day 10: 8, 16 and 24 hours postdose
- Day 12: Time-matched to 24-hour postdose vital signs

d. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Participants should be standing for approximately 2 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:

- Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs.
- Day 1, Day 4 and Day 10: 8, 16 and 24 hours postdose
- Day 12: Time-matched to the 24-hour postdose orthostatic vital signs

e. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.

f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:

- Day 1: Triplicate measurements within 2 hours prior to dosing
- Day 1, Day 4 and Day 10: 8, 16 and 24 hours post-dose

g. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.

Part 2 Panel E/G Titration Regimen 1 MK-8189/matching placebo 16 mg x 3 days and 24 mg x 7 days																			
	Screening	Washout		Intervention														Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	~17		

h. Additional BARS, AIMS and SAS assessments will be conducted as soon as possible when there are observed or reported complaints of dystonia and/or akathisia (See Section 8.3.6).

i. MK-8189 plasma PK sample collection:
- Day 1 and Day 4: predose, 2, 6, 8, 10, 12, 16 and 24 hours postdose.
- Day 10: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
- Optional sample when signs of dystonia and/or akathisia occur.
- Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.

j. This sample will be drawn for CYP2C9 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research.

1.3.4 Schedule of Activities: Part 2 (Panel E/G Titration Regimen 2)

Part 2 Panel E/G Titration Regimen 2 MK-8189/matching placebo 24 mg x 7 days																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~14		
Administrative Procedures																
Informed Consent	X															Section 8.1.1
Informed Consent for Future Biomedical Research	X															Section 8.1.12
Inclusion/Exclusion Criteria	X			X												Only specific criteria will be reviewed prior to randomization. Section 5
Participant Identification Card	X															Section 8.1.3
Medical History (includes psychiatric history and substance usage)	X															Substances: drugs, alcohol, and caffeine Section 8.1.4
Prior/Concomitant Medication Review	X----------X															Section 8.1.5
Washout from Antipsychotics (Panel E only)		X	X													Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day- 1. Section 8.1.5.1

Part 2 Panel E/G Titration Regimen 2 MK-8189/matching placebo 24 mg x 7 days																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~14		
Assignment of Allocation Number (Randomization)					X											Section 8.1.7
MK-8189/Placebo Administration					X	X	X	X	X	X	X					Sections 8.1.8 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X				Section 5.3.1
Domiciling in Clinic[b]		X----------X														Section 8.1.11
Follow-up Phone Call														X		
Safety Procedures																
Full physical examination	X			X									X		X	Section 8.3.1
Height	X															Section 8.3.1
Weight	X				X								X		X	Section 8.3.1
Full Neurological Exam	X			X												Section 8.3.7 and Appendix 11
Targeted Neurological Exam						X			X				X		X	Section 8.3.7 and Appendix 11
Vital Signs (heart rate, blood pressure)[c]	X			X	X			X			X		X		X	Section 8.3.2 and Section 8.3.2.1
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X	X			X			X		X		X	Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X				X			X					X		X	Section 8.3.2 and Section 8.3.2.1
12-lead ECG[f]	X				X			X					X		X	Section 8.3.3
Serum β-hCG (WOCBP only)	X															
Urine Pregnancy Test (WOCBP only)				X												

Part 2 Panel E/G Titration Regimen 2 MK-8189/matching placebo 24 mg x 7 days																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~14		
Serum FSH (WONCBP only)	X															Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X															Appendix 2
UDS/BDS (per site SOP)[g]	X			X												Appendix 2
Laboratory Safety Test (hematology, chemistry, urinalysis)[e]	X			X		X					X		X		X	Appendix 2
Columbia Suicide Severity Rating Scale (C-SSRS)- Baseline Version	X															Section 4.2.3
Columbia Suicide Severity Rating Scale (C-SSRS)- Since Last Assessment Version[e]				X		X			X				X		X	Section 4.2.3
Barnes Akathisia Rating Scale (BARS)[e, h]				X		X			X				X		X	Section 4.2.1.1
Abnormal Involuntary Movement Scale (AIMS)[e, h]				X		X			X				X		X	Section 4.2.1.1
Simpson Angus Scale (SAS)[e, h]				X		X			X				X		X	Section 4.2.1.1
Bond and Lader Visual Analog Scale (VAS)[e]				X		X			X				X		X	Section 4.2.1.1

Part 2 Panel E/G Titration Regimen 2 MK-8189/matching placebo 24 mg x 7 days																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~14		
Brief Psychiatric Rating Scale (BPRS) (Panel E only)[e]	X			X		X			X				X		X	Section 4.2.1.1
AE/SAE review	X----------														-X	Section 8.4
Pharmacokinetics																
Blood for Plasma MK-8189 and/or Metabolites Assay[i]					X	X	X				X	X	X			Section 8.6.1
Biomarkers																
Blood for Genetic Analysis[j]					X											Collect predose from enrolled participants only. Section 8.8

AE=adverse event; BDS=blood draw screen; ECG=electrocardiogram; FSH=follicle stimulating hormone; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Meals should be given at approximately the same time every day starting on Day -1 through Day 8. Day -1 will be time-matched to Day 1. Breakfast will be given at ~1-hour postdose, lunch given at ~4 hours postdose, a snack given at ~8 hours postdose and dinner at ~12 hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

b. Participants will be confined minimally from Day -1 until Day 9 procedures are complete.

c. Single HR and BP measurements will be obtained at all timepoints unless otherwise noted. On the following days, specific timepoints are noted:
   - Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs.
   - Day 1, Day 4 and Day 7: 8, 16 and 24 hours postdose
   - Day 9: Time-matched to 24-hour postdose vital signs

d. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Participants should be standing for approximately 2 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:
   - Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs.
   - Day 1, Day 4 and Day 7: 8, 16 and 24 hours postdose
   - Day 9: Time-matched to 24-hour postdose orthostatic vital signs

e. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.

f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:
   - Day 1: Triplicate measurements within 2 hours prior to dosing
   - Day 1 and Day 4: 8, 16 and 24 hours post-dose

Part 2 Panel E/G Titration Regimen 2 MK-8189/matching placebo 24 mg x 7 days																
	Screening	Washout		Intervention											Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	~14		

g. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.
h. Additional BARS, AIMS and SAS assessments will be conducted as soon as possible when there are observed or reported complaints of dystonia and/or akathisia (See Section 8.3.6).
i. MK-8189 plasma PK sample collection:
   - Day 1: predose, 2, 6, 8, 10, 12 and 16 hours postdose
   - Day 2 and Day 3: predose, 2, 6 and 8 hours postdose
   - Day 7: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
   - Optional sample when signs of dystonia and/or akathisia occur.
   - Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.
j. This sample will be drawn for CYP2C9 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research.

1.3.5 Schedule of Activities: Part 2 (Panel E/G Titration Regimen 3)

Part 2 Panel E/G Titration Regimen 3 MK-8189/matching placebo 8 mg x 1 day, 16 mg x 1 day and 24 mg x 7 days																		
	Screening	Washout		Intervention													Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~16		
Administrative Procedures																		
Informed Consent	X																	Section 8.1.1
Informed Consent for Future Biomedical Research	X																	Section 8.1.1.2
Inclusion/Exclusion Criteria	X			X														Only specific criteria will be reviewed prior to randomization. Section 5
Participant Identification Card	X																	Section 8.1.3
Medical History (includes psychiatric history and substance usage)	X																	Substances: drugs, alcohol, and caffeine Section 8.1.4
Prior/Concomitant Medication Review	X----------X																	Section 8.1.5
Washout from Antipsychotics (Panel E only)		X	X															Discontinue medication at least 5 days or at least 3 half-lives (whichever is longer) prior to Day- 1 Section 8.1.5.1
Assignment of Allocation Number (Randomization)					X													Section 8.1.7

Part 2 Panel E/G Titration Regimen 3 MK-8189/matching placebo 8 mg x 1 day, 16 mg x 1 day and 24 mg x 7 days																		
	Screening	Washout		Intervention													Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~16		
MK-8189/Placebo Administration					X	X	X	X	X	X	X	X	X					Sections 8.1.8 and 6.3.1
Standard Meals[a]				X	X	X	X	X	X	X	X	X	X	X				Section 5.3.1
Domiciling in Clinic[b]		X----------														X		Section 8.1.11
Follow-up Phone Call																X		
Safety Procedures																		
Full physical examination	X			X											X		X	Section 8.3.1
Height	X																	Section 8.3.1
Weight	X				X										X		X	Section 8.3.1
Full Neurological Exam	X			X														Section 8.3.7 and Appendix 11
Targeted Neurological Exam						X			X			X			X		X	Section 8.3.7 and Appendix 11
Vital Signs (heart rate, blood pressure)[c]	X			X	X	X	X						X		X		X	Section 8.3.2 and Section 8.3.2.1
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X			X	X	X	X						X		X		X	Section 8.3.2.2
Vital Signs (respiratory rate, body temperature)[e]	X				X		X						X		X		X	Section 8.3.2 and Section 8.3.2.1
12-lead ECG[f]	X				X	X	X						X		X		X	Section 8.3.3
Serum β-hCG (WOCBP only)	X																	
Urine Pregnancy Test				X														
Serum FSH (WONCBP only)	X																	Appendix 2
HIV, Hepatitis B and C Screen (per site SOP)	X																	Appendix 2
UDS/BDS (per site SOP)[g]	X			X														Appendix 2

Part 2 Panel E/G Titration Regimen 3 MK-8189/matching placebo 8 mg x 1 day, 16 mg x 1 day and 24 mg x 7 days																		
	Screening	Washout		Intervention													Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~16		
Laboratory Safety Test (hematology, chemistry, urinalysis)[e]	X			X		X							X		X		X	Appendix 2
Columbia Suicide Severity Rating Scale (C-SSRS)- Baseline Version	X																	Section 4.2.3
Columbia Suicide Severity Rating Scale (C-SSRS)- Since Last Assessment Version[e]				X		X			X			X			X		X	Section 4.2.3
Barnes Akathisia Rating Scale (BARS)[e, h]				X		X			X			X			X		X	Section 4.2.1.1
Abnormal Involuntary Movement Scale (AIMS)[e, h]				X		X			X			X			X		X	Section 4.2.1.1
Simpson Angus Scale (SAS)[e, h]				X		X			X			X			X		X	Section 4.2.1.1
Bond and Lader Visual Analog Scale (VAS)[e]				X		X			X			X			X		X	Section 4.2.1.1
Brief Psychiatric Rating Scale (BPRS) (Panel E only)[e]	X			X		X			X			X			X		X	Section 8.4
AE/SAE review	X----------															----------X		Section 8.6.1
Pharmacokinetics																		
Blood for Plasma MK-8189 and/or Metabolites Assay[i]					X	X	X						X	X	X			

Part 2 Panel E/G Titration Regimen 3 MK-8189/matching placebo 8 mg x 1 day, 16 mg x 1 day and 24 mg x 7 days																		
	Screening	Washout		Intervention													Poststudy	Notes
Scheduled Day		-6	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~16		
Biomarkers																		
Blood for Genetic Analysis[j]					X													Collect predose from enrolled participants only. Section 8.8

AE=adverse event; BDS=blood draw screen; FSH=follicle stimulating hormone; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Meals should be given at approximately the same time every day starting on Day -1 through Day 10. Day -1 will be time-matched to Day 1. Breakfast will be given at ~1-hour postdose, lunch given at ~4 hours postdose, a snack given at ~8 hours postdose and dinner at ~12 hours postdose. All meals will follow the completion of all specified procedures at that timepoint.

b. Participants will be confined minimally from Day -6 until Day 11 procedures are complete.

c. Single HR and BP measurements will be obtained at all timepoints unless otherwise noted. On the following days, specific timepoints are noted:
- Day -1 (triplicate measurements): Time-matched to 8, 16 and 24 hours postdose vital signs.
- Day 1, Day 2, Day 3 and Day 9: 8, 16 and 24 hours postdose
- Day 11: Time-matched to 24-hour postdose vital signs

d. Orthostatic assessments in HR and BP will follow semi-recumbent vital sign assessments. Participants should be standing for approximately 2 minutes prior to the orthostatic assessments. Orthostatic HR and BP measurements will be obtained on:
- Day -1: Time-matched to 8, 16 and 24 hours postdose orthostatic vital signs.
- Day 1, Day 2, Day 3 and Day 9: 8, 16 and 24 hours postdose
- Day 11: Time-matched to 24-hour postdose orthostatic vital signs

e. Scheduled assessments are completed predose on dosing days and at any time on non-dosing days.

f. Single 12-lead safety ECG measurements will be taken at all postdose timepoints. On the following days, specific timepoints are noted:
- Day 1: Triplicate measurements within 2 hours prior to dosing
- Day 1, Day 2, Day 3 and Day 9: 8, 16 and 24 hours post-dose

g. Screening UDS is mandatory; any additional UDS are conducted per site SOP. UDS prior to randomization will be done on the day of admission.

h. Additional BARS, AIMS and SAS assessments will be conducted as soon as possible when there are observed or reported complaints of dystonia and/or akathisia (See Section 8.3.6).

i. MK-8189 plasma PK sample collection:
- Day 1 and Day 2: predose, 2, 6, 8, 10, 12 and 16 hours postdose
- Day 3: predose, 2, 6, 8, 10, 12, 16 and 24 hours postdose
- Day 9: predose, 2, 6, 8, 10, 12, 16, 24, 36 and 48 hours postdose
- Optional sample when signs of dystonia and/or akathisia occur.
- Leftover main study plasma will be stored for future biomedical research if the participant consents to future biomedical research.

j. This sample will be drawn for CYP2C9 and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research.

2 INTRODUCTION

2.1 Study Rationale

Part 1

This study part is being conducted to assess the safety and tolerability of alternate titration regimens for MK-8189 as well as safety and tolerability of initiating MK-8189 treatment at the highest likely target clinical dose without titration. Based on results from the single ascending dose trial (P001) in healthy participants following treatment with the 3-mg and 6-mg IR formulation, dystonia was observed around the time of peak MK--8189 concentration. One hypothesis for the observed acute dystonia is that the high MK--8189 peak to trough ratio led to rapid-cycling of MK-8189 on and off the target enzyme, PDE10A. [redacted] a titration approach in the target patient population was implemented in the multiple ascending dose studies (P003 and P007) and the POC (P005) study, which found the incidence of dystonia across these trials to be acceptable. Of note, in P007, where the highest likely clinical dose of 24 mg as well as supratherapeutic doses up to 48 mg have been evaluated, no MK-8189 related dystonia has been reported. [redacted] Tolerability in healthy participants and the patient populations was found to be similar in P003 and P007, suggesting that the dystonia observed in P001 was unlikely due to the study being conducted in healthy participants. Across P003 and P007, the starting dose has increased from 2 mg to 4 mg to 8 mg without an increase in the incidence in dystonia. Thus, it appears reasonable to evaluate whether a titration scheme is necessary to mitigate the potential for dystonia [redacted] A simplified dose regimen would be beneficial for patients and health care providers.

Part 2

As schizophrenia is a life-long disease, it is likely the elderly will be an important segment of MK-8189 treatment population. This study part is being conducted to evaluate the safety, tolerability and PK of MK-8189 in the elderly population with and without schizophrenia. This study will support enrollment of elderly participants with and without schizophrenia in later phase studies evaluating the safety and efficacy of MK-8189.

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 target nucleus of the corticostriatal pathway, the

striatum [Seeger, T. F., et al 2003]. Preclinical pharmacology studies demonstrate that PDE10A inhibition increases cAMP/cGMP signaling in pathways that have been associated with underlying pathology (glutamate) as well as clinically validated therapeutics (dopamine D2 receptor antagonists) for schizophrenia. Enhanced signaling in these pathways is hypothesized to restore behavioral inhibition that is impaired in schizophrenia [Grauer, S. M., et al 2009] [Schmidt, C. J., et al 2008]. PDE10A inhibitors may potentially be an alternative treatment as monotherapy and/or adjunct treatment in schizophrenia patients who have inadequate response to first line AAP treatment.

2.2.2 Preclinical and Clinical Studies

Preclinical trial information can be found in the MK-8189 IB.

Clinical Studies

As part of the Phase 1 program, three single-dose clinical studies, one DDI study, and two multiple- dose clinical studies have been completed with MK-8189. Overall, 146 participants have received at least one dose of MK-8189; 71 healthy participants and 75 participants with schizophrenia. [redacted] Ten healthy male and female participants received multiple doses titrated up to 12 mg over 14 days (P003 Part 3) and 12 healthy male and female participants received doses titrated up to 24 mg titrated over 18 days (P007 Panel A). Thirty-three male and female participants with schizophrenia were titrated up to doses of 16 mg over 14 days (P003), 25 participants with schizophrenia were titrated up to 24 mg over 18 days (P007 Panel B and C) and 17 participants with schizophrenia were titrated up to 48 mg over 15 days (P007 Panel D). [redacted]

MK-8189 was generally well tolerated across the Phase 1 studies. The most common treatment-related adverse events [AEs] (≥5%) following treatment of MK-8189 (n=146) across the completed 6 Phase 1 studies were headache (16.4%) somnolence (12.3%), decreased appetite (10.3%), nausea (9.6%), fatigue (8.9%), dizziness (8.9%), vomiting (6.2%) diarrhea (6.2%), akathisia (6.2%), and anxiety (6.2%). Most AEs were mild to moderate in severity. There were no deaths and two SAEs. One participant experienced an SAE of gastroenteritis in P003 which was not considered treatment related (see IB for additional details). The other SAE of psychosis occurred in P007 and is described below. Individual studies are summarized in the IB with the exception of P007 which is summarized below:

Protocol 007 was a 4- panel (A, B, C and D) randomized (3:1), placebo-controlled, multiple-dose safety, tolerability and PK study of MK-8189 in participants with schizophrenia and healthy participants. The study is clinically complete and data are unblinded. In this study, 16 healthy participants (Japanese and non-Japanese) were enrolled in Panel A and 16 participants with schizophrenia were enrolled in Panel B. Participants were washed off their standard of care during screening. The treatment regimen for Panel A and Panel B was as follows: MK-8189 4- mg/placebo Days 1-3, MK-8189 8- mg/placebo Days 4-6, MK-8189

12- mg/placebo Days 7-9, MK-8189 16- mg/placebo Days 10-12, MK-8189 20- mg/placebo Days 13-15 and MK-8189 24- mg/Days 16-18.

In Panel A (healthy participants), overall, multiple oral doses of MK-8189 4 to 24 mg administered in a titration regimen were generally and similarly well tolerated by healthy Japanese and non- Japanese participants. There were no serious adverse events (SAEs), events of clinical interest (ECIs) or deaths reported. Of the 16 participants included in the safety analysis, 13 (81.3%) experienced 1 or more AEs during the study; 10 (83.3%) participants after MK-8189 and 3 (75%) participants after placebo. All AEs were mild to moderate in intensity and resolved by the end of the study. Nine participants (56.3%) reported 1 or more AEs that were determined by the investigator to be study intervention related; 7 (58.3%) participants after MK-8189 and 2 (50%) participants after placebo. The most commonly reported study intervention-related AEs in 2 or more participants were dizziness (n=4 [33.3%] following MK-8189 4 mg, 16 mg and 24 mg), headache (n=3 [25%] following MK-8189 12 mg, 16 mg and 24 mg), decreased appetite (n=3 [25%] following MK-8189 4 mg and 8 mg, n=1 [25%] following placebo), abdominal discomfort (n=2 [16.7%] following MK-8189 16 mg and 24 mg) and dry skin (n=1 following each of MK-8189 8 mg [8.3%] and placebo [25%]).

In Panel B, multiple oral doses of MK-8189 4 to 24 mg administered in a titration regimen were generally well tolerated by participants with schizophrenia. There were no SAEs, ECIs or deaths reported. Of the 16 participants included in the safety analysis, 14 (87.5%) experienced 1 or more AEs during the study; 10 (83.3%) participants after MK-8189 and 4 (100%) participants after placebo. The majority of AEs were mild to moderate in intensity. All AEs resolved by the end of the study. Nine participants (56.3%) reported 1 or more AEs that were determined by the investigator to be study intervention related; 8 (66.7%) participants after MK-8189 and 1 (25%) participant after placebo. The most commonly reported study intervention-related AEs in 2 or more participants were headache (n=5 [41.7%] following MK-8189 8 mg to 24 mg), constipation (n=4 [33.3%] following MK-8189 16 mg and 20 mg) and nausea (n=2 [16.7%] following MK-8189 16 mg and 20 mg, n=1 [25%] following placebo).

In Panel C, multiple oral doses of MK-8189 4 to 24 mg administered in a titration regimen (with permitted concomitant antipsychotic standard of care) were generally well tolerated by participants with schizophrenia. Of the 17 participants included in the safety analysis, 14 (82.4%) experienced 1 or more AEs during the study; 13 (100%) participants after MK-8189 and 1 (25%) participants after placebo. The majority of AEs were mild to moderate in intensity. All AEs resolved by the end of the study except several mild to moderate AEs (insomnia, dry mouth, pruritus, back pain and arthralgia) for 1 participant (received placebo) who withdrew consent and for which AE status is unknown; all of these AEs were considered not related to intervention by the investigator. Thirteen participants (76.5%) reported 1 or more AEs that the investigator considered study intervention related; 12 (92.3%) participants after MK-8189 and 1 (25%) participant after placebo. The most commonly reported study intervention- related AEs in 2 or more participants were decreased appetite (n=5 [38.5%] following MK-8189 4 mg, 8 mg, 12 mg and 20 mg), nausea (n=3 [23.1%] following MK-8189 8 mg, 12 mg and 20 mg), vomiting (n=3 [23.1%] following

MK-8189 8 mg, 12 mg and 20 mg), headache (n=3 [23.1%] following MK-8189 8 mg and 16 mg), abdominal pain upper (n=2 [15.4%] following MK-8189 4 mg and 24 mg), constipation (n=2 [15.4%] following MK-8189 16 mg and 24 mg), dizziness (n=2 [15.4%] following MK-8189 8 mg and 12 mg, n=1 [25%] following placebo) and anxiety (n=2 [15.4%] following MK-8189 4 mg and 12 mg). There were no serious adverse events (SAEs), or deaths reported. One participant experienced a nonserious ECI of severe dystonia following MK-8189 4 mg (with concurrently administered lurasidone, venlafaxine and quetiapine) which resolved within ~4 hours. The investigator considered this ECI not related to intervention as it was identified that the participant had a history of lurasidone hypersensitivity not reported at screening. The participant was subsequently discontinued from intervention (after 2 doses) due to a protocol deviation.

In Panel D, multiple oral doses of MK-8189 8 to 48 mg administered in a titration regimen were generally well tolerated by participants with schizophrenia. Of the 26 participants included in the safety analysis, 23 (88.5%) experienced 1 or more AEs during the study; 14 (82.4%) participants after MK-8189 and 9 (100%) participants after placebo. The majority of AEs were mild to moderate in intensity and resolved except for AEs of pruritus, nausea and vomiting (all mild) in 1 participant who withdrew consent due to pregnancy (discussed below), AEs of dry mouth, headache and muscle tightness (all mild, each AE in 1 participant only) in 3 participants who completed the study, an AE of mild contact dermatitis in 1 participant who discontinued intervention due to another AE (atrial fibrillation, following treatment with placebo), and an AE of moderate psychotic disorder in 1 participant who discontinued intervention for same. Intervention for the participants with AEs of psychotic disorder and contact dermatitis was placebo and for the remaining participants was MK-8189.

Seventeen participants (65.4%) reported 1 or more AEs that the investigator considered study intervention related; 12 (70.6%) participants after MK-8189 and 5 (55.6%) participants after placebo. The most commonly reported study intervention related AEs (excluding the SAE which is discussed below) in 2 or more participants were nausea (n=4 [23.5%] following MK-8189 8 mg, 16 mg and 48 mg, n=1 [11.1%] following placebo), anxiety (n=2 [11.8%] following MK-8189 16 mg and 24 mg, n=1 [11.1%] following placebo), headache (n=4 [23.5%] following MK-8189 8 mg to 36 mg, n=1 [11.1%] following placebo), somnolence (n=4 [23.5%] following MK-8189 8 mg, n=1 [11.1%] following placebo), dizziness (n=3 [17.6%] following MK-8189 48 mg), extrapyramidal disorder (n=1 [5.9%] following MK-8189 48 mg, n=1 [11.1%] following placebo) and palpitations (n=2 [11.8%] following MK-8189 36 mg and 48 mg).

One participant experienced 1 SAE of severe psychotic disorder which began one day following their last dose of intervention (MK-8189 36 mg), resulting in hospitalization and intervention discontinuation. The SAE duration was 6 days and resolved following initiation of an antipsychotic and anti-anxiolytic. No other AEs were reported by this participant. The investigator considered this SAE related to study intervention. Two participants experienced non-serious ECIs. One participant experienced an ECI of moderate dystonia 2 days following the final dose of study intervention (placebo) which resolved within 3.5 hours. One participant experienced ECIs of mild dystonia and mild dyskinesia 3 days following

completion of study intervention (MK-8189 48 mg) and one day following re-initiation of their antipsychotic. Both ECIs resolved within 2 days. The investigator considered all ECIs not related to intervention. One participant who received MK-8189 (4 mg titrated up to 36 mg) experienced pregnancy. The initial exposure to intervention was at ~6 weeks of pregnancy (based on an ultrasound) that was unknown at that time. The participant withdrew consent and discontinued intervention; the outcome of maternal exposure to pregnancy was a live birth with no congenital or other abnormalities. There were no deaths reported.

In a Phase 2 POC trial (P005), MK-8189 was generally well tolerated up to 12 mg QD. Adverse Events that occurred in ≥5% of participants in the MK-8189 intervention group and had greater incidence than placebo were diarrhea, nausea, vomiting, decreased appetite, akathisia, dystonia, headache, sedation, somnolence, anxiety, and insomnia. No deaths were reported in the P005 study. No SAEs were reported for participants on MK-8189.

In P005, for the primary endpoint of PANSS total score change from baseline at Week 4, although the MK-8189 group showed meaningful improvement in symptoms, the improvement missed statistical significance (difference [95% CI] in LS mean change was -4.7 [-9.8, 0.5]; p=0.074). Risperidone was superior to placebo with respect to this endpoint (difference [95% CI] in LS mean change was -7.3 [-14.0, -0.6]; p=0.033). There was no difference in magnitude of effect between MK-8189 and risperidone (difference [95% CI] in LS mean change was 2.6 [-4.0, 9.2]; p=0.440). For the exploratory endpoint of PANSS positive subscale score at Week 4, both MK-8189 and risperidone were superior to placebo. There was no significant difference in effect between MK-8189 and risperidone. Neither risperidone nor MK-8189 demonstrated significant improvement in the CGI-S.

[redacted] Median Tmax of MK-8189 as monotherapy ranged from 10 to 20 hours with a t1/2 of approximately 8.4 hours (37.8% GCV).

Data suggest that the exposures at steady state for a given dose are generally lower in healthy participants compared to participants with schizophrenia administered MK-8189 as monotherapy.

In a DDI study (P006) the coadministration of extended release 240-mg diltiazem increased MK-8189 AUC and Cmax by approximately 2-fold and 1.3-fold, respectively, confirming that MK-8189 is a CYP3A substrate.

2.2.3 Ongoing Clinical Studies

As of March 11, 2021, two Phase 1 trials and one Phase 2 trial are ongoing. P011 is a Phase 1 multiple-dose randomized (3 active:1 placebo), double-blind, placebo-controlled, multicenter, 2 -part study. Part 1 is evaluating the safety and tolerability of different titration regimens or initiating MK-8189 treatment without titration. Part 2 is evaluating the multiple dose safety, tolerability and PK of MK-8189 in participants with schizophrenia that are between 61 and 80 years of age with and/or without titration. In Part 1, Panel A participants initiated dosing with 16 mg of MK-8189/placebo for 3 days and then were escalated to 24

mg/placebo for 4 days. Panel B initiated dosing with 24 mg of MK-8189 (no titration) for 7 days. Part 1 has completed enrollment and dosing and all data are preliminary and blinded. No SAEs or deaths were reported. In Panel A, all 8 participants enrolled completed treatment. The majority of AEs were mild and no AEs were severe in intensity. Of the 8 participants, one participant did not dose escalate to 24 mg due to moderate somnolence which lasted for 3 days. For the duration of the somnolence AE, the participant was also receiving hydroxyzine, a sedating antihistamine. Two participants reported an AE of dystonia. One participant reported mild transient dystonia which began 14 hours after the first dose and lasted 2 days. The dystonia was treated with benztropine until it resolved. Another participant reported mild transient dystonia which began 6.5 hours following the first dose and resolved in 22 hours. While experiencing dystonia the participant was treated with benztropine. AEs reported that were considered related to study drug included decreased appetite (n=2), dystonia (n=2) somnolence (n=2), nightmare (n=1), worsening psychosis (n=1), and insomnia (n=1).

Panel B completed enrollment and dosing. Eighteen participants were randomized and 14 completed treatment per protocol. Of the 4 participants that discontinued treatment, one discontinuation was due to an AE of gastroesophogeal reflux disease that was not considered related to treatment. The majority of AEs were mild. AEs considered related to treatment included hypertonia (n=1), decreased appetite (n=1), somnolence (n=1) and increased ALT (n=1). The participant with the AE of elevated ALT had an elevated screening value of 61 IU/L (normal range 7-52 IU/L). The Day -1 predose ALT value was also elevated (98 IU/L) and continued to increase on Day 7 (116 IU/L) and Day 9 (133 IU/L). At the post study the ALT was still elevated but below the predose value (71 IU/L). ALP (normal range 34-104 IU/L) followed a similar pattern with elevations at screening (130 IU/L), Day -1 predose (136 IU/L), Day 7 (143 IU/L), Day 9 (134 IU/L) and at the post study visit (124 IU/L). While AST was within the normal range (13-39 IU/L) at screening (26 IU/L) and Day -1 predose (37 IU/L), values were elevated above the normal range on Day 7 (44 IU/L) and Day 9 (51 IU/L). At the post dose visit, AST was within the normal range (26 IU/L). Bilirubin was normal throughout the study. Preliminary data suggest initiation of MK-8189 at a 16 or 24 mg dose was generally well tolerated.

Treatment is ongoing in Part 2. One participant has been dosed to date with no complaints of AEs.

P012 is a Phase 1 study to evaluate the safety, tolerability and PK in participants with hepatic impairment and group mean-matched healthy participants. The trial has initiated but no participants have been dosed.

Protocol 008 is an ongoing Phase 2B randomized, double-blind, placebo- and active controlled trial of the efficacy and safety of MK-8189 in adult participants 18 to 50 years of age who are experiencing an acute episode of schizophrenia according to DSM-V™ criteria.

A total of 576 participants from approximately 80 sites across the USA, Europe and Asia will be recruited into this trial. Treatment duration will be for a period of 12 weeks and includes a 6-week acute treatment period followed by a 6-week extension period. Eligible participants will be randomized to receive one of five treatment sequences with target doses of MK-8189

(8 mg, 16 mg and 24 mg QD), risperidone (6 mg QD), or placebo. Placebo completers at 6 weeks will be allocated to receive MK-8189 24 mg for the remainder of the trial. This trial is being conducted in a hospital/acute care setting followed by an outpatient setting. Recruitment was initiated Dec2020.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses for this study.

In male or female participants with schizophrenia (young adults and elderly) and healthy elderly participants:

Objectives	Endpoints
Primary	
<u>Part 1</u> • To evaluate the safety and tolerability of MK-8189 oral, once-daily titration regimens in young adult participants with schizophrenia <u>Part 2</u> • To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in elderly participants with schizophrenia and healthy elderly participants	<u>Part 1 and Part 2</u> • Adverse experiences, laboratory safety tests, electrocardiograms and vital signs

Objectives	Endpoints
Secondary	
<u>Part 1</u> • To characterize MK-8189 pharmacokinetics following different titration regimens in young adult participants with schizophrenia <u>Part 2</u> • To characterize the pharmacokinetics of MK-8189 following multiple once-daily oral doses in elderly participants with schizophrenia and healthy elderly participants.	<u>Part 1 and Part 2</u> • AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd and apparent t1/2
Tertiary/Exploratory	
<u>Part 1 and Part 2</u> • To investigate the relationship between CYP2C9 genetic polymorphs and the PK of MK-8189. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study. • To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study. <u>Part 2</u> • To compare the pharmacokinetics of MK-8189 in elderly participants with schizophrenia to dose-matched young adult participants with schizophrenia • To compare the pharmacokinetics of MK-8189 in elderly healthy participants to dose-matched healthy young adult participants	<u>Part 1 and Part 2</u> • Germline genetic variation in CYP2C9 and association to clinical data collected in this study • Germline genetic variation and association to clinical data collected in this study. <u>Part 2</u> • AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd and apparent t1/2

4 STUDY DESIGN

4.1 Overall Design

This is a 2-part randomized, placebo-controlled, parallel-group, double-blind study of MK-8189 in participants with schizophrenia and healthy participants. Part 1 will enroll young adult participants with schizophrenia and Part 2 will enroll healthy elderly participants and elderly participants with schizophrenia.

Part 1

In all panels, participants will be washed off their current antipsychotic therapy. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants should not receive antipsychotics for at least 5 days or 3 half-lives (whichever is longer) prior to Day -1. For longer half-life antipsychotics (e.g. aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment (i.e. cessation of AAP) as an outpatient, but should be confined to the clinical research unit within a week of stopping treatment and minimally beginning on Day -6.

Decisions regarding the initiation of an alternate titration regimen will be made jointly between the principal investigator(s) and Sponsor and will be based on safety and tolerability from ~ 8 subjects as further detailed later in this section.

Panel A will enroll up to 16 participants with schizophrenia disorder who will receive Titration Regimen 1. An initial cohort of 8 participants will be randomized to active or placebo. Beginning on Day 1, participants randomized to MK-8189 will receive 16 mg (1 x 12-mg tablet and 1 x 4-mg tablet) of MK-8189 on Days 1 to 3 and 24 mg of MK-8189 (2 x 12-mg tablets) on Days 4 to 7. Participants randomized to placebo will receive the same number of tablets matching the MK-8189 tablet strengths in the active group.

After dosing of the initial cohort of 8 participants completes in Panel A, Panel B or Panel C will be enrolled. If safety and tolerability data from Panel A indicate a starting dose of MK-8189 16 mg is generally well tolerated, Panel B will be enrolled. If a starting dose of MK-8189 16 mg is not generally well tolerated, Panel C will be enrolled.

Panel B will enroll an initial cohort of 8 participants with schizophrenia disorder who will receive Titration Regimen 2. Participants will be randomized to MK-8189 or placebo. On Days 1 to 7, participants will receive MK-8189 24 mg (2 x 12-mg tablets) or matched placebo.

If tolerability issues are due to elimination of dose titration, it will likely be evident within the first few days of dosing MK-8189. Thus, an initial assessment of tolerability will be made following 3 days of dosing in approximately 8 participants. If MK-8189 is generally well tolerated based on AEs, an additional 8 participants will be enrolled into Panel B receiving Titration Regimen 2. If Titration Regimen 2 is not generally well tolerated in Panel B (either after assessment of the initial cohort [n=8] or full cohort [n=16]), an additional 8 participants

will be enrolled in Panel A such that a total of 16 participants will receive Titration Regimen 1.

Panel C will enroll 16 participants with schizophrenia disorder and receive Titration Regimen 3. Participants will be randomized to active or placebo. Participants randomized to MK-8189 will receive 8 mg on Day 1 (2 x 4-mg tablets), 16 mg on Day 2 (1 x 12-mg tablet and 1 x 4-mg tablet) and 24 mg (2 x 12-mg tablets) on Days 3 to 7. Participants randomized to placebo will receive the same number of tablets matching the MK-8189 tablet strength in the active group.

All participants will be confined to the unit from at least Day -6 until Day 9 assessments are complete.

Part 2

The goal of Part 2 is to evaluate MK-8189 safety, tolerability and PK and titration regimens in elderly participants with schizophrenia disorder (Panels D and E) and healthy elderly participants (Panel F and G). Participants will be randomized to MK-8189 or placebo. Participants with schizophrenia will be washed off their current antipsychotic therapy. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. Participants should not receive antipsychotics for at least 5 days or 3 half-lives (whichever is longer) prior to Day -1. For longer half-life antipsychotics (e.g. aripiprazole and brexpiprazole), if deemed appropriate by the investigator, a participant may stop treatment (i.e. cessation of AAP) as an outpatient, but should be confined the clinical research unit within a week of stopping treatment and minimally beginning on Day -6. Healthy elderly participants (Panel F and G) will be domiciled by Day -1.

Panel D will run concurrently with Part 1. Panel D will enroll up to 16 participants with schizophrenia disorder. An initial cohort of 8 participants will be randomized to active or placebo. Beginning on Day 1, participants randomized will begin to receive MK-8189/placebo QD and will be titrated from 8 mg to 24 mg or placebo over the course of a 13-day treatment period as follows: 8 mg (2 x 4 mg/placebo tablets) Days 1 to 3, 16 mg (1 x 12 mg/placebo tablet and 1 x 4 mg/placebo tablet) Days 4 to 6, 24 mg (2 x 12 mg/placebo tablets) Days 7 to 13. This titration schedule has been shown to be well tolerated in a previous trial (P007) in young adults with schizophrenia.

Each dose titration decision for each individual participant will occur after 3 days of dosing per dose level. If a participant does not tolerate escalation to the next dose, the participant may be titrated down to the previous dose. If appropriate medical care necessitates a down-dose, the investigator may do so independent of consultation with the Sponsor. If the participant tolerates continued dosing following down-titration, the participant may continue in the trial at that dose until study completion or may be rechallenged at a higher dose. During the titration period, rechallenges are only to occur on a regularly scheduled dose titration day, ie, Day 7, and will not extend the participant's time in the study. Any changes to the protocol specified titration schedule (eg, the participant remains at their current dose or is down titrated) will be documented in a protocol clarification letter.

Participants will be confined to the unit from Day -6 until the Day 15 postdose assessments are complete.

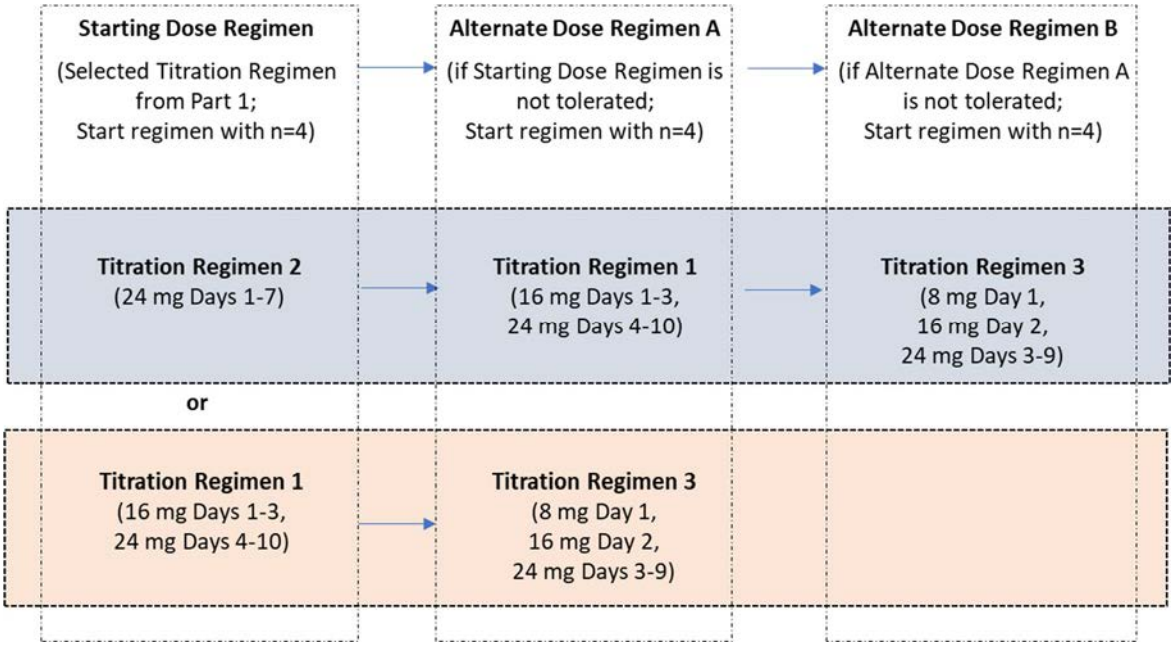
After dosing of the initial cohort of approximately 8 participants, if the dose regimen is found to be generally well tolerated, Panel E will be enrolled. If additional data are required for evaluation, additional participants (up to 8) may be enrolled. The decision to enroll additional participants in Panel D or initiate Panel E will be made jointly between the investigator(s) and the Sponsor and documented in a protocol clarification letter.

Panel E will be initiated after completion of Part 1 and dosing of at least 8 participants in Panel D. If dosing in Panel D is generally well tolerated and at least 1 of the titration regimens evaluated in Part 1 of the current protocol is found to be generally well tolerated, 1 of those 3 regimens will be administered in Panel E.

Assuming that dosing was generally well tolerated in Panel D, the selection of the titration regimen for Panel E will be dependent on the safety and tolerability data observed in Part 1 and will be made jointly between the investigator(s) and the Sponsor and documented in a protocol clarification letter. Note: as shown in the Protocol Summary (Section 1), if Titration Regimen 1 or 3 is selected for evaluation, dosing at 24 mg will be extended to ensure evaluation of this MK-8189 dose for 7 days in the elderly population.

An initial cohort (n=4) will be dosed with the selected titration regimen from Part 1 to initially assess tolerability in a small number of participants. Tolerability will be assessed after the third dose and will determine the dose regimen scheme for the remainder of the participants; if well tolerated, the remainder of the cohort will be enrolled in the selected dose regimen (n=12). However, if the selected regimen is not well tolerated, an additional cohort of 4 participants will be enrolled in an alternate (more conservative) dose regimen as shown in [Figure 2]. Depending on the initial dose regimen selected for evaluation, this process may be repeated as outlined in [Figure 2] such that up to 3 Titration Regimens may be evaluated with the objective to have 1 of the titration regimens evaluated in ~ 16 participants. The decision to initiate an alternate titration regimen will be documented in a protocol clarification letter.

Figure 2 Part 2 Panel E/G Alternate Dose Regimens if Starting Regimen is Titration Regimen 1 or Titration Regimen 2



Participants will be confined to the unit from at least Day -6 until the 48-hour postdose assessments are complete (Day 12, Day 9 and Day 11 for Titration Regimen 1, Titration Regimen 2 and Titration Regimen 3, respectively).

For Part 1 and Part 2, all dose titration decisions (where applicable) will be made jointly by the investigator and the Sponsor. However, if appropriate medical care necessitates a down-titration, the investigator may do so independent of consultation with the Sponsor. Any changes to the protocol-specified titration schedule (eg, the participant remains at their current dose or is down titrated) will be documented in a protocol clarification letter.

In Part 1 and Part 2 Panel E, the dose titration decisions will occur as follows: For Titration Regimen 1, each dose titration decision for each individual participant will occur after administration of the 16-mg dose on Day 3. For Titration Regimen 3, the titration decision for each participant will be made following the 16-mg dose (Day 2). For Titration Regimen 2 (no titration), the safety will be reviewed following 3 days of dosing to evaluate safety and tolerability for continued dosing.

Panel F (healthy elderly) will be conducted in the same manner as Panel D; however, up to approximately 12 participants will be enrolled. An initial cohort of 6 participants will be randomized to active or placebo. If the dose regimen is found to be generally well tolerated, Panel G will be enrolled. If additional data are required for evaluation, additional participants (up to 6) may be enrolled. The decision to enroll additional participants in Panel G or initiate Panel F will be made jointly between the investigator(s) and the Sponsor and documented in a protocol clarification letter.

Panel G (healthy elderly) will be conducted in the same manner as Panel E following completion of at least 6 participants in Panel F. However, up to approximately 12 participants will be enrolled and evaluated within a dose titration regimen (See Figure 2).

In Part 1 and Part 2, safety and tolerability of MK-8189 will be monitored by clinical assessment of AEs, repeated measurements of ECGs and VS, physical and neurological examinations, and standard laboratory tests (hematology, chemistry, urinalysis). In addition, EPS of dystonia and akathisia will be monitored along with psychological effects using rating scales. PK of MK-8189 will also be evaluated in both parts of the study.

Because this is a Phase 1 assessment of MK-8189 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

Part 1

In the current trial, a staged approach will be implemented to evaluate the need for titration. Alternate dose regimens will be evaluated based on tolerability as described in Section 4.1. While MK-8189 was generally well tolerated in both healthy participants and participants with schizophrenia (P003 and P007), the schizophrenia population was selected for evaluation in the current trial as preliminary PK data suggest that MK-8189 exposures may be greater in the patient population at doses greater than 12 mg. A matched placebo-control will be included to reduce bias with regards to the patient reporting and investigator assessment of AEs.

Part 2

As schizophrenia is a life-long disease, it is likely the elderly will be an important segment of the MK-8189 treatment population. This study part is being conducted to evaluate the safety, tolerability and PK of MK-8189 in the elderly population. For Panel D and Panel F, the dose regimen selected has been tolerated in young adult participants with schizophrenia and will be the dose regimen in the Phase 2b study. For Panel E and Panel G, the titration regimen selected will be based on safety and tolerability results of Part 2, Panel D and Panel F, respectively and from Part 1 of the current protocol. In Panel E and Panel G, a small cohort will initially be dosed. If there are no tolerability concerns, the remainder of the cohort will proceed with dosing on the selected regimen. If there are tolerability concerns, the remainder of patients may be dosed with an alternative titration regimen as described in Section 4.1.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

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

As EPS are associated with antipsychotics and have been observed in the MK-8189 clinical program, the BARS, AIMS and SAS will be used to quantify any EPS observed in the study. The BARS is an akathisia rating scale with objective and subjective measures and an overall rating from 0 to 5. A score of 0 presents no evidence for akathisia, a score of 3 is moderate akathisia and a score of 5 is severe akathisia. The AIMS evaluates 12 items and uses a 5-point scale to assess abnormal movement in 3 areas (orofacial, extremities, trunk). The SAS evaluates 10 items and uses a 5-point scale to measure symptoms of parkinsonism or parkinsonian side effects (including rigidity, tremor, akinesia, and salivation).

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

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

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

4.2.1.2 Pharmacokinetic Endpoints

An objective of this study is to characterize the PK of MK-8189. Therefore, individual plasma concentration and actual sample collection times of MK-8189 will be used to derive the PK parameter values AUC0-24hr, Cmax, Tmax, C24hr, CL, Vd and apparent t1/2.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 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.

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

4.2.1.4 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

A matched placebo-control will be included to reduce bias with regards to the participant reporting and investigator assessment of AEs.

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

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

4.3.1 Starting Dose for This Study

Part 1

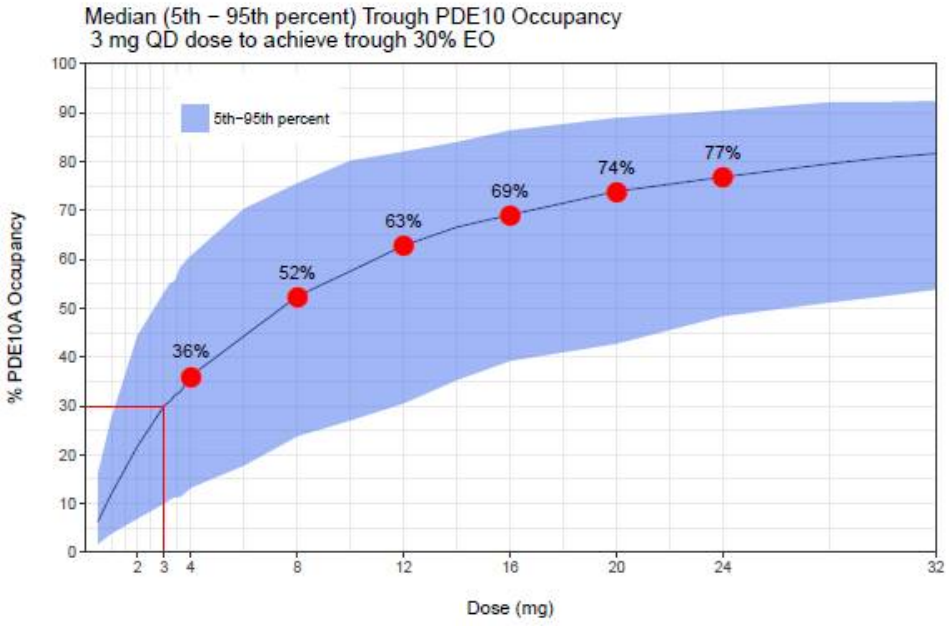
Starting doses of up to and including 8 mg have been generally well tolerated. [redacted] While based on PK/EO modelling, it is anticipated that the EO will increase on average from 52% at the 8-mg dose to 69% at the 16-mg dose [Figure 3], there is considerable overlap in EO between the doses. [redacted] There is no clear dose relationship for other AEs based on P003 and preliminary data from P007. However, in the case of poor tolerability, the next panel would follow a more conservative dose escalation.

Part 2

Panel D/F: The starting dose and titration regimen used in this Panel has been shown to be generally well tolerated in young adults with schizophrenia in a previous protocol (P007).

Panel E/G: The starting dose of Panel E and G will be dependent on the safety and tolerability results from Part 2 Panel D and Panel F, respectively, as well as safety and tolerability results from Part 1, with the goal to evaluate the most simplified but generally well tolerated dose scheme from Part 1 in Part 2. As described in Section 4.1, there will be flexibility to modify the dosing scheme based on tolerability results from an initial small cohort.

Figure 3 MK-8189 Dose-Enzyme Occupancy



4.3.2 Maximum Dose/Exposure for This Study

The current trial will evaluate doses up to and including 24 mg. As described in Section 2.2.2 and 2.2.3, previous and ongoing clinical studies have demonstrated that MK-8189 has been generally well tolerated up to and including doses of 24 mg. In addition, currently ongoing P007 Panel D is evaluating doses up to 48 mg.

Based on a population PK model, the steady-state Cmax and AUC0-24hr at the 24-mg dose is predicted to be 0.975 µM and 19 µM.hr. Based on data from the chronic toxicology studies, the exposure multiple at the 24-mg dose for AUC0-24hr would be ~ 7-fold based on the 6-month rat study and ~9-fold based on the 9-month monkey study. Brief summaries of the chronic toxicology studies supporting dose escalation are provided below:

In the 6-month rat study, doses of 0, 25, 100 and 750 mg/kg/day were evaluated. Two high-dose (750 mg/kg/day) female rats were found dead (Week 13 and Week 24) with acute tubular necrosis (with and without tubular mineralization). Therefore, the 100 mg/kg/day dose was considered the no observed adverse effect level (NOAEL) for this study (AUC0-24hr = 130 µM·hr), providing an exposure margin of ~ 7-fold over the predicted supratherapeutic exposure of 19 µM·hr at the 24-mg dose.

In the 9-month monkey study, doses of 0, 30/10/3, 150 or 600/300 mg/kg/day of MK-8189 were administered. Renal tubular degeneration was observed in the high-dose group (600/300 mg/kg/day). The NOAEL for target organ toxicity is 150 mg/kg/day

(AUC0-24hr = 170 µM·hr), providing ~9-fold over the predicted supratherapeutic exposure of 19 µM·hr at the 24-mg dose.

The effects of MK-8189 on measures of cardiac conduction and repolarization were assessed in both in vitro (hERG current [IKr] evaluation) and in vivo (anesthetized guinea pigs and conscious telemetered monkey models). MK-8189 inhibited hERG current with an IC50 value of 44 μM, providing a margin of 1,128-fold to the projected median unbound Cmax in humans at 24 mg (0.039 μM). In an anesthetized guinea pig study, MK-8189 had no effects on HR and ECG parameters. Average peak plasma concentrations of MK-8189 measured during the 20-min infusions of 10, 30 and 60 mg/kg were 56, 150 and 236 μM, respectively. Thus, the NOEL/NOAEL in this study was 236 μM, providing an exposure margin of ~ 242-fold relative to the projected clinical Cmax of 0.975 μM.

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

Therefore, clinical and preclinical data support dose escalation to 24 mg in the current study.

In addition, during the study, safety and tolerability will be carefully assessed including scales to assess dystonia. Dose escalation may be stopped based on tolerability.

4.3.3 Rationale for Dose Interval and Study Design

Part 1

To date, across the multiple-dose clinical trials, MK-8189 has been titrated to the highest dose; each dose was administered for 3 days prior to escalation and the starting dose has ranged from 2 mg to 8 mg. This study will evaluate whether simplified titration schemes or no titration are generally well tolerated. This study will initiate with 16 mg QD for 3 days prior to dose escalation. If this titration scheme is well tolerated, then the next panel will initiate dosing at the highest likely clinical dose of 24 mg. If tolerability is not considered acceptable, then the next panel will follow a more conservative dose escalation scheme and initiate dosing at 8 mg, as described in Section 4.1.

Part 2

Panel D and Panel F: The regimen has been shown to be generally well tolerated in young adults with schizophrenia and the tolerability profile of titration regimens up to 24 mg has been similar in healthy participants and participants with schizophrenia. These data support evaluation in the elderly population with and without schizophrenia.

Panel E and Panel G: The dosing scheme will be based on the regimen in Panel D and Panel F, respectively, being generally well tolerated as well as the safety and tolerability profile observed in Part 1. If the dosing scheme selected is not well tolerated it will also be adjusted as described in Section 4.1.

4.4 Beginning and End of Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female participants with schizophrenia (Parts 1 and 2) and healthy elderly participants (Part 2 only) between the ages of 18 and 60 years (Part 1) and 61 and 80 years (Part 2) will be enrolled in this study. However, in Part 2, only approximately 25% of participants between the ages of 61 and 64 years may be enrolled in each panel.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

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

2. Has a BMI ≤40 kg/m^2 (participants with schizophrenia) or ≤32 kg/m^2 (healthy participants), inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

3. Has no clinically significant abnormality on 12-lead safety ECG performed at the prestudy (screening) visit and/or prior to randomization. The Day 1 predose assessment (prior to randomization) is based on the mean of the triplicate measures. Note: The QTcF duration must be ≤450 msec and the PR interval <230 msec. Repeat 12-lead safety ECGs may be performed in participants whose parameters are, per investigator discretion, minimally outside the designated range. Appendix 9 provides a table of the 12-Lead Electrocardiogram Abnormality Criteria.

4. Has a normal resting BP (systolic BP is ≥90 mmHg and ≤140 mmHg; diastolic BP is ≥60 mmHg and ≤90 mmHg) and normal resting heart rate (≥45 beats per minute [bpm] and ≤100 bpm) in the semirecumbent position at the prestudy (screening) visit and/or prior to randomization. Repeat evaluations may be done if the values for a participant are, per investigator discretion, minimally outside the designated range. The assessment prior to randomization is based on the mean of the triplicate measures for the Day -1 8 hour time-matched assessment. Participants may be included if values are outside the normal range but considered not clinically significant per investigator discretion.

5. Participants with hypothyroidism, diabetes, high BP, chronic respiratory conditions or other mild forms of these medical conditions could be considered as candidates for study enrollment if their condition is stable and the prescribed dose and regimen of medication is stable for at least 3 months prior to screening and there are no expected changes in comedication during the study.

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

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

8. Has a total BPRS score of <48 with a BPRS score <4 for #10 (hostility) and #14 (uncooperativeness) at the screening visit (applies to participants with schizophrenia only).

9. Is in the nonacute phase of their illness and clinically stable for 3 months prior to screening as demonstrated by (applies to participants with schizophrenia only):

    a. no clinically significant change in dose of prescribed antipsychotic medication, or clinically significant change in antipsychotic medication to treat symptoms of schizophrenia for 2 months prior to screening;

b. no increase in level of psychiatric care due to worsening of symptoms of schizophrenia for 3 months prior to screening.

10. Has a history of receiving and tolerating antipsychotic medication within the usual dose range employed for schizophrenia (applies to participants with schizophrenia only).

11. Has a stable living situation in which the patient or a contact person can be reached by the investigator if there is a need for follow up (applies to participants with schizophrenia only).

12. Is able to discontinue the use of all antipsychotic medication at least 5 days prior to the start of the treatment period and during the study period (applies to participants with schizophrenia only).

Demographics

13. Is male or female, from 18 (Part 1) or 61 (Part 2) years to 60 (Part 1) or 80 (Part 2) years of age inclusive, at the time of signing the informed consent.

Female Participants

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

- Is not a WOCBP

  OR

- Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Note: participants intending to rely on abstinence as a birth control method should agree to use double-barrier control methods if they engage in intercourse.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 48 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

15. The participant (or legally acceptable representative if applicable) has provided written documented informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is a WOCBP who has a positive urine pregnancy test within 48 hours before the first dose of study intervention (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

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

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

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

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

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

7. Has an untreated or uncompensated clinically significant renal, endocrine, hepatic, respiratory, gastrointestinal, psychiatric, neurologic, cardiovascular, hematological,

immunological or cerebrovascular disease, malignance, allergic disease or other chronic and/or degenerative process at screening.

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

9. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

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

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

12. Has a family history of sudden death.

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

14. For Part 2 participants only: Participant has an estimated eGFR <60 mL/min/1.73 m^2 based on the MDRD.

    - Participants who have an eGFR or measured creatinine clearance of up to10% below of either 60 mL/min (for creatinine clearance) or 60 mL/min/1.73m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

    MDRD Equation:

    eGFR (mL/min/1.73 m^2) =
    175 x (serum creat)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if African American])

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

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

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

17. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

18. Has evidence or history of a primary DSM-5 axis I psychiatric diagnosis other than schizophrenia or schizoaffective disorder per the allowed DSM-5 criteria within 1 month of screening (applies to participants with schizophrenia only).

19. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator (applies to healthy participants only).
20. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months (applies to participants with schizophrenia only).

21. Is at imminent risk of self-harm, based on clinical interview and responses on the C SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the CSSRS) in the past 5 years or suicidal behavior in their lifetime (applies to healthy participants only).

Prior/Concomitant Therapy

22. Has received treatment with clozapine for schizophrenia or treatment with monoamine oxidase inhibitors within 3 months of screening or cariprazine within 2 months of screening.

23. Has received a parenteral depot antipsychotic medication within 3 months of screening.

24. Is unable to refrain from the use of co-medication with a moderate or strong inhibiting or inducing effect on CYP3A and/or CYP2C9 beginning approximately 2 weeks or 5 half-lives, whichever is longer, prior to administration of the initial dose of trial drug and throughout the trial or is unable to refrain from the use of sensitive substrates of CYP2B6. (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

Not Applicable.

Other Exclusions

26. Is under the age of legal consent.

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

28. Is a current smoker (applies to healthy participants only) or is a smoker (applies to participants with schizophrenia only) that does not agree to follow the smoking restrictions as defined by the CRU.

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

30. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

31. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 years. Participants must have a negative UDS (with the exception of cannabis and/or prescribed concomitant medications permitted at the discretion of the PI and Sponsor) prior to randomization.

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

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

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

On full **PK sampling days,** participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration until 1-hour postdose. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points

indicated in the Schedule of Activities. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each full PK sampling day in each panel (for this study the meal content should be consistent within a given clinical site). After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during study drug administration. Water will be restricted 1 hour prior to and 1 hour after study drug administration.

On **all other days,** participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will remain fasted until 1-hour postdose. Meals and snacks will be unrestricted in caloric content, composition and timing.

Standard meals on Day -1 will be time-matched to Day 1.

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

5.3.1.2 Fruit Juice Restrictions

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

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

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

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

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

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

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

5.3.2.2 Alcohol Restrictions

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

5.3.2.3 Tobacco Restrictions

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

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the prestudy (screening) visit until administration of the initial dose of study drug, throughout the study and until the poststudy visit.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen	Use	IMP/ NIMP	Sourcing
Active	Experi-mental	MK-8189	Drug	Tablet	4 mg 12 mg	All dose levels	Oral	Titration Regimens 1, 2, 3 and Panel D/F dose regimen	Experi-mental	IMP	Provided Centrally
Placebo	Placebo Comparator	MK-8189	Drug	Tablet	0 mg	All dose levels	Oral	Titration Regimens 1, 2, 3 and Panel D/F dose regimen	Placebo	IMP	Provided Centrally
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in [Table 1] will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

The sample allocation schedule for Parts 1 and 2 is provided in [Table 2].

Table 2 Sample Allocation Schedule

Part 1					
Panel	Patients (n)	Day 1	Day 2	Day 3	Days 4-7
A	12	16 mg QD			24 mg QD
	4	PBO			PBO
B	12	24 mg			
	4	PBO			
C	12	8 mg QD	16 mg QD	24 mg QD	
	4	PBO	PBO	PBO	
Part 2					
Panel	Patients (n)	Days 1-3	Days 4-6	Days 7-13	
D/F	12 (Panel D); 10 (Panel F)	8 mg QD	16 mg QD	24 mg QD	
	4 (Panel D); 2 (Panel F)	PBO	PBO	PBO	
Part 2					
Panel	Patients (n)	Days 1-3	Days 4-10		
E/G TR1	12 (Panel E); 10 (Panel G)	16 mg QD	24 mg QD		
	4 (Panel E); 2 (Panel G)	PBO	PBO		
Part 2					
Panel	Patients (n)	Days 1-7			
E/G TR 2	12 (Panel E); 10 (Panel G)	24 mg QD			
	4 (Panel E); 2 (Panel G)	PBO			
Part 2					
Panel	Patients (n)	Day 1	Day 2	Days 3-9	
E/G TR 3	12 (Panel E); 10 (Panel G)	8 mg QD	16 mg QD	24 mg QD	
	4 (Panel E) 2 (Panel G)	PBO	PBO	PBO	
TR = Titration Regimen; n=number; PBO=placebo; QD=once daily					

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

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

6.5 Concomitant Therapy

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

Acetaminophen and antacids (eg, magnesium hydroxide) may be used for minor ailments without prior consultation with the Sponsor.

Medications to treat mild chronic conditions such as hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other mild medical conditions are allowed during the study if the prescribed dose and regimen of medication is stable for at least three months prior to screening and there are no expected changes in co-medication during the study. Moderate to strong inhibitors or inducers of CYP3A and/or CYP2C9 are not allowed as MK-8189 is being metabolized by these CYP enzymes and co-administration of inhibitors or

inducers may potentially alter the metabolism and PK of MK-8189. In addition, MK-8189 is a mild inducer of CYP2B6 in human hepatocytes at drug concentrations of ≥10 μM and therefore co-medication with substrates for CYP2B6 should be avoided (ie, efavirenz and bupropion). See also Section 6.5.1 on rescue medication.

6.5.1 Rescue Medications and Supportive Care

For the treatment of EPS, such as **acute dystonia**, all participants may be treated with an anticholinergic. If the symptoms are unresponsive to anticholinergic treatment, a benzodiazepine can be used.

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

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

Patients will be washed off from their antipsychotic treatment (Section 8.1.5.1). During the washout and treatment period, a benzodiazepine and zolpidem may be used to treat withdrawal symptoms. The drugs indicated above should not be inhibitors or inducers of CYP3A and CYP2C9 (see Section 6.5 for further details), thus no effect on the PK of MK-8189 would be expected during coadministration.

6.6 Dose Modification (Escalation/Titration/Other)

In Part 1, Panel A (Titration Regimen 1), Panel C (Titration Regimen 3), and if applicable for Part 2 (ie, a treatment with a titration scheme is selected), dose titration decisions will be made jointly by the investigator and the Sponsor. However, if a participant needs to be discontinued or have a dose reduction based on safety/tolerability, the principal investigator may do so independent of consultation with the Sponsor.

For Titration Regimen 1 and the dose regimen given in Panel D and Panel F, each dose titration decision for each individual participant will occur after 3 days of dosing per dose level. For Titration Regimen 3, the titration decision for each individual will be made following the 16 mg Dose (Day 2).

For Titration Regimen 2 (no titration), safety and tolerability data will be reviewed following 3 Days of dosing to determine if dosing for an individual participant should continue at that dose level.

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

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

- Skip a single dose and dosing may continue at the same dose level or adjusted downwards
- Receive the same dose level to further explore safety and tolerability at that level
- Receive a lower dose of the study intervention
- Stop dosing

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

Participant discontinuation criteria are outlined in Section 7.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

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 future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

- The maximum amount of blood collected from each participant over the duration of the study will not exceed 278 mL (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the 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 dated signature or by the participant's legally acceptable representative's dated signature.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. This will also include any psychiatric history of the participant.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Administration of study intervention(s) will be monitored by the investigator and/or study staff.

8.1.8.1 Timing of Dose Administration

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

8.1.9 Discontinuation and Withdrawal

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

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

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

8.1.11 Domiciling

Healthy elderly participants will be domiciled by Day -1. Participants with schizophrenia will report to the CRU at least 6 days prior to treatment with MK-8189 on Day 1 and all participants will remain in the unit until the 48-hours postdose procedures are complete. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

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

BMI

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

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

8.3.2 Vital Signs

- Body temperature, heart rate, respiratory rate, and blood pressure will be assessed at prespecified timepoints noted in the SoA (Section 1.3).
- Blood pressure and heart rate measurements (to be taken before blood collection for laboratory tests) will be assessed in a semirecumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart on Day -1 as indicated in the SoA. The mean of Day -1 time-matched triplicate measurements will be used as the baseline to calculate change from baseline for postdose safety evaluations (and for rechecks, if needed). Screening and postdose VS measurements will be single measurements.

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained. Participants should be semirecumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic VS.

8.3.3 Electrocardiograms

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

Participants should be resting in the semirecumbent for at least 10 minutes prior to each ECG measurement.

At baseline, when triplicate ECG are required, 3 individual ECG tracings should be obtained as close as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes. The mean of these measurements will be used as the baseline measurement to calculate change from baseline for safety evaluations (and for rechecks, if needed).

Single 12-lead ECGs will be obtained postdose and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and withdrawal criteria and additional QTc readings that may be necessary.

The correction formula to be used for QTc is Fridericia.

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

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

If the QTc interval is ≥500 msec on any postdose ECG, the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a cardiac or intensive care unit) is available.

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

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the operations manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

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

8.3.5 Suicidal Ideation and Behavior Monitoring

8.3.5.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

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

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

The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior at screening, the

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

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an 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). Subsequent to that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety.

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

8.3.6 Monitoring for Extrapyramidal Symptoms

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

8.3.7 Assessment of Neuropsychological Effects

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

In addition, the BPRS will also be completed at times specified in the SoA.

A general (full) Neurological Exam will be performed at the Screening visit and Baseline (Day -1). A targeted Neurological Exam will be administered at times specified in the SoA.

The operations manual contains sample forms of the VAS, BPRS and Appendix 11 contains the general and targeted Neurological Exams.

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

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

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

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

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

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

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	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
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

This section is not applicable to this study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

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

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

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

3. Dystonia

4. New or worsening tardive dyskinesia

5. QTcF interval of ≥500 msec (the average of 3 QTcFs will be used)

6. Suicidal ideation, suicidal behavior

8.5 Treatment of Overdose

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

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8189

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

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C9 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C9. Leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent.

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

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover main study plasma from MK-8189 and/or metabolites assay stored for future research.

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 4 weeks prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

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

8.10.2 Treatment Period

Part 1

Participants who meet selection criteria for enrollment will participate in Panel A, Panel B or Panel C after washing off their current atypical antipsychotic medication. Approximately 32 participants may be enrolled in Part 1.

On treatment days between Day 1 and Day 7, participants will be dosed once daily with MK-8189 or matching placebo and have procedures completed per the SoA. Participants will remain in the unit until Day 9 procedures are complete.

Part 2

Participants with Schizophrenia: Participants who meet selection criteria for enrollment will participate in Part 2 after washing off their current atypical antipsychotic medication. Up to approximately 16 participants will be enrolled in Panel D. In Panel E, 24 participants may be enrolled if more than 1 titration regimen is evaluated as described in Section 4.1. The intent is to have ~16 participants complete one titration regimen in Panel E.

Healthy elderly participants: Up to approximately 12 participants will be enrolled in Panel F. In Panel G, up to 20 participants may be enrolled if more than 1 titration regimen is evaluated as described in Section 4.1. The intent is to have ~12 participants complete one titration regimen in Panel G.

Panel D/F Dose Regimen: On treatment days between Day 1 and Day 13, participants will be dosed once daily with MK-8189 or matching placebo and have procedures completed per the SoA. Participants will remain in the unit until Day 15 procedures are complete.

Panel E/G Titration Regimen 1: On treatment days between Day 1 and Day 10, participants will be dosed once daily with MK-8189 or matching placebo and have procedures completed per the SoA. Participants will remain in the unit until Day 12 procedures are complete.

Panel E/G Titration Regimen 2: On treatment days between Day 1 and Day 7, participants will be dosed once daily with MK-8189 or matching placebo and have procedures completed per the SoA. Participants will remain in the unit until Day 9 procedures are complete.

Panel E/G Titration Regimen 3: On treatment days between Day 1 and Day 9, participants will be dosed once daily with MK-8189 or matching placebo and have procedures completed per the SoA. Participants will remain in the unit until Day 11 procedures are complete.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.10.4 Poststudy

After completion of treatment, participants will resume the use of their own antipsychotic medication after the 48-hour postdose procedures are complete per the SoA and be discharged at the discretion of the investigator. A phone call should occur ~ 5 days after discharge from the unit to check for any side effects and medication compliance.

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

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-8189 is the critical procedure.

At any postdose time point, the blood sample for MK-8189 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director. Blood samples should be taken after vital sign and ECG assessments or there should be a 10-minute window between a blood draw and the start of a vital sign or ECG assessment.

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

The following variance in procedure collection times will be permitted.

- PK collections may be obtained:
  - Predose within 1 hour prior to dosing
  - within +/- 20 minutes of all postdose theoretical timepoints.
- Predose standard safety evaluations:
  - Vital signs within 15 minutes from the theoretical timepoint
  - ECG within 2 hours prior to first dose
  - Laboratory safety tests and physical exam within 48 hours prior to first dose
- Postdose standard safety evaluations:
  - Vital signs and ECG within 20 minutes from the theoretical timepoint
  - Laboratory safety tests within 90 minutes prior to the theoretical timepoint
- Study intervention administration may be given within 30 minutes from the theoretical timepoint.

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

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

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

- Repeat of or decrease in the dose of the study intervention administered in any given panel
- Repeat of a Panel at the same dose regimen or more conservative dose regimen.
- Entire panels may be omitted
- Adjustment of the dosing interval (eg, divided doses [BID to QD, QD to BID, TID, or vice versa])

- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK sample processing and shipping details based on newly available data
- A single dose may be skipped, and dosing may continue at the same dose level or adjusted downward.

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

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

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

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

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

Safety: Summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). For vital signs, time-matched Day -1 readings will be used as baseline. For all other endpoints, baseline is defined as average of predose Day 1 or Day -1 readings.

For all panels, summary statistics and plots will be generated for BARS, AIMS and SAS, VAS, and BPRS as well as for change from baseline. Responses to the C-SSRS will be listed.

Pharmacokinetics:

Separately for each part and each PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose and a random effect for subject. For each PK parameter, GM and corresponding ninety-five percent Cis for each dose will be provided.

The comparison of elderly participants with schizophrenia to young adults with schizophrenia will be made using data from Part 2 and Part 1, and historical data from P007 (Panel B and D). Separately for each PK parameter individual values of AUC0-24hr, Cmax, and C24hr at each dose level (16 mg and 24 mg at steady state) will be natural log-transformed and evaluated with a linear mixed effects model containing fixed effects for dose, population (elderly, adult), and population by dose interaction and a random effect for subject. For each population, GMs and corresponding 95% CIs for each dose will be provided. Similarly, the comparison of healthy elderly participants (Panels F and G) to healthy young adults (Panel A in P007) will be made using the above described model.

9.2 Responsibility for Analyses

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

9.3 Hypotheses/Estimation

Objectives

Primary

Part 1

- To evaluate the safety and tolerability of MK-8189 oral, once-daily titration regimens in young adult participants with schizophrenia

Part 2

To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in elderly participants with schizophrenia and healthy elderly participants.

Secondary

Part 1

- To characterize MK-8189 pharmacokinetics following different titration regimens in young adult participants with schizophrenia

Part 2

- To characterize the pharmacokinetics of MK-8189 following multiple once-daily oral doses in elderly participants with schizophrenia and in healthy participants.

Exploratory

Part 1 and Part 2

- To investigate the relationship between CYP2C9 genetic polymorphs and the PK and PD of MK-8189. Genetic variation in CYP2C9 may be analyzed for association with any laboratory or clinical data collected in this study.

- To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

Part 2

- To compare the pharmacokinetics of MK-8189 in elderly participants with schizophrenia to dose-matchedyoung adult participants with schizophrenia

To compare the pharmacokinetics of MK-8189 in elderly healthy participants to dose-matched healthy young adult participants.

9.4 Analysis Endpoints

Safety: Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, 12-lead ECGs, and VS. For vital signs, time-matched Day -1 readings will be used as baseline. For all other endpoints, baseline is defined as the predose Day 1 or Day -1 readings, as appropriate.

For all panels, summary statistics will be generated for BARS, AIMS, SAS, VAS, and BPRS as well as for change from baseline. The difference from baseline will be computed on the original scale (raw change from baseline). Responses to the C-SSRS will be listed. The C-SSRS will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (ie, ideation and behavior). Responses on the C-SSRS are classified according to 11 prespecified categories as described in the operations manual. The most severe treatment-emergent ideation and behavior event reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it newly emerged or is more severe compared to recent history (ie, protocol-defined recent history prior to entering the trial as stated in the Inclusion/Exclusion criteria for suicidal ideation/behavior, up to and including the randomization visit).

Secondary Endpoints

Pharmacokinetics: MK-8189 PK variables (AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd and t1/2) are of secondary interest in adult and elderly participants with schizophrenia and healthy participants

Exploratory Endpoints

Comparison of young adults versus elderly: MK-8189 PK variables MK-8189 (AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd, and apparent t1/2).

9.5 Analysis Populations

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

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

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

9.6 Statistical Methods

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, 12-lead ECGs, and/or VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). For vital signs, time-matched Day -1 readings will be used as baseline. For all other endpoints, baseline is defined as the predose Day 1 or Day -1 readings, as appropriate.

For both parts, summary statistics and plots will be generated for BARS, AIMS, SAS, VAS, and BPRS as well as for change from baseline. Responses to the C-SSRS will be listed.

Pharmacokinetics

Separately for each part and each PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for dose and a random effect for subject. For each PK parameter, GM and corresponding 95% CI for each dose will be provided.

Comparison of Elderly Participants and Young Adults

The comparison of elderly participants with schizophrenia to young adults with schizophrenia will be made using data from Part 2 (Panels D and E) and Part 1, and historical data from P007 (Panels B and D). Separately for each PK parameter, individual values of AUC0-24hr, Cmax, and C24hr at each dose level (16 mg and 24 mg at steady state) will be natural log-transformed and evaluated with a linear mixed effects model containing fixed effects for dose, population (elderly, adult), and population by dose interaction and a random effect for subject. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. For each population, 95% CIs for the least squares means for each dose will be constructed on the natural log scale. Exponentiating the least-squares means, and lower and upper limits of these CIs will yield estimates for the population GMs and CIs about the GMs on the original scale. Individual PK values, GMs and 95% CIs will be shown graphically by population. A two-sided 90% CIs for the true differences in mean for log-transformed AUC0-24r, Cmax, and C24hr (elderly – adults) will also be computed from the model. These CIs will be exponentiated to obtain the 90% CIs for the AUC0-24hr, Cmax, and C24hr true geometric mean ratios (elderly/adults). Additionally, a plot of GMR with corresponding 90% CI will also be provided.

Similarly, the comparison of healthy elderly participants (Panels F and G) to healthy young adults (Panel A in P007) will be made using the above described model.

The exploratory objective pertaining to the assessment of relationship between CYP2C9 genetic polymorphs and the laboratory, and PK of MK-8189, and the relationship between genetic variation and response to the treatment may be addressed in a separate report.

Descriptive Statistics

For each Part and panel, individual values will be listed for each PK parameter AUC0-24hr, Cmax, C24hr, Tmax, CL, Vd, and t1/2 by dose (and day where applicable), and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) – 1), where s^2 is the observed variance on the natural log-scale).

9.7 Interim Analyses

No interim analyses are planned

9.8 Multiplicity

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

9.9 Sample Size and Power Calculations

Since there are no hypotheses, no power calculations are provided.

Comparison of Elderly vs Young Adults (Exploratory): The between-subject standard deviation estimates for healthy and participants with schizophrenia used in the calculations below were obtained from 24 mg dose in MK-8189 PN007 Panel A and Panel B, respectively. At each of the comparable doses, the precision of the estimates of GMR obtained from the study can be assessed by calculating the half-width of the 90% CIs for the GMRs (elderly/adults) expected for the given sample size and assumed between-subject standard deviation. [Table 4] below shows the half-width of the 90% CI for the true GMR for PK parameters, AUC0-24hr, Cmax, and C24hr.

Table 4 Precision Estimates for AUC0-24hr, Cmax, and C24hr

PK Parameter	Observed (Log) Between-Subject SD	N	(Log) Half-Width of 90% CI	Observed GMR (elderly/adults)	90% CI Based on Observed GMR
elderly with schizophrenia vs adults with schizophrenia					
AUC0-24hr	0.38	12 elderly 12 adults	0.266	1.00	(0.77, 1.31)
Cmax	0.37	12 elderly 12 adults	0.259	1.00	(0.77, 1.30)
C24hr	0.48	12 elderly 12 adults	0.336	1.00	(0.71, 1.40)
healthy elderly vs healthy adults					
AUC0-24hr	0.60	10 elderly 12 adults	0.443	1.00	(0.64, 1.56)
Cmax	0.48	10 elderly 12 adults	0.354	1.00	(0.70, 1.43)
C24hr	1.11	10 elderly 12 adults	0.822	1.00	(0.44, 2.27)

AUC=area under the time-concentration curve from 0 to 24 hours; C24hr=concentration at 24 hours; CI=confidence interval: Cmax=maximum concentration; GMR=geometric mean ration; N=number; PK = pharmacokinetic, SD = standard deviation ,

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design 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 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish 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. 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, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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 prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the 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 trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and 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, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 5] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 5 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or CO2	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines); If the clinical site's drug evaluation routinely detect additional agents, the relevance of positive findings for exclusion will be discussed with the Sponsor. • Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, hepatitis B surface antigen [HbsAg], and hepatitis C virus antibody)
NOTES: The investigator (or medically qualified designee) must document their review of each laboratory safety report.	

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

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

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

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 Sponsor's product cause the AE?

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

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

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. [f] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

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

5. Biorepository Specimen Usage

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

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

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

7. Retention of Specimens

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

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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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: Blood Volume Table

Part 1: All Panels	Pre-study (Screening)	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests including Serum β-hCG (WOCBP only) or Serum FSH (WONCBP only)	1	3	1	5	12.5	62.5
HIV/Hepatitis Screen (per site SOP)	1			1	8.5	8.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-8189 and/or metabolites assay (Panel A)		26		26	4.0	104.0
Blood for MK-8189 and/or metabolites assay (Panel B)		25		25	4.0	100.0
Blood for MK-8189 and/or metabolites assay (Panel C)		34		34	4.0	136.0
Blood for IV catheter flush (Panel A) [a]				33	2.0	66.0
Blood for IV catheter flush (Panel B) [a]				32	2.0	64.0
Total Blood Volume per Participant for Panel A[b]						249.5 mL
Total Blood Volume per Participant for Panel B[b]						243.5 mL
Total Blood Volume per Participant for Panel C[b]						215.5 mL

[a] If IV catheter use is necessary to support blood collection, additional blood (up to 2 mL per collection) may be collected and discarded prior to drawing the sample.

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained.

Part 2: All Panels	Pre-study (Screening)	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests including Serum FSH (Panel D/F)	1	3	1	5	12.5	62.5
Laboratory Safety Tests including Serum FSH (Panel E/G Titration Regimen 1)	1	5	1	7	12.5	87.5
Laboratory Safety Tests including Serum FSH (Panel E/G Titration Regimens 2 & 3)	1	4	1	6	12.5	75.0
HIV/Hepatitis Screen (per site SOP)	1			1	8.5	8.5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-8189 and/or metabolites assay (Panel D/F and Panel E/G Titration Regimen 3)		34		34	4.0	136.0
Blood for MK-8189 and/or metabolites assay (Panel E/G Titration Regimen 1)		26		26	4.0	104.0
Blood for MK-8189 and/or metabolites assay (Panel E/G Titration Regimen 2)		25		25	4.0	100.0
Blood for IV catheter flush (Panel D/F) [a]				41	2.0	82.0
Blood for IV catheter flush (Panel E/G Titration Regimen 1) [a]				35	2.0	70.0
Blood for IV catheter flush (Panel E/G Titration Regimen 2) [a]				33	2.0	66.0
Blood for IV catheter flush (Panel E/G Titration Regimen 3) [a]				42	2.0	84.0
Total Blood Volume per Panel D/F Participant[b]						297.5 mL
Total Blood Volume per Panel E/G Titration Regimen 1 Participant[b]						278.5 mL
Total Blood Volume per Panel E/G Titration Regimen 2 Participant[b]						258.0 mL
Total Blood Volume per Panel E/G Titration Regimen 3 Participant[b]						312.0 mL

[a] If IV catheter use is necessary to support blood collection, additional blood (up to 2 mL per collection) may be collected and discarded prior to drawing the sample..

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria (if criteria diverges from inclusion/exclusion criteria, more conservative criteria should be used)

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

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post Randomization Findings (clarification on action to take)**
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

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

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

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

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

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

   1. The participant may be excluded from the study;

   2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

      OR

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

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

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

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

10.11 Appendix 11: General (Full) and Targeted Neurological Exam

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

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

The General (Full) Neurological Examination

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

MODULE 1 – MENTAL STATUS EXAMINATION

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

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

C. Orientation (time, place, person)

D. Attention/Concentration

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

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

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

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

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

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

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

D. V – Facial Sensation, Jaw Strength

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

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

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)

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

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

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

   1. Ask the volunteer to relax.

   2. Flex and extend the volunteer's elbows and at the knees (bilaterally).

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

   4. Observe for involuntary movements (e.g., tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

      Score: ***left and right***

      Grade: **NORMAL, INCREASED or DECREASED**

B. Muscle Strength

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

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

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

   Test bilaterally, and compare one side to the other.

   Score: ***left and right***

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

   4/5: movement against resistance impaired;

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

   2/5: visible movement but not against gravity;

   1/5: visible contraction;

   0/5: no visible activity

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

   Test bilaterally, and compare one side to the other.

   Score: ***left and right***

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

   4/5: movement against resistance impaired;

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

   2/5: visible movement but not against gravity;

   1/5: visible contraction;

   0/5: no visible activity

C. Pronator Drift

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

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

Score: ***left and right***

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

MODULE 4 - REFLEXES

A. Biceps

B. Knee

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

Score: ***left and right***

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

C. Babinski

Score: ***left and right***

Grade: **NORMAL or ABNORMAL**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

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

Score: ***left and right***

Grade: **NORMAL or IMPAIRED**

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

B. Point-to-Point Movements

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

   Score: ***left and right***

   Grade: **NORMAL or IMPAIRED**

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

C. Romberg

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

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

   Grade: **NORMAL or IMPAIRED**

D. Gait

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

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

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

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

MODULE 6 - SENSORY

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

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

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

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

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

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

Score: ***left and right***

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

Targeted Neurological Exam

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

MODULE 1 – MENTAL STATUS EXAMINATION

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

MODULE 2 – CRANIAL NERVE ASSESSMENT

B. II, III – Pupil Size and Reactivity

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

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

MODULE 3 - MOTOR SYSTEM

B. Muscle Tone

1. Ask the volunteer to relax.

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

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

Score: ***left and right***

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

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

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

   Score: ***left and right***

   Grade: **NORMAL or IMPAIRED**

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

D. Gait

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

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

MODULE 6 - SENSORY

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

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
AAP	atypical anti-psychotics
AE	adverse event
AIMS	abnormal involuntary movement scale
ALT	alanine aminotransferase
APasT	All participants as treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC0-24hr	area under the concentration-time curve from 0 to 24 hours
AV	atrioventricular
BARS	Barnes Akathisia Rating Scale
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BPRS	Brief Psychiatric Rating Scale
BUN	Blood Urea Nitrogen
C24hr	concentration at 24 hours
cAMP	cyclic adenosine monophosphate
CGI-S	Clinical Global Impression – severity scale
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CNS	central nervous system
CR	controlled release
CRF	case report form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CYP2B6	Cytochrome P450 2B6
CYP2C9	Cytochrome P450 2C9
CYP3A	cytochrome P4503A
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EO	enzyme occupancy
EPS	extrapyramidal symptoms
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GI	gastrointestinal
GM	geometric mean
GMR	eometric mean ratio
hERG	human ether-á-go-go-related gene
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	investigational new drug
IR	immediate release
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhoea method
LS	least squares means
MDRD	modification of diet in renal disease
NCS	not clinically significant
NDA	new drug application
NIMP	Non-Investigational Medicinal Product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PANSS	Positive and Negative Syndrome Scale
PBO/pbo	placebo
PCL	protocol clarification letter
PD	pharmacodynamic
PDE10A	phosphodiesterase 10A
PK	pharmacokinetic
PP	Per-protocol
POC	proof of concept
PRO	patient-reported outcome
QD	once a day
RBC	Red blood count
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	schedule of activities
SOP	Standard operating procedure

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
TID	three times a day
Tmax	time of maximum concentration
UDS	urine drug screen
VAS	Bond and Lader Visual Analog Scale
Vd	volume of distribution
VS	vital sign
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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