Official Protocol Title:	A Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of the Long-Acting Injectable of MK-5720 in Participants with Schizophrenia
NCT number:	NCT05953740
Document Date:	08-Aug-2023

TITLE PAGE

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Protocol Title: A Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of the Long-Acting Injectable of MK-5720 in Participants with Schizophrenia

Protocol Number: 001-02

Compound Number: MK-5720

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

Legal Registered Address:

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	N/A
EU CT	N/A
EudraCT	N/A
JAPIC-CT	N/A
WHO	N/A
UTN	N/A
IND	158448

Approval Date: 08 August 2023

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	08-AUG-2023	Section 4.1 of the protocol was updated to include an oral run-in period with MK-8189 prior to dosing MK-5720.
Amendment 1	16-JUN-2023	Section 9.5.2 of the protocol was updated to include language that was excluded unintentionally in the original protocol.
Original Protocol	06-JUN-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

Section 4.1 Overall Design was updated based on feedback from the FDA to include an oral run-in period with MK-8189 prior to dosing MK-5720.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1 Overall Design	This section was updated to include an oral run-in period with MK-8189 prior to dosing MK-5720.	This change was made to address feedback from the FDA.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Throughout	Minor grammatical and typographical errors were corrected.	These were non-substantial editorial corrections.
Throughout	Period 1 and Period 2 were added throughout the protocol.	This change provides clarification on timing of events based on treatment period.
Section 1 Protocol Summary	The estimated duration of the study was updated from 10 to 12 months. The estimated duration of participation was updated from 16 to 17 weeks.	The change was made to accurately reflect the change in time requirements for the updated study design.
Section 1.2 Schema	Table 1 and Figure 1 were updated to include Period 1 and Period 2.	This change reflects the change of the study design on the dose escalation scheme and overall study design.
Section 1.3 Schedule of Activities	This section was split into two SoAs for each treatment period, Section 1.3.1 for Period 1 and Section 1.3.2for Period 2.	This modification was made to simplify the SoA.
Section 1.3.1 Schedule of Activities: Period 1 Oral Run-in with MK-8189	Section 1.3.1 contains information for the Screening Period, Washout Period, and the MK-8189 treatment period, and MK-8189 Washout Period.	This modification was made to accommodate the change in study design.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.2 Schedule of Activities: Period 2 MK-5720 Treatment	Section 1.3.2 was the previous SoA which has been modified to remove the Screening Period and related activities and Washout Period and related activities. Footnote "a" was updated to remove details regarding the washout period and updated the duration of domiciling. The row and footnote related to samples for genetic analysis were moved to Section 1.3.1.	These modifications were made to accommodate changes to study design and sort activities based on when they occur within the study.
	Footnote "j" was updated to include windows for MRI exams to be completed.	This modification was made to provide clarification on what the windows were for collecting the MRI exams.
Section 3 Hypothesis, Objectives, and Endpoints	The following primary objective and endpoint was added: Objective: To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia. Endpoint: Adverse events, Discontinuation due to adverse events The following exploratory objective and endpoint was added: Objective: To assess the pharmacokinetics of oral MK-8189 after multiple doses in participants with schizophrenia. Endpoint: AUC0-24, Cmax, Tmax and C24	This modification was made to reflect the update to the study design.
	The imaging exploratory objective and endpoint was reworded.	This modification was made to clarify that imaging will be done at multiple timepoints.
Section 4.2 Scientific Rationale for Study Design	Rationale for the Period 1 study design with MK-8189 was added.	Refer to Section 4.1 Rationale
Section 4.2.2 Rationale for the Use of Comparator/Placebo	The following bolded text was added "Placebo will be used in this study to allow for an appropriate assessment of the safety data of **oral MK-8189 and** MK-5720 LAI and to maintain study blinding to reduce bias."	Refer to Section 4.1 Rationale

Section Number and Name	Description of Change	Brief Rationale
Section 4.3 Justification for Dose	Rationale was added for the MK-8189 doses and duration of the run-in period.:	Refer to Section 4.1 Rationale
Section 4.3.2 Maximum Dose Exposure for This Study	Table 4 was updated to include the projected steady state PK parameters following multiple oral doses of MK-8189 for the 48 mg dose.	Refer to Section 4.1 Rationale
Section 4.2.2 Rationale for Dose Interval and Study Design	Rationale for the oral run-in Period with MK-8189 was added.	Refer to Section 4.1 Rationale
Section 5.1 Inclusion Criteria	The following criterion was added: "Has regular bowel movements and, in the opinion of the investigator, no clinically significant diarrhea or constipation".	This change was added based on oral MK-8189 being used.
Section 5.2 Exclusion Criteria	Exclusion criteria #15 and #16 were updated to include a note clarifying these criteria only apply to panels who are receiving imaging as described in PCL #1.	This change was made based on feedback from one of the study investigators to help with enrollment of non-MRI panels.
Section 5.3.1.1 Diet Restrictions	This section was divided up into subsections to clarify restrictions for Period 1, Period 2, and all Periods. New restrictions were provided for MK-8189 in Period 1.	This modification provides clarification on diet restrictions based on new study intervention.
Section 5.5 Participant Replacement Strategy	Clarification on replacement strategy to include both participant withdraw and discontinuation due to tolerability concerns was added. The following text was removed: "The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion."	This modification expands the scope of using replacements for participants who withdraw or discontinue the study. This modification was made to reflect the parallel study design and there are no subsequent dose level for a given panel.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1 Study Intervention(s) Administered	Table 6 was updated with study intervention information for the oral run-in period with MK-8189 for all panels.	This change was made to reflect the new study intervention being added.
	The following footnote was added to the table: "Those who receive placebo in Period 1 will receive placebo in Period 2. Those receiving MK-8189 in Period 1 will receive MK-5720 in Period 2."	This modification was made to clarify on study intervention assignment for both periods.
Section 6.2.1 Dose Preparation	The following section was subdivided into MK-8189 and MK-5720 and language was added for MK-8189.	This modification was made to provide clarification on how study intervention is to be prepared and guidance for MK-8189 dose preparation.
Section 6.3.1 Intervention Assignment	Table 7 was updated to include the treatments for Period 1 and Period 2.	This modification reflects the changes to the current treatment groups in the study based on the new study design.
Section 6.3.3 Blinding	The MK-8189 was added to the following statement: "MK-8189, MK-5720 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel."	This modification was made to include MK-8189 in the blinding of study intervention.
Section 8.1.8 Study Intervention Administration	This section was subdivided into Period 1 and Period 2. New text was added for Period 1 for MK-8189 dosing.	This section was modified to provide guidance on how each study intervention is to be administered for each period.
Section 8.1.8.1 Timing of Dose Administration	This section was subdivided into Period 1 and Period 2. Dosing instructions for MK-8189 in Period 1 was added.	Refer to Section 8.1.8 rationale.
Section 9.3.1 Primary Endpoints	Information regarding the analysis of safety and tolerability data for MK-8189 was added.	The SAP section was updated to align with new study design updates.
Section 9.3.3 Exploratory Endpoints	Information regarding the analysis of the PK endpoints for MK-8189 in Period 1 was added.	Refer to Section 9.3.1 rationale.
Section 9.4.1 All Participants as Treated Population	Updated to include two APaT populations for this study.	Refer to Section 9.3.1 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 9.5 Statistical Methods	This section was updated to provide clarification on the statistical methods for data obtained in Period 1 and Period 2.	Refer to Section 9.3.1 rationale.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of the Long-Acting Injectable of MK-5720 in Participants with Schizophrenia

Short Title: MK-5720 SAD Study

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in participants with schizophrenia.

Primary Objective	Primary Endpoint
To evaluate the safety and tolerability of single-ascending doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia.	Adverse Events Study discontinuation due to adverse events
To assess the plasma pharmacokinetics of MK-5720 and MK-8189 following single doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia. CCI [redacted]	Plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2 Plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2
To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia.	Adverse Events Study discontinuation due to adverse events

Secondary Objective	Secondary Endpoints
To assess the plasma pharmacokinetics of MK-8189 following single doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia CCI [redacted]	CCI [redacted]
To compare the effect of the site of administration of MK-5720 long-acting injectable on plasma pharmacokinetics of MK-5720 and MK-8189 following a single dose of MK-5720 long-acting injectable administered intramuscularly in the gluteal muscle relative to its administration in the deltoid muscle. Estimation: The effects of the site of administration on plasma pharmacokinetics of MK-5720 and MK-8189 following a single dose of MK-5720 long-acting injectable administered intramuscularly in the gluteal muscle will be estimated and compared to a single dose of MK-5720 long-acting injectable administered intramuscularly in the deltoid muscle.	Plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2 Plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Schizophrenia
Population	Participants with schizophrenia or schizoaffective disorder
Study Type	Interventional
Intervention Model	Sequential This is a multi site study.
Type of Control	Placebo

Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 12 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 64 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Panel A	MK-8189	4 mg	4 mg	Oral	Period 1	Test Product
Panel A	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel A	MK-5720	350 mg/mL	35 mg	IM	Period 2	Test Product
Panel A	Placebo	0 mg	0 mg	IM	Period 2	Placebo
Panel B	MK-8189	4 mg	8 mg	Oral	Period 1	Test Product
Panel B	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel B	MK-5720	350 mg/mL	70 mg	IM	Period 2	Test Product
Panel B	Placebo	0 mg	0 mg	IM	Period 2	Placebo
Panel C	MK-8189	4 mg 12 mg	16 mg	Oral	Period 1	Test Product
Panel C	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel C	MK-5720	350 mg/mL	140 mg	IM	Period 2	Test Product
Panel C	Placebo	0 mg	0 mg	IM	Period 2	Placebo
Panel D	MK-8189	12 mg	24 mg	Oral	Period 1	Test Product
Panel D	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel D	MK-5720	350 mg/mL	280 mg	IM	Period 2	Test Product
Panel D	Placebo	0 mg	0 mg	IM	Period 2	Placebo
Panel E	MK-8189	12 mg	48 mg	Oral	Period 1	Test Product
Panel E	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel E	MK-5720	350 mg/mL	≤560 mg	IM	Period 2	Test Product
Panel E	Placebo	0 mg	0 mg	IM	Period 2	Placebo
Panel F	MK-8189	12 mg	48 mg	Oral	Period 1	Test Product
Panel F	Placebo	0 mg	0 mg	Oral	Period 1	Placebo
Panel F	MK-5720	350 mg/mL	≤560 mg	IM	Period 2	Test Product
Panel F	Placebo	0 mg	0 mg	IM	Period 2	Placebo

Other current or former name(s) or alias(es) for study intervention(s) are as follows: Not applicable.

Total Number of Intervention Groups/Arms	6
Duration of Participation	Each participant will participate in the study for approximately 17 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 12.

1.2 Schema

The study design is depicted in [Table 1] and [Figure 1].

Table 1 Dose Escalation Scheme

Panels[a,b]	MK-8189 Oral Run-In Dose[c] (Period 1)	Dose Escalation of MK-5720 (Period 2)									
A	4 mg	35 mg[d]		PK Break[e]		PK Break[e]		PK Break[e]		PK Break[e]	
B	8 mg		70 mg[d]								
C	≤16 mg				≤140 mg[d]						
D	≤24 mg						≤280 mg[f,g]				
E	≤48 mg								≤560 mg[f,g]		
F	≤48 mg										≤560 mg[f,g]

IM=intramuscular; LAI= long acting injectable; MRI=magnetic resonance imaging; PK=pharmacokinetics

Note: During Period 1, MK-8189 will be administered once daily for 7 days followed by a washout period of at least 72 hours prior to dosing MK-5720.

[a] The suggested doses (with the exception of the starting dose) may be adjusted downward based on evaluation of safety, tolerability and PK data observed in previous intervention panels. Refer to Section 6.6 (Dose Modification) for the safety and PK data that will be reviewed prior to dose escalation.

[b] Panels A to B, 6 participants will be randomized to receive MK-5720 and 2 participants to receive matching placebo. Panels C to F, 9 participants will be randomized to receive MK-5720 and 3 participants to receive matching placebo. Patients will be randomized according to a computer-generated allocation schedule.

[c] The dose of MK-8189 during the oral run-in period may be adjusted downward based on the corresponding dose of MK-5720 administered in the panel to match steady state peak plasma exposures of MK-8189 from oral MK-8189 and MK-5720 IM injection.

[d] MK-5720 LAI will be administered IM in the deltoid muscle

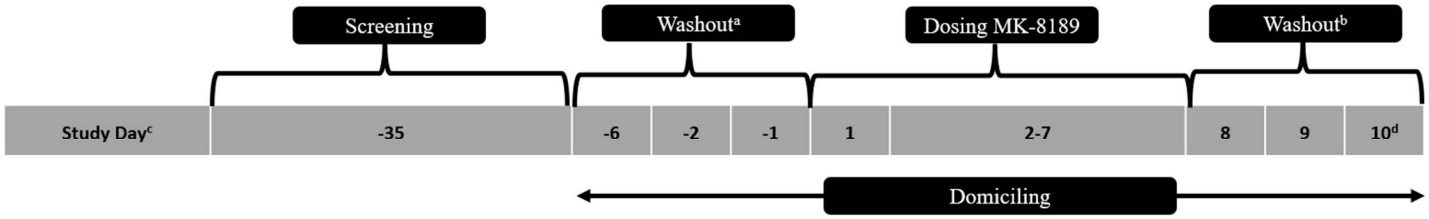
[e] There will be a PK break following Panel B, C, D, and E

[f] MK-5720 LAI will be administered IM in the deltoid, or the gluteal muscle based on PK from Panels A to C

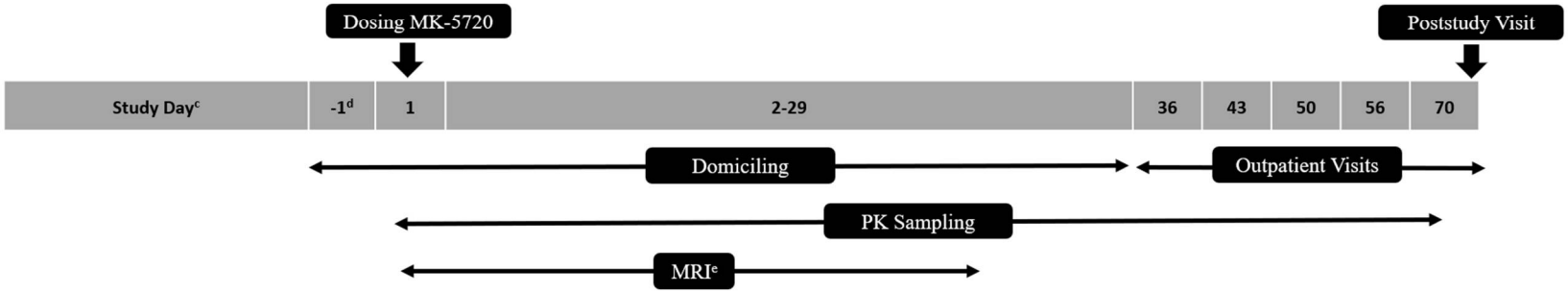
[g] MRI imaging shall be performed in panels at or 1 dose level below the highest dose of MK-5720 administered IM in the deltoid and gluteal muscle

Figure 1 Overall Study Design

Period 1: MK-8189 Oral Run-In



Period 2: MK-5720 Treatment Period



MRI=Magnetic resonance imaging; PK=pharmacokinetic
[a]Participants not currently being treated with antipsychotic medication may be domiciled minimally starting on Day -2 in Period 1.
[b]The washout period for MK-8189 will be ≥72 hours.
[c]Study Day is relative to dosing of study drug for each study drug.
[d]Day 10 in Period 1 corresponds to Day-1 in Period 2 (the last day of the MK-8189 washout period will correspond to Day -1 in Period 2).
[e]Imaging will be conducted in select panels and in all participants for Days 1 and 14 and select participants on Days 7 and 19.

1.3 Schedule of Activities

1.3.1 Schedule of Activities: Period 1 Oral Run in with MK-8189

All Panels															
Study Period	**Screening**	**Washout and Check-In**		**Intervention**											**Notes**
Scheduled Day	**Up to -35**	**-6**	**-2**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
				Predose	**Up to 24 h**										
Administrative Procedures															
Informed Consent	X														Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X														Sec 5.1, 8.1.1.2
Participant ID Card	X														Sec. 8.1.3
Inclusion and Exclusion Criteria	X			X											Sec. 5.1, 5.2, 8.1.5
Medical History (includes psychiatric history and substance abuse)	X														Substances: Drugs, alcohol, tobacco, and caffeine Sec. 8.1.4
Prior and Concomitant Medication Review	X----------X														Sec. 5.2, 6.5, 8.1.5

All Panels															
Study Period	**Screening**	**Washout and Check-In**		**Intervention**											**Notes**
Scheduled Day	**Up to -35**	**-6**	**-2**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
				Predose	**Up to 24 h**										
Assignment of Screening Number	X														Sec. 8.1.6
Washout from current antipsychotic therapy	X	X													Medication discontinued at least 5 days or at least 3 half-lives (whichever is longer) prior to Day -1 Sec. 8.1.5
Assignment of Randomization Number				X											Sec. 5.5, 8.1.7
MK-8189 or Placebo Administration					X	X	X	X	X	X	X				Sec. 8.1.8
Washout from MK-8189												X	X	X	Section 4.1
Standard Meals		X----------												----------X	Sec. 5.3.1
Domiciling[a]		X----------												----------X	Sec. 8.1.11
Safety Procedures															
Full physical examination	X			X											Sec. 8.3.1, 8.10.5
Height	X														Sec. 8.3.1
Weight[b]	X			X											BMI to be taken only at Screening Sec. 8.3.1

All Panels															
Study Period	**Screening**	**Washout and Check-In**		**Intervention**											**Notes**
Scheduled Day	**Up to -35**	**-6**	**-2**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
				Predose	**Up to 24 h**										
Full neurological exam[c]	X														Sec. 8.3.7, Appendix 11
Targeted neurological exam[c]				X		X			X		X		X		Sec. 8.3.7, Appendix 11
Orthostatic VS (HR and BP)[d,f,g]	X			X	X	X	X	X		X				X	Sec. 8.3.2.2, 8.10.5
Vital Signs (HR, BP)[d,f,g]	X			X	X	X	X	X		X				X	Sec. 8.3.2., 8.10.5
Vital Signs (RR, temperature) [d,e,f]	X			X	X	X	X	X		X				X	Sec. 8.3.2.1, 8.10.5
12-lead ECG [d,f,g]	X			X	X	X	X	X		X				X	Sec. 8.3.3, 8.10.5
HIV, hepatitis B and C screen	X														Per site SOP Sec. 5.2, 8.3.4, Appendices 2 and 8
UDS	X	X													To be completed at screening and upon admission Sec. 5.2, 8.3.4, Appendix 2
Hematology [g]	X			X										X	Sec. 8.3.4, 8.10.5, Appendices 2 and 8
Urinalysis [g,h]	X			X										X	Sec. 8.3.4, 8.10.5, Appendix 2
Chemistry [g,h]	X			X										X	Sec. 8.3.4, 8.10.5, Appendices 2 and 8
AE/SAE review	X----------X														Sec. 8.4, Appendix 3
BPRS [g]	X			X									X		Sec. 5.1, 8.3.7, 8.10.5

All Panels															
Study Period	**Screening**	**Washout and Check-In**		**Intervention**											**Notes**
Scheduled Day	**Up to -35**	**-6**	**-2**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
				Predose	**Up to 24 h**										
C-SSRS Baseline Version	X														Sec. 5.2, 8.3.5, 8.10.5
C-SSRS Since Last Assessment Version			X	X			X			X			X		Sec. 8.3.5, 8.10.5
BARS [g,i]				X		X			X		X		X		Sec. 8.3.6, 8.10.5
AIMS [g,i]				X		X			X		X		X		Sec. 8.3.6, 8.10.5
SAS [g,i]				X		X			X		X		X		Sec. 8.3.6, 8.10.5
Pharmacokinetics															
Blood for Plasma MK-8189 Assay[j]				X	X	X					X	X	X		Sec. 8.6.1, 8.10.5, Appendix 8
Biomarkers															
Blood for Genetic Analysis[k]				X											Collect predose from enrolled participants in Period 1 only. Sec. 8.8.1, Appendix 8, Study Operations Manual

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BDS=blood drug screen; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia Suicide Severity Rating Scale; CRU=clinical research unit; DNA=deoxyribonucleic acid; EC=exclusion criteria; ECG=electrocardiogram; FBR=future biomedical research; HIV=human immunodeficiency virus; HR=heart rate; IC=inclusion criteria; ID=identification;; PK=pharmacokinetic; RR=respiratory rate; SAE=serious adverse event; SAS=Simpson Angus Scale; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs

Note: Day 10 (or last day of MK-8189 washout) corresponds with Day -1 in Period 2.

a. Participants currently treated with antipsychotic therapy will be domiciled from Day -6 prior to dosing on Day 1 in Period 1 (to start washout period) and will remain in the CRU until 28 days postdose in Period 2. Participants not currently being treated with antipsychotic therapy may be domiciled minimally starting on Day -2. Participants may stay longer at investigator's discretion.
b. After Day 1, assessments should be completed at the same time of day in relation to MK-8189 administration.
c. Targeted neurological exam can occur at any time on Day 1 as long as the other neurological exams (general and targeted) can occur at the same time of day for the remained of the study.
d. Day 1 Safety Assessments
    1. Predose: VS assessments (HR and BP) and ECG will be completed in triplicate (postdose assessments will be single measurements), RR and orthostatic VS (HR and BP) will be single measurements.
    2. Up to 24 hours: VS assessments (including orthostatic VS) (HR, BP, RR) will be collected at 2-, 6-, and 12-hour postdose in single measurements.
e. Temperature will be assessed at Screening and Predose Day 1 only and will require single measurements.
f. Vitals and ECG on Days 2, 4 will be taken only for Panel E and F if the daily MK-8189 oral dose exceeds 24 mg corresponding to MK-5720 dose greater than 280 mg..
g. The assessment can be done at any time during the day however an attempt should be made for consistent timing across days and periods.
h. Hematology, chemistry, urinalysis can be use for predose labs in Period 2 as long as they are obtained 24 hours prior to dosing MK-5720.
i. Additional BARS, AIMS, and SAS assessments should be conducted, as soon as reasonably possible, when there are observed or reported complaints of dystonia and/or akathisia
j. PK Timepoints for MK-8189
    1. Day 1: predose, 2, 6, 8, 10, 12, and 16 hours postdose
    2. Day 2: 24-hour postdose relative to D1 dose administration
    3. Day 7: predose, 2, 6, 8, 10, 12, 16 hours postdose
    4. Day 8: 24 hours postdose for D7 dose administration
    5. Day 9: 48 hours postdose for D7dose administration
    6. Day 10: 72 hours postdose for D7 dose administration
k. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

1.3.2 Schedule of Activities: Period 2 MK-5720 Treatment

All Panels																								
Study Period	**Intervention**																						**P**	**Notes**
	1																							
Scheduled Day	**Pre-Dose**	**Up to 24 h hours**	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**13**	**14**	**15**	**16**	**17**	**19**	**20**	**22**	**29**	**36 43 50**	**56**	**Poststudy**	
Administrative Procedures																								
Prior and Concomitant Medication Review	X----------X																							Sec. 5.2, 6.5, 8.1.5
MK-5720 or Placebo Administration		X																						Sec. 8.1.8
Standard Meals	X----------X																							Sec. 5.3.1
Domiciling[a]	X----------X																							Sec. 8.1.11
Outpatient Visits																					X	X	X[b]	
Safety Procedures																								
Full physical examination	X																			X		X		Sec. 8.3.1, 8.10.5
Height																								Sec. 8.3.1
Weight[c]	X																			X		X		Sec. 8.3.1
Full neurological exam[d]	X																			X		X		Sec. 8.3.7, Appendix 11
Targeted neurological exam[d]		X	X		X		X		X	X	X	X	X	X	X	X	X		X		X			Sec. 8.3.7, Appendix 11
Orthostatic VS (HR and BP)[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Sec. 8.3.2.2, 8.10.5
Vital Signs (HR, BP) [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Sec. 8.3.2., 8.10.5
Vital Signs (RR, temperature) [e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		Sec. 8.3.2.1, 8.10.5
12-lead ECG[e,g]	X	X	X		X		X		X	X	X	X	X	X	X	X	X		X	X	X	X		Sec. 8.3.3, 8.10.5
Hematology[g]	X										X									X		X		Sec. 8.3.4, 8.10.5, Appendices 2 and 8
Urinalysis[g]	X										X									X		X		Sec. 8.3.4, 8.10.5, Appendix 2

All Panels																								
Study Period	**Intervention**																						**P**	**Notes**
Scheduled Day	**1**		**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**13**	**14**	**15**	**16**	**17**	**19**	**20**	**22**	**29**	**36 43 50**	**56**	**Poststudy**	
	Pre-Dose	**Up to 24 h hours**																						
Chemistry[g]	X										X									X		X		Sec. 8.3.4, 8.10.5, Appendices 2 and 8
AE/SAE review	X----------																					X		Sec. 8.4, Appendix 3
BPRS[g]	X																			X				Sec. 5.1, 8.3.7, 8.10.5
C-SSRS Since Last Assessment Version	X			X				X			X			X						X		X		Sec. 8.3.5, 8.10.5
BARS [g,h]	X				X					X				X					X	X		X		Sec. 8.3.6, 8.10.5
AIMS [g,h]	X				X					X				X					X	X		X		Sec. 8.3.6, 8.10.5
SAS [g,h]	X				X					X				X					X	X		X		Sec. 8.3.6, 8.10.5
MRI[i,j,]		X					X						X				X							Refer to Site Imaging Manual
Pharmacokinetics																								
Blood for Plasma MK-5720, MK-8189, and or Metabolites Assay[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Sec. 8.6.1, 8.10.5, Appendix 8

All Panels																										
Study Period	**Intervention**																								**P**	**Notes**
	1																									
Scheduled Day	**Pre-Dose**	**Up to 24 h hours**	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**13**	**14**	**15**	**16**	**17**	**19**	**20**	**22**	**29**	**36 43 50**	**56**	**Poststudy**			

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BDS=blood drug screen; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia Suicide Severity Rating Scale; CRU=clinical research unit; DNA=deoxyribonucleic acid; EC=exclusion criteria; ECG=electrocardiogram; FBR=future biomedical research; HIV=human immunodeficiency virus; HR=heart rate; IC=inclusion criteria; ID=identification; LAI=long acting injectable; MRI=magnetic resonance imaging; PK=pharmacokinetic; RR=respiratory rate; SAE=serious adverse event; SAS=Simpson Angus Scale; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs

Note: Day -1 in Period 2 corresponds to Day 10 in Period 1 (or last day of the MK-8189 washout period).

a. Participants currently treated with antipsychotic therapy will be domiciled from Day -6 prior to dosing on Day 1in Period 1 (to start washout period) and will remain in the CRU until 28 days postdose in Period 2. P Participants may stay longer at investigator's discretion.
b. Poststudy follow-up visit will occur 14 ± 2 days after the last study procedure has occurred.
c. After Day 1, assessments should be completed at the same time of day in relation to MK-5720 administration.
d. Targeted neurological exam can occur at any time on Day 1 as long as the other neurological exams (general and targeted) can occur at the same time of day for the remained of the study.
e. Day 1 Safety Assessments
    1. Predose: VS assessments (HR and BP) and ECG will be completed in triplicate (postdose assessments will be single measurements), RR and orthostatic VS (HR and BP) will be single measurements.
    2. Up to 24 hours: VS assessments (including orthostatic VS) (HR, BP, RR) will be collected at 2-, 6-, and 12-hour postdose in single measurements.
f. Temperature will be assessed at Predose and Day 56 only and will require single measurements.
g. The assessment can be done at any time during the day however an attempt should be made for consistent timing across days and periods.
h. Additional BARS, AIMS, and SAS assessments should be conducted, as soon as reasonably possible, when there are observed or reported complaints of dystonia and/or akathisia.
i. Imaging (MRI) will occur in 2 panels at or 1 dose level below the highest dose of MK-5720 LAI administered in the deltoid and gluteal muscles.
j. Imaging will occur on Day 1 and Day 14 within 6 to 12 hours postdose in the panels that receive the MK-5720 LAI in the deltoid and gluteal muscle and additionally on Day 7, and Day 19 in half of the number of participants in the panel (~ 6 participants) that receive the LAI injection in the deltoid muscle.
    1. Windows for completion of MRIs: Day 1 (4-12 hrs); Day 7 (+/-1 Day); Day 14 and 19 (+/-2 days)
k. PK Sample Timepoints: Predose, 0.5, 1, 2, 4, 6, 24, 48, 96, 120, 144, 168, 192, 216, 264, 288, 312, 336, 360, 384, 432, 456, 504, 672, 840, 1008, 1176, and 1320 hours postdose.

2 INTRODUCTION

2.1 Study Rationale

MK-5720 is a novel ester carbamate acetal prodrug of the PDE10A inhibitor MK-8189 and is being developed as a LAI formulation of MK-8189 for the QM treatment of schizophrenia. The primary bioconversion pathway involves systemic esterase-mediated hydrolysis of MK-5720 to the metabolite, MK-8189. MK-8189 is a potent and highly selective competitive inhibitor of PDE10A that is being developed as an orally administered, novel therapeutic for the treatment of schizophrenia. MK-5720 and its metabolite, MK-8189, are not considered compounds with a high potential for risk of harm to schizophrenic participants based on preclinical safety data available for MK-5720 and the clinical safety experience gathered across multiple clinical studies conducted with oral MK-8189 to date. No dose-limiting toxicities were observed in the 1-month rat and rhesus toxicity studies with MK-5720 and substantial preclinical safety margins were obtained over initial human doses. Preclinical studies with MK-5720 as well as clinical safety experience observed with MK-8189 in schizophrenic patients to date support the study of MK-5720 in participants with schizophrenia for the FIH study.

This study constitutes the first administration of MK-5720 to humans. The main objective of this FIH study is to evaluate the safety, tolerability, and PK of MK-5720 LAI after administration of single-IM doses in adult participants with schizophrenia. Since the developmental and reproductive toxicological data for MK-5720 has not been generated at this stage, the potential effect of MK-5720 in reproductive healthy women is unknown. As a result, only healthy men and PONCBP, ages 18 to 60 years of age inclusive, who meet the inclusion criteria are eligible to participate in the study. Data from this study will be used to guide the selection of doses and dosing regimens for upcoming clinical studies in patients with schizophrenia.

The number of participants in each panel (n=8 to 12, allocated n=6 to 9 to MK-8189/MK-5720 and n=2 to 3 to placebo) was chosen for this early Phase 1 study to balance scientific requirements for statistical significance with the study's objectives regarding the ethical use of human participants in a clinical study.

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

2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-5720.

2.2.1 Pharmaceutical and Therapeutic Background

MK-5720 is a novel ester carbamate acetal prodrug of the PDE10A inhibitor, MK-8189 and is being developed as a LAI formulation of MK-8189 for the QM treatment of schizophrenia. 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 or SGA treatment.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Preclinical Studies with MK-5720

MK-5720

Refer to the IB for detailed preclinical information on MK-5720.

2.2.2.2 Clinical Studies with MK-5720 and MK-8189

MK-5720

There have been no clinical studies conducted with MK-5720.

MK-8189

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

Summary of Completed Phase 1 Clinical Studies

Three single-dose clinical studies (P001, P002, and P004) in healthy participants, a single-dose study in healthy participants and participants with moderate hepatic impairment (P012), 2 CYP3A DDI studies in healthy participants (P006, P015), and 4 multiple-dose clinical studies in participants with schizophrenia and healthy participants (P003, P007, P011, and P016) have been completed with MK-8189. P011 included elderly (>60 years of age, n=12) participants with schizophrenia and healthy elderly (>60 years of age, n=18) participants. Overall, across the completed studies, 231 participants have received at least one dose of MK-8189; 124 participants without schizophrenia and 107 participants with schizophrenia.

Overview of MK-8189 Pharmacokinetics

CCI [redacted] Median Tmax of MK-8189 as monotherapy ranged from 10 to 24 hours with a t1/2 of approximately 10.9 hours. CCI [redacted]

CCI [redacted]

MK-8189 is a CYP3A substrate and in a DDI study (P006), the coadministration of extended release 240-mg diltiazem, a moderate CYP3A inhibitor, increased MK-8189 AUC and Cmax by approximately 2-fold and 1.27-fold, respectively. Additionally, a subsequent DDI study (P015) demonstrated that coadministration of itraconazole, a strong CYP3A inhibitor, increased MK-8189 AUC and Cmax by approximately 1.2-fold and 1.16-fold, respectively, and these results were generally consistent with the results observed in the diltiazem study. Collectively, these results confirm that MK-8189 is a CYP3A substrate. CCI [redacted]

Overview of MK-8189 Safety Profile

Across completed and ongoing studies, MK-8189 was generally well tolerated up to 24 mg in healthy participants and up to 80 mg in participants with schizophrenia. The most common treatment-related AEs (≥5%) following treatment of MK-8189 (n=231) across the completed Phase 1 studies which included, healthy participants (nonelderly and elderly), participants with schizophrenia (nonelderly and elderly) and participants with hepatic impairment, were headache (13.0%) somnolence (13.4%), dystonia (10.4%), decreased appetite (9.5%), nausea (8.7%), fatigue (5.6%), dizziness (6.5%), vomiting (6.1%), diarrhea (4.8%), akathisia (6.1%), anxiety (5.2%) and insomnia (5.2%). Most AEs were mild to moderate in severity. There were no deaths; however, there was 1 treatment-related SAE across the Phase 1 studies. In P007, one participant discontinued due to a treatment-related SAE of increased psychosis which resulted in hospitalization. The SAE occurred following treatment with the 36-mg dose. The AE was considered severe and had a duration of 6 days. The SAE resolved following initiation of an antipsychotic and benzodiazepine.

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

In a Phase 2 POC trial (P005), MK-8189 was generally well tolerated by the 90 participants who received at least 1 dose of the once daily MK-8189 (titrated every 3 days from 4 mg to 8 mg and 12 mg, as tolerated). Participants were dosed after they were able to taper off psychotropic medications. AEs that occurred in ≥5% of participants in the MK-8189 intervention group and had greater incidence than placebo were diarrhea, nausea, vomiting, decreased appetite, akathisia, dystonia, headache, sedation, somnolence, anxiety, and insomnia. No deaths were reported in the P005 study. No SAEs were reported for

participants on MK-8189. Eight participants (8.9%) had an AE of dystonia and 2 participants (2.2%) had an AE of oromandibular dystonia. Detailed PK and safety information from individual completed studies are summarized in the IB.

2.2.3 Completed Clinical Studies (MK-8189)

2.2.3.1 Protocol 011

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

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

Overall, multiple oral doses of MK-8189 titrated from 16 to 24 mg were generally well tolerated in participants with schizophrenia. Of the 8 participants included in the safety analysis in Panel A, 6 (75%) experienced 1 or more AEs during the study; 5 participants (83.3%) after MK-8189 and 1 participant (50%) after placebo. All AEs were mild or moderate in intensity and resolved prior to the end of the study. No participants were discontinued from the study intervention due to an AE.

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

Dystonia and new or worsening tardive dyskinesia per protocol were defined as ECIs. There were 2 (33.3%) participants administered MK-8189 who experienced a nonserious ECI. One participant, who prior to the study was being treated with benztropine to prevent EPS, experienced mild intermittent bilateral dystonia of the upper extremities after MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 2 days. The participant had also experienced moderate somnolence (3-day duration; related to MK-8189) which resulted in this participant remaining at the 16-mg dose for all 7 days of dosing. This participant was also taking a sedating antihistamine, hydroxyzine, for the duration of the AE. One participant had moderate dystonia of the tongue, lips, facial muscles, and left hand after MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 22 hours. The participant was titrated to

MK-8189 24 mg per protocol and completed the study without recurrence of dystonia. The investigator considered both events related to study intervention.

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

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

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

One (7.1%) MK-8189 treated participant, who had a history of gastroesophageal reflux disease, discontinued intervention due to mild vomiting following administration of MK-8189 24 mg. The investigator treated the participant with ondansetron 4 mg and symptoms resolved after 3 days. This participant also reported nausea on Day 2. The investigator considered both AEs not related to intervention. One (7.1%) participant had a mild AE of increased ALT (116 IU/L; NR: 7 to 52 IU/L) following treatment of MK-8189 24 mg that the investigator considered related to study intervention. This participant had mildly elevated screening (61 IU/L) and predose (98 IU/L) values of ALT which continued to increase during the study. The AE was reported on the last day of study intervention and resolved in ~ 2 weeks. Alkaline phosphatase followed a similar pattern. AST was normal at screening and predose but the participant experienced an elevation throughout the study. Bilirubin remained within normal range throughout the study.

Part 1 Panel C: Not initiated.

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

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

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

One participant (8.3%) in the MK-8189 intervention group experienced an AE of severe intensity (somnolence) and a nonserious related ECI (dystonia). On Day 1 following administration of the MK-8189 8-mg-dose, the participant experienced severe somnolence which resolved after 3 days with continued dosing. No action was taken regarding study intervention. On Day 3 following the 8-mg-dose, this participant experienced moderate bilateral upper extremity dystonia. The event lasted for 3 days and resolved with cyclobenzaprine 10 mg. This participant also reported moderate akathisia beginning on Day 3 with a duration of 3 weeks. This same participant did not receive the Day 6 dose (MK-8189 16 mg) due to moderate AEs of conjunctivitis (3-day duration) and a maculo-papular rash (4-day duration). The investigator considered all AEs related to study intervention. The participant did not titrate to the MK-8189 24-mg-dose and was dosed with 16 mg on Day 7. The participant withdrew consent on Day 8 and discontinued from study intervention. Three participants (n=2 [16.7%] following MK-8189 and n=1 [25.0%] following placebo) were discontinued from study intervention due to an AE. One participant discontinued intervention due to moderate pain that the investigator did not consider related to study medication. The AE started on Day 3 following administration of MK-8189 8 mg and resolved after ~ 1.5 weeks. The subject discontinued prior to the 16-mg intervention administration on Day 5. One participant discontinued intervention due to moderate restlessness after administration of MK-8189 16 mg (Day 3). This participant also experienced moderate dyskinesia (verbatim: involuntary movement of lower extremities) (Day 6). Both AEs resolved after 23 hours with no action taken. The investigator considered both AEs related to study intervention. One participant discontinued intervention due to mild dystonia (described below) after administration of placebo.

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

One participant (25.0%) in the placebo treatment group had 2 laboratory AEs: mild decreased eGFR on 2 occasions. One reported on Day 4 with a duration of 4 days. The other reported after the last dose of study intervention along with a mild increased blood glucose. The increased blood glucose resolved in 2 weeks; however, the decreased eGFR lasted approximately 1.25 months and was considered recovered/resolved with sequelae. The participant had a screening eGFR value of 55 mL/min/1.73 m^2(NR: >59) with a creatinine of 1.23 mg/dL (NR: 0.76 to 1.27). The eGFR was low at screening but within 10% of the lower limit of normal permitted by the protocol. The participant had a medical history of diabetes and hypertension. The investigator felt the eGFR decreases were due to the poorly controlled

diabetes, hypertension, and reluctance to hydrate. All AEs were considered not related to study intervention.

Part 2 Panel E: Not initiated

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

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

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

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

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

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

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

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

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

Three (23.1%) participants administered MK-8189 discontinued study intervention due to an AE. One participant discontinued due to a severe hypnagogic hallucination on Day 8. This participant experienced mild akathisia (20-hour duration) and moderate headache (8-hour duration) on Day 7 after MK-8189 24 mg. The participant was treated with benztropine 1 mg as needed for the akathisia. Overnight, prior to the Day 8 24-mg administration, the participant experienced moderate tactile hallucination (5-minute duration), moderate hyperhidrosis (5-hour duration) and mild palpitations (2-minute duration). Early morning upon waking on Day 8, the participant experienced a severe hypnagogic hallucination (5-minute duration). The participant did not receive the Day 8 dose due to these AEs. Later that day (Day 8), the participant experienced moderate tactile hallucination (15-minute duration), moderate hyperhidrosis (15-minute duration), mild hypertonia (5-day duration) and moderate sinus tachycardia (39-minute duration). Since similar AEs reoccurred on Day 8, the participant decided not to continue dosing due to the possibility of a reoccurrence of the hypnagogic hallucination. This participant also reported a mild ECI of oromandibular dystonia (30-minute duration) on Day 1 (MK-8189 16 mg) and a mild headache on Day 10 (MK-8189 24 mg). The investigator considered all AEs related to study intervention except the mild headache on Day 10. One participant discontinued intervention due to mild akathisia following Day 3 administration of MK-8189 16 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 2 days. The investigator considered the

AE related to study intervention. This participant also reported mild fatigue (6-day duration) and moderate wheezing (2-day duration) 8 days following intervention discontinuation. The investigator considered these AEs not related to study intervention. One participant discontinued intervention due to moderate ECI of oromandibular dystonia of the jaw on Day 4 following administration of MK-8189 24 mg. The investigator treated the participant with benztropine 1 mg and symptoms resolved after 6.5 hours. The participant also reported moderate anxiety (~ 11-hour duration; treated with lorazepam 1 mg), mild myalgia (14.5-hour duration; treated with ibuprofen 800 mg) and mild apathy (23-hour duration) on Day 4. The investigator considered all Day 4 AEs related to study intervention. Prior to the Day 4 AEs, the participant experienced on Day 2 moderate apathy (2-day duration), mild dysphonia (6-day duration), mild involuntary muscle contractions (verbatim: fasciculation, 2-day duration) and mild parosmia (~ 1-week duration), all considered related to intervention by the investigator. On Day 3, the participant experienced mild back pain (3-day duration; treated with paracetamol 1000 mg), salivary hypersecretion (3-day duration) and mild muscle tightness of the legs (10.5-hour duration). The only AE considered related to intervention on Day 3 by the investigator was the salivary hypersecretion.

One participant (7.7%) had a mild laboratory AE of decreased eGFR on Day 12 after MK-8189 24 mg which was not considered related to study intervention. The decreased eGFR lasted around 1.5 months and was considered recovered/resolved with sequelae by the investigator. The participant had a normal screening eGFR value of 75 mL/min/1.73 m^2 (NR:>59) with a creatinine value of 0.81 mg/dL (NR: 0.76 to 1.27). The eGFR fluctuated between 65 and 75 mL/min/1.73 m^2throughout the study but was never below the NR until Day 12 (eGFR value of 58 mL/min/1.73 m^2; creatinine value of 1.01 mg/dL). The participant had a history of hypertension, and the investigator felt the eGFR decrease was related to their baseline hypertension. The investigator referred the participant to their PCP for further treatment of hypertension (participant was prescribed lisinopril by the PCP).

Across all Panels, there were no dose-related trends for increases in specific AEs. There were no clinically meaningful trends for MK-8189-treatment related changes in safety laboratory values, VS, including orthostatic VS, ECGs, or physical exams. There were no SAEs nor deaths reported and no participant reported suicidal ideation or behavior per the C-SSRS.

2.2.3.2 Protocol 012

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

Overall, MK-8189 4 mg was generally well tolerated in the moderate hepatic impairment and healthy participants in the study. No deaths nor SAEs nor ECIs were reported. No participant discontinued from the study due to an AE. Of the 14 participants included in the safety analysis, 4 (28.6%) experienced 1 or more AEs during the study: 4 (57.1%) in the moderate hepatic impairment group and none in the healthy participants group. Ten (71.4%) participants did not report an AE. All AEs were mild in intensity and all AEs resolved by the end of the study. The most frequently (>1 participant) reported AE amongst the moderately hepatic impaired participants was vomiting (n=2/7; 28.6%). One participant vomited on Day

1, ~ 5 hours after dosing and another participant on Day 3. All other AEs were reported by 1 participant only.

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

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

2.2.3.3 Protocol 016

P016 was a randomized, placebo-controlled, parallel-group, single-site, double-blind, multiple-ascending dose study of MK-8189 in healthy participants. Up to approximately 25 healthy participants were planned to be enrolled to ensure 20 participants completed the study. Participants were randomized to receive single rising doses of MK-8189 or placebo on Days 1 through 6 (Day 1=8 mg, Day 2=16 mg, Day 3=24 mg, Days 4, and 5=48 mg, and Day 6=72 mg). Participants were domiciled from Day -2 until Day 9.

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

Of the 12 participants included in the safety analysis, 100.0% (n=12/12) experienced 1 or more AEs during the study. In general, more AEs were observed with higher doses of

MK-8189, and all participants receiving placebo reported AEs; 28.6% (n=2/7) for MK-8189 8 mg (Day 1), 57.1% (n=4/7) for 16 mg (Day 2), 42.9% (n=3/7) for 24 mg (Day 3), 100.0% (n=6/6) for 48 mg (Days 4 and 5), 100% (n=4/4) for 72 mg (Day 6), and 100.0% (n=5/5) for placebo. Most AEs were mild or moderate in intensity; one AE of akathisia was rated severe. All but 1 unrelated AE of leukocyturia resolved by study completion. There were no deaths nor other SAEs.

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

(Day 9) mild affect lability with a duration of 3.43 weeks, as well as mild restlessness which started after the 24-mg-dose (duration 3 days).

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

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

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

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

participant to treat severe akathisia (see above). Another participant received a single dose of 10-mg propranolol hydrochloride on Day 7 to treat an acute stress disorder of moderate intensity that started 33 hours after the last dose (72 mg on Day 6) and resolved in 4 hours. The AE was not considered related to study intervention.

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

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

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

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

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

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

2.3 Benefit/Risk Assessment

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

No clinical studies with MK-5720 have been conducted to date. The conduct of the proposed clinical first-in-human study described in the clinical protocol is supported by the safety profile of MK-5720 established in the preclinical toxicological studies and that of its

metabolite, MK-8189 in clinical studies. Furthermore, there is no evidence of mutagenicity or genotoxicity in a standard core battery of genetic toxicity assays conducted with MK-5720 and MK-8189.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in participants with schizophrenia.

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of single-ascending doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia.	Adverse Events Study discontinuation due to adverse events
To assess the plasma pharmacokinetics of MK-5720 and MK-8189 following single doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia. CCI [redacted]	Plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2 Plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2
To evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia.	Adverse Events Study discontinuation due to adverse events
Secondary Objectives	**Secondary Endpoints**
To assess the plasma pharmacokinetics of MK-8189 following single doses of MK-5720 long-acting injectable administered intramuscularly in participants with schizophrenia CCI [redacted]	CCI [redacted]

To compare the effect of the site of administration of MK-5720 long-acting injectable on plasma pharmacokinetics of MK-5720 and MK-8189 following a single dose of MK-5720 long-acting injectable administered intramuscularly in the gluteal muscle relative to its administration in the deltoid muscle. Estimation: The effects of the site of administration on plasma pharmacokinetics of MK-5720 and MK-8189 following a single dose of MK-5720 long-acting injectable administered intramuscularly in the gluteal muscle will be estimated and compared to a single dose of MK-5720 long-acting injectable administered intramuscularly in the deltoid muscle.	Plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2 Plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To characterize the morphology of the injection site depot over time, using direct visualization of the depot.	Depot volume and surface area, measured at multiple time points via segmentation of the intramuscular depot on T2-weighted magnetic resonance imaging, after a single dose of MK-5720 long-acting injectable administered intramuscularly in both the deltoid and gluteal muscles.
Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	Germline genetic variation and association to clinical data collected in this study
Objective: To assess the pharmacokinetics of oral MK-8189 following multiple doses of MK-8189 in participants with schizophrenia.	AUC0-24, Cmax, Tmax, terminal t1/2, and C24

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, multisite, double blind, single ascending dose, parallel group study of MK-5720 in participants with schizophrenia to be conducted in conformance with GCP. The primary objective of the study is to assess the safety, tolerability, and to characterize the PK of single rising doses of MK-5720 administered IM and to evaluate the safety and tolerability of multiple once-daily oral doses of MK-8189 in participants with schizophrenia.

MK-5720-001 clinical study will consist of 6 panels (A, B, C, D, E, and F) and two treatment periods, Periods 1 and 2. Period 1 will include an oral tolerability run-in period with participants receiving once-daily administration of MK-8189 (or corresponding placebo) for 7 days followed by a washout period of at least 72 hours prior to initiation of Period 2. Participants will receive rising single dose IM injection of MK-5720 (or corresponding placebo) in Period 2. The dose of MK-8189 (or placebo) used in Period 1 will vary based on each panel as mentioned in [Table 1]. Approximately 8 participants (n=6 for MK-8189/MK-5720 and n=2 for placebo) will be in Panels A and B and approximately 12 participants (n=9 for MK-8189/MK-5720 and n=3 for placebo) in Panels C through F. Each panel will sequentially receive single rising IM doses of MK-5720 and the corresponding dose of oral MK-8189 as mentioned in Table 1. Each participant will be assigned to 1 of 6 panels and will participate in both treatment periods. Participants will be randomized to receive a single IM injection of MK-5720 or placebo and oral MK-8189 or placebo in a blinded fashion. Panels A through C will investigate IM doses of MK-5720 in the deltoid muscle while Panels D through F will investigate IM doses in the deltoid or gluteal muscle based on PK data obtained from Panels A to C. Since patient preference for injection sites differ between geographic regions, the effect of the site of administration of MK-5720 LAI on plasma PK of MK-5720 and MK-8189 following a single dose of MK-5720 LAI administered IM in the gluteal muscle relative to administration in the deltoid muscle will be compared. Currently, the literature on this topic is sparse, but the published data show discrepancies in the elimination half-life, peak plasma concentration, and absorption rate that are dependent on the site of injection. Hence, both PK and safety of MK-5720 LAI will be compared between both IM sites of administration at the highest well tolerated dose of MK-5720 to potentially offer the choice of administration into either the deltoid or gluteal muscle to meet patient and physician preference in future clinical studies. MK-5720 LAI will be administered as a suspension for injection for doses up to ≤560 mg that will be administered IM using the appropriate needle size/gauge based on the participant's BMI and site of LAI administration.

MRI exam will be incorporated in 2 panels at or 1 dose level below the highest dose of MK-5720 LAI that are administered IM in the deltoid and gluteal muscles to visualize the injection site depot using multislice spin-echo T2-weighted and assess the location of the depot in the muscle and to quantify drug depot characteristics, including volume and surface area over time. This information will be utilized to better understand any differences in PK between patients and to build models to better predict human PK from preclinical animal models in subsequent clinical studies.

Decision to dose participants with MK-5720 in any given panel will be based on demonstrating acceptable tolerability in individual participants with oral MK-8189 from the oral tolerability run-in period and based on key safety variables including AEs, VS, 12-lead ECGs, laboratory safety tests, neurological and physical examinations, and C-SSRS. The decision for a participant to proceed to Period 2 will be a joint decision between the PI and the Sponsor. Dose escalation decisions for MK-5720 will be based on key safety variables including AEs, VS, 12-lead ECGs, laboratory safety tests, neurological and physical examinations, C-SSRS, and local and systemic reactions assessed in Period 2. The decision to proceed to the next higher dose level will be based upon acceptable safety of MK-5720 at the previous dose. When available, plasma PK data will be reviewed to aid dose escalation decisions. For dose escalation to Panel B, the decision to proceed will be based on 14 days of safety and tolerability data from Panel A. CCI [redacted] Plasma concentrations of MK-5720 from the preceding panels will be determined at the allocated PK breaks to ensure that the NOAEL AUC exposure limits are not exceeded at the doses in the subsequent panels. Similarly, plasma concentrations of MK-8189 from the preceding panels will also be determined at the allocated PK breaks to ensure that MK-8189 exposures do not exceed exposures observed with oral MK-8189 at doses that are generally well tolerated in participants with schizophrenia. Dose escalation decisions for Panels C through F will be informed by safety, tolerability, and PK data from all patients in the prior panel through 28 days postdose.

If applicable, participants will be washed off their current antipsychotic therapy prior to MK-8189 dose administration in Period 1. The washout may start with a down titration of the antipsychotic treatment during the screening phase per direction of the investigator. If participants are not currently receiving antipsychotic therapy, they may be domiciled as late as Day -2 prior to dosing administration in Period 1. All participants will be domiciled from the initial washout period prior to dosing MK-8189 in Period 1 and until 28 days postdose for monitoring of safety, tolerability, and intensive PK sampling in Period 2. At the discretion of the investigator, the participants may be domiciled for a longer duration if further observation is required. Participants will return to the clinic for outpatient procedures as outlined in Section 1.3.2 (SoA).

Because this is a Phase 1 assessment of MK-5720 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

The study design selected is deemed optimal for the initial evaluation of safety, tolerability, and PK of MK-5720 in schizophrenic patients.

This is the first instance of administration of MK-5720 to humans with the study aimed to evaluate the safety and tolerability of MK-5720 and characterize the PK profile of MK-5720 as single ascending doses in participants with schizophrenia with the protocol specifically designed in a manner to ensure the safety of the participant. The study incorporates an oral tolerability run-in period with MK-8189 to demonstrate and establish acceptable tolerability with MK-8189 in individual participants prior to administration of MK-5720 IM injection given the inability to reduce daily exposure levels of MK-8189 once MK-5720 injection is administered to participants. Data from the study will be instrumental in guiding dose selection and dosing regimen for future clinical studies. Since the developmental and reproductive toxicological data for MK-5720 has not been generated at this stage, the potential effect of MK-5720 in reproductive healthy women is unknown and hence, only adult men and PONCBP, ages 18 to 60 years of age inclusive, who meet the inclusion criteria are eligible to participate in the study.

The protocol has been designed in a manner to ensure the safety of clinical study participants. In all preclinical studies the bioconversion of prodrug MK-5720 to MK-8189 is rapid and generally similar between monkey and human but found to be more rapid in rat. Following IV administration of MK-5720 in rats and monkeys, the plasma concentration of MK-5720 was undetectable at timepoints beyond 15 minutes postdose. Additionally, the exposure of MK- 5720 was less than 1% of the MK-8189 exposure (AUC0-inf) seen after IM administration of MK-5720 in monkeys. The rapid bioconversion prevented determination of t1/2 of MK-5720. Given MK-5720 is approximately 650-fold less potent compared to MK-8189 based on in vitro binding assays and that the bioconversion of MK-5720 in humans is anticipated to be rapid, concentrations are expected to be well below pharmacologically active concentrations and therefore, the main pharmacological activity expected in the clinic is as a result of the MK-8189 metabolite. Both, prodrug and MK-8189 concentrations will be actively monitored in the clinic.

Furthermore, the structure of this study is designed based upon the projected PK of MK-8189 derived from MK-5720 LAI, that is estimated to have a t1/2 of ~ 10 days in humans. This study will collect PK samples for 55 days postdose to ensure MK-8189 washout of at approximately 5 half-lives.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

No efficacy endpoints will be evaluated in this study.

4.2.1.2 Safety Endpoints

No treatment related findings were identified in the GLP 1-month single dose IM toxicity studies with 3-month recovery period conducted with MK-5720 in rats and NHPs. The

NOAELs were the highest dose tested, 510 mg/kg in rats [redacted] for MK-5720. Clinical pathology changes were not considered toxicologically meaningful, given the small magnitude and transient nature, and were attributed to an inflammatory response associated with MK-5720 histomorphology changes in the injection sites noted in rats at ≥30 mg/kg [redacted] In both species these findings resolved after a 3-month recovery period. Histological findings at the injection sites in rats and NHPs were consistent with those typically observed following administration of a long-acting formulation that produces an extended-release depot [Paquette SM, et al 2014].

Because studies in preclinical species are not always predictive of what may occur in humans, the safety and tolerability of MK-5720 will be assessed throughout the study by monitoring participants frequently for clinical AEs as well as through the conduct of neurological exams, physical exams, ECGs, VS, and laboratory safety tests (chemistry, hematology, urinalysis). The timing of the safety endpoints has been planned to ensure adequate safety monitoring throughout the treatment period also taking into consideration the range of potential half-life predictions of MK-8189 from the MK-5720 LAI. Key safety data such as VS, 12-lead ECGs, lab safety tests and physical/neurological examinations will be reviewed for up to at least 14-days postdose for Panel A prior to dose escalation to Panel B and up to 28-days postdose prior to dose escalation to the next higher dose level in all other treatment periods. The C-SSRS will be administered to monitor mood and suicidal ideation and behavior in all trial participants (see Section 4.2). In addition, scales will be included to evaluate 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).

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.

Rescue medications for the management of EPS side effects and administration of standard of care practice (oral antipsychotics) in the event of worsening of psychosis while on MK-5720 LAI to control symptoms associated with schizophrenia during washout of MK-5720 are detailed in Section 6.5.1.

4.2.1.3 Pharmacokinetic Endpoints

One of the primary objectives of the study is to characterize the PK profile of MK-5720 as well as MK-8189 as rising single doses of administration of the IM MK-5720 LAI in Period 2. In order to characterize the PK profile of MK-5720 and MK-8189, noncompartmental PK parameters, AUC0-last (MK-5720 only), AUC0-inf, AUC0-28d (MK-8189 only), Cmax, C28d (MK-8189 only), Tmax, apparent t1/2, apparent CL/F, and apparent Vz/F will be estimated after single-dose IM administration of the MK-5720 LAI. The dose escalation criteria based on PK analysis are listed below in [Table 2]. Additionally, in Period 1 of the study, one of the exploratory objectives is to characterize the PK profile of MK-8189 following multiple oral doses of MK-8189. Therefore, the noncompartmental PK parameters, AUC0-24, Cmax, Tmax, terminal t1/2 and C24 will be estimated on day 1 and day 7. Plasma samples will be analyzed based on prespecified time point sampling mentioned in Section 1.3.

Table 2 Dose Escalation Criteria Based on PK Analysis

Dose (Panel)	Dose Escalation Decision Criteria
140 mg (C)	28d postdose PK analysis from the preceding doses from Panels A and B
280 mg (D)	28d postdose PK analysis from the preceding dose in Panels C
≤560 mg (E)	28d postdose PK analysis from the preceding dose in Panel D
≤560 mg (F)	28d postdose PK analysis from the preceding dose in Panel E
28d=28 days; PK=pharmacokinetics	

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints will be evaluated in this study.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic

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

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

4.2.1.6 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

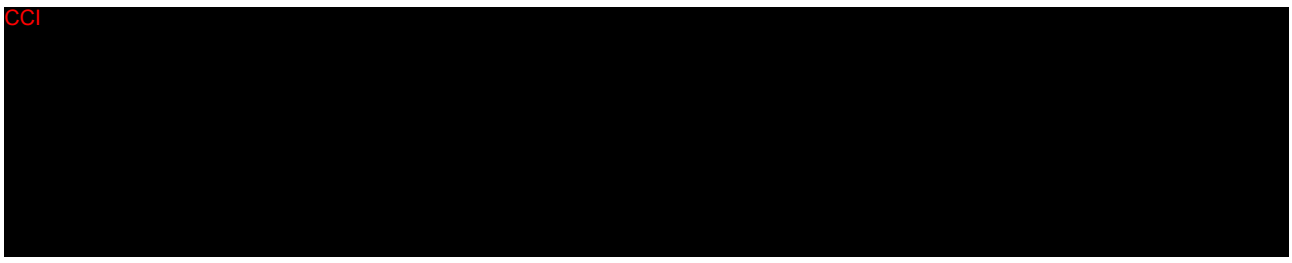
Placebo will be used in this study to allow for an appropriate assessment of the safety data of oral MK-8189 and MK-5720 LAI and to maintain study blinding to reduce bias.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

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

4.3 Justification for Dose

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



CCI [redacted]

An oral tolerability run-in period with MK-8189 is included before administration of the IM MK-5720 injection. Due to the short half-life of oral MK-8189 (8-9 h), steady-state plasma exposures are likely to be achieved within the first two days following once daily administration of MK-8189. Hence, MK-8189 will be administered once-daily for 7 consecutive days in the oral-run in period to establish individual tolerability in participants at steady state prior to IM administration of MK-5720.

CCI [redacted]

As this is a Phase 1 assessment of MK-5720 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.10.6.

4.3.1 Starting Dose for This Study

The starting dose of 35 mg is proposed in conformance with the "Guideline on Strategies to Identify and Mitigate Risks for First-in- Human Clinical Trials with Investigational Medicinal Products" [European Medicines Agency 2007] as well as the MRSD calculation [Food and Drug Administration 2005], the MRSD for the first such instance of drug administration in humans is based on NOAEL determined in nonclinical safety studies performed in the most sensitive and relevant animal species adjusted with allometric scaling factors to calculate the HED.

A 4-week, 3-dose level toxicity study was conducted with MK-5720 in rats at (12, 30, 510 mg/kg/day) and rhesus (12, 36,140 mg/kg/day) to assess the potential toxicity and toxicokinetic profile of MK-5720. No treatment related findings were identified in the GLP 1-month single dose IM toxicity studies with 3-month recovery period conducted with MK-5720 in rats and NHPs. Histological findings at the injection sites in rats and NHPs were consistent with those typically observed following administration of a long-acting formulation that produces an extended-release depot and the inflammatory response associated with MK-5720 histomorphology changes at the injection sites findings were resolved after a 3-month recovery period in both species.

The NOAELs for MK-5720 were the highest dose tested, 510 mg/kg in rats and 140 mg/kg in rhesus. While the NOAEL was the highest dose studied in both species in the 1-month GLP

compliant toxicological study, given the rat provides lower overall exposures for M-5720 and lower EMs to the projected efficacious dose of MK-5720, rat is determined to be the most sensitive species. Therefore, rat NOAEL Cmax and AUC exposure cap for MK-5720 will be used for the purposes of safety multiple calculations that corresponds to 2.05 µM*hr and 0.0129 µM plasma exposures for AUC0-28d and Cmax respectively. See [Table 3] for PK exposures of MK-5720 at NOAEL doses in rats and rhesus.

Table 3 Pharmacokinetic Exposures of MK-5720 at NOAEL Doses

Species	Dose (mg/kg)	Cmax (µM)	AUC0-28d(µM.hr)
Rat	510	0.0129	2.05
Rhesus	140	0.0713	9.27
AUC0-28d= area under the concentration-time curve from 0 to 28 days, Cmax=maximum plasma concentration			

The calculated HED corresponding to the rat NOAEL adjusted by using an allometric scaling factor is 4957 mg (510 mg/kg x 0.162 [rat to human dose conversion factor] x 60 kg [estimated human adult weight]). The MRSD calculated by applying a safety factor of 10, yields a starting dose of 495 mg. However, a safety factor of 50 has been applied to account for variability in the preclinical to clinical translation of input rate for the LAI. This results in a MRSD of 99 mg based on rat NOAEL (1/50*4957=99 mg) and 54 mg based on rhesus NOAEL (HED=140 mg/kg x 0.324 [rhesus to human dose conversion factor] x 60 kg=2722 mg; 1/50*2722 =54 mg).

The MK-5720 proposed starting dose of 35 mg provides a ~ 1.5- to 2.8-fold safety margin to the MRSD of 54 and 99 mg based on the rhesus and rat NOAEL, respectively. The lowest weight permitted in the study is 50 kg; even for a 50-kg participant the starting dose of 35 mg offers a 1.2-fold safety factor to the more conservative MRSD of 54 mg based on rhesus NOAEL. The 35-mg starting dose is also the lowest possible dose of the LAI that can be administered accurately via the IM route based on a 0.1-mL administration volume.

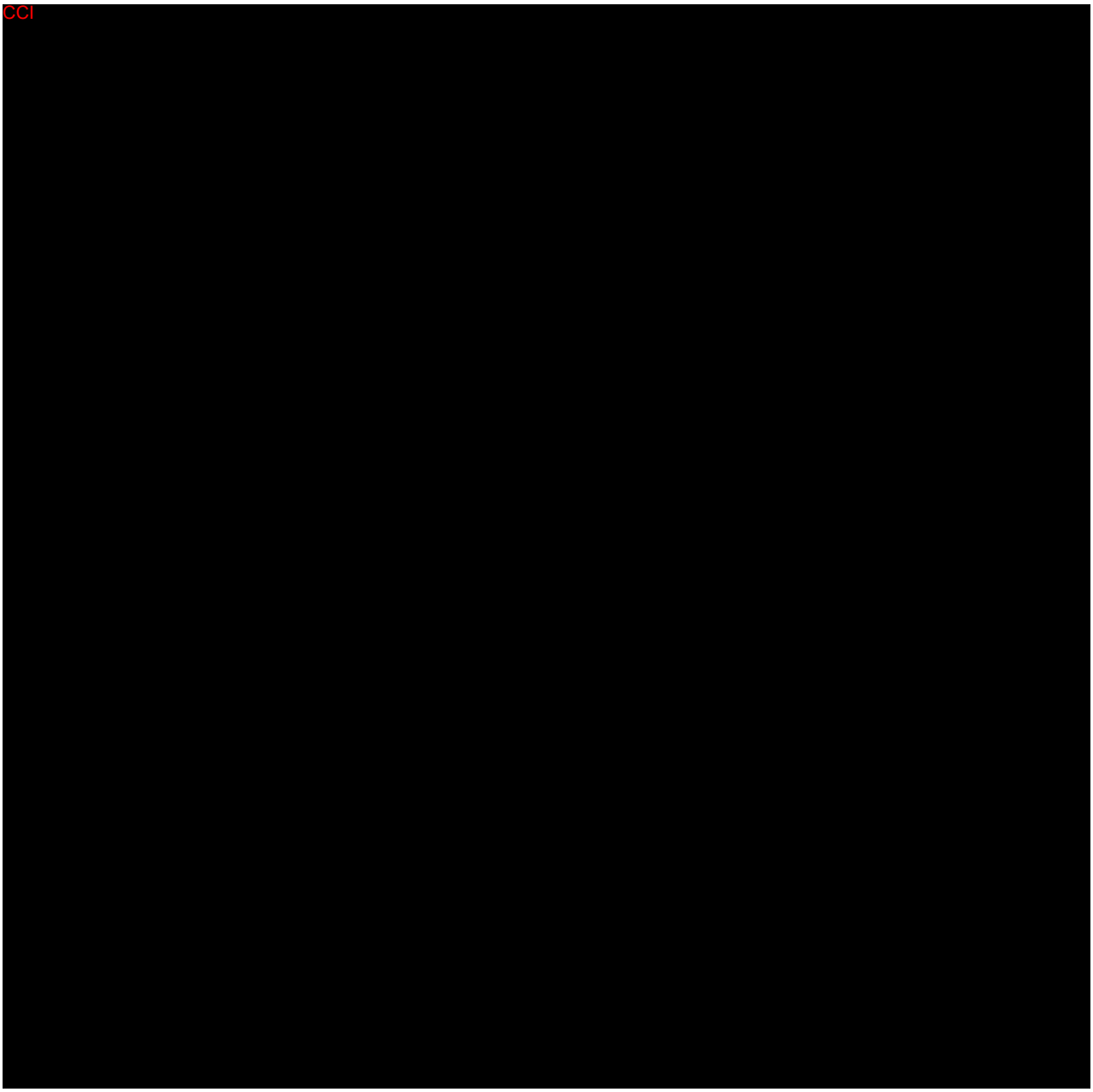
The starting dose of 35 mg is estimated to yield a human MK-5720 AUC0-28d of 0.09 µM*hr with a MK-5720 Cmax of 0.00019 µM that is approximately 23- and 68-fold lower than the rat AUC0-28d and Cmax NOAEL exposure cap and 103- and 375-fold lower than the rhesus AUC0-28d and Cmax NOAEL, respectively. CCI [redacted]

For more detailed information regarding results from the rat and rhesus toxicological studies, please refer to the IB for MK-5720.

4.3.2 Maximum Dose Exposure for This Study

The maximum dose planned in this study is supported by the 4-week GLP repeat dose toxicity study with MK-5720 and also supported by clinical experience with MK-8189 across multiple Phase 1 and Phase 2 studies. As recommended by the EMA "Guideline on Strategies to Identify and Mitigate Risks for First in-Human Clinical Trials With Investigational Medicinal Products" [European Medicines Agency 2007], the maximum exposure in humans should be predefined and justified based on all available non clinical and clinical data, including PD, PK and findings in toxicity studies and exposures at the therapeutic dose range.

CCI



CCI

[redacted]

Administration of MK-5720IM injection of 12, 30, or 510 mg/kg and 12, 36 and 140 mg/kg of MK-5720 formulated as a LAI was administered as a single dose in rats and monkeys respectively, with a 1-month toxicity assessment and a 3-month treatment-free period to determine the potential toxicity and TK profile of MK-5720. The high-dose was selected to assess systemic toxicity at supratherapeutic exposures while the low and mid-dose were selected to assess local tolerability at relevant therapeutic exposures.

IM injection of MK-5720 LAI was generally well-tolerated at all doses (12, 30 and 510 mg/kg) in rats in the 1-month GLP toxicological study. There were no test article-related unscheduled deaths, and no test article-related changes in food consumption, ophthalmic, hematology, coagulation, serum biochemistry, or urinalysis parameters. There were no test article-related findings in other tissues of any rats in the 510 mg/kg group, indicating no systemic toxicity by the test article.

By the end of the 1-month toxicity assessment period, clinical signs (limited to injection site swelling) and body weight changes were generally resolved. Alterations in inflammatory biomarkers (A2M and AGP) were resolved and were not considered toxicologically meaningful. Chronic inflammation or a less pronounced change of local infiltrates at the intramuscular injection site observed at final necropsy (1 month after injection) in animals at ≥30 mg/kg was an expected finding typically observed with administration of long-acting formulations in rodents and had resolved in recovery animals necropsied approximately 4 months after dosing. The NOAEL was 510 mg/kg as injection sites reactions were not considered adverse at all dose levels, were reversible at the dose level examined (30 mg/kg)

and were consistent with findings typically observed after administration of long-acting injectable formulations to rats.

IM injection was considered to be generally well tolerated at all doses (12, 36 and 140 mg/kg) in monkeys in the 1-month GLP toxicological study. There were no test article-related unscheduled deaths, and no test article-related changes in body weight, ECG, ophthalmic, hematology, or urinalysis parameters. By the end of the 1-month toxicity assessment period at doses ≤140 mg/kg, clinical signs had generally resolved and alterations in serum markers of inflammation (fibrinogen and C-reactive protein) were not considered toxicologically meaningful.

Minimal to moderate chronic inflammation at the IM injection site observed at final necropsy (1-month after injection) was an expected finding typically observed with administration of long-acting formulations in nonhuman primates. At the recovery sacrifice (limited to Cohort B animals in the low- and mid-dose groups), no test article-related gross or histomorphologic findings were observed at the injection site. No foci of chronic inflammation were observed in the quadriceps muscle group. Overall, the injection site reaction in the mid- and low-dose groups was considered to be in either a resolution phase or recovered after a 1-month toxicity assessment and a 3-month treatment-free period.

Based on the presence of test article-related findings at all dose levels, the NOAEL was 140 mg/ as injection sites reactions were not considered adverse, were reversible at the dose levels examined (12 and 36 mg/kg) and were consistent with findings typically observed after administration of long-acting injectable formulations to monkeys.

Since the rat NOAEL provides a ~ 1.4X EM for the AUC0-28d compared to 6.4X EM for the rhesus relative to the highest planned dose of 560 mg of MK-5720 based on the 1-month repeat dose toxicological studies, rat is considered the most sensitive species. Thus, the NOAEL for the purposes of establishing maximum allowable exposures is 2.05 µM*hr and 0.0129 µM for AUC0-28d and Cmax, respectively. The highest planned dose of 560 mg of MK-5720[CCI] provides a 4.3-fold safety margin to the rat Cmax NOAEL exposure cap. Furthermore, no MK-5720-related effects on QTc or HR were noted in anesthetized NHPs up to the highest dose tested [CCI]

Maximal MK-5720 LAI single doses of up to 560 mg are proposed in the study to generate safety margins to the 280-mg dose of MK-572 [CCI]
Importantly, MK-5720 dose flexibility is built in the study as a contingency in the event resulting MK-8189 plasma concentrations from MK-5720 LAI are lower than that projected due to faster depletion of drug from the LAI or due to differences in LAI input rate observed in the clinic compared to that observed preclinically resulting in sub-efficacious MK-8189 plasma concentrations. MK-5720 LAI doses in the study have been selected in the study to result in MK-8189 plasma concentrations that remain within the clinical experience generated with the oral MK-8189 program in participants with schizophrenia and supported

by having sufficient safety margins at the highest dose proposed based on preclinical safety data generated with MK-5720 and MK-8189.

The projected MK-5720 exposures corresponding to the highest planned dose of 560 mg of MK-5720 LAI [redacted] provides a 4.3 and 1.4-fold safety margin to the rat (more sensitive compared to rhesus) MK-5720 C_{max} and AUC NOAEL exposure cap [refer to Section 4.3.1.2 of MK-5720 IB]. Furthermore, the projected MK-8189 C_{max} and $AUC_{0\text{-}28d}$ corresponding to the 560 mg-dose of MK-5720 LAI [redacted], provides a ~15 and 2.5-fold safety margin to the rat MK-8189 C_{max} and AUC NOAEL and ~ 9 and 3.3-fold to the rhesus C_{max} and NOAEL exposure cap, based on the 6 and 9-month repeat dose GLP tox study conducted with oral MK-8189 [refer to Section 4.3.2 of MK-5720 IB]. The projected MK-8189 Cmax exposures corresponding to the 560- mg dose of LAI (~ 3 µM) is within the range of the highest MK-8189 mean Cmax exposure observed with 80-mg dose of oral MK-8189 on Day 2 of ~ 2.63 µM (95% CI 2.08, 3.32 µM; preliminary data) that was generally well tolerated in participants with schizophrenia (P014).

Because studies in preclinical species are not always predictive of what may occur in humans, safety of MK-5720 will be assessed throughout the study by monitoring AEs, physical/neurological examinations, VS, ECGs, and laboratory safety tests (chemistry, hematology, urinalysis). The timing of the safety endpoints has been planned to ensure adequate safety monitoring throughout the treatment period, taking into consideration the range of potential t1/2 predictions of MK-5720. Participants will be followed for at least 55 days to allow for adequate MK-5720 washout (~ 5-half-lives based on an estimated t1/2 of 10 days for MK-8189 in humans). Safety data from each dosing period will be carefully reviewed before escalation to the next higher dose. Key safety data such as VS, 12-lead ECGs, lab safety tests and physical/neurological examinations will be reviewed for up to at least 14 days postdose (Panel A) and up to 28 days postdose for all other panels prior to dose escalation to the next higher dose level. Plasma concentrations of MK-5720 from the preceding panels will be determined at the allocated PK breaks to ensure that the NOAEL AUC exposure limits are not exceeded at the doses in the subsequent panels. Since this is the first instance of administration of MK-5720 to humans, the dose levels and interval between doses may be adjusted based on safety and/or PK data from the prior periods.

4.3.3 Rationale for Dose Interval and Study Design

MK-5720, prodrug of MK-8189, a PDE10A inhibitor, is not considered a compound that can pose a potential safety risk to participants and is not a biological molecule and does not exhibit species-specific action and is not directed towards immune system targets. MK-5720 is approximately 650-fold less potent compared to MK-8189 based on in-vitro binding assay (MK-5720 PDE10 IC50 of 18.7 nM vs. 0.029 nM for MK-8189) and furthermore, due to the rapid bioconversion of MK-5720 to MK-8189 in vivo, MK-5720 concentrations anticipated in the clinic should be well below pharmacologically active concentrations and therefore, the main pharmacological activity expected in the clinic is a result of the MK-8189 metabolite. Furthermore, concentrations of MK-5720 will be monitored in the clinic so as not to exceed the NOAEL AUC0-28d and Cmax exposure cap.

The study design consists of 6 sequential panels (Panels A to F) and 3 PK breaks between Panels B to C, C to D, and E to F, respectively. In each treatment period for each panel of the study, participants will be randomized to receive MK-8189/MK-5720 (n=6 to 9) or placebo (n=2 to 3) in a blinded manner. All participants in a given panel shall receive the treatment or placebo on the same day in time spaced intervals based on Phase 1 clinical research standards for compounds not considered to be of high risk of harm. An oral tolerability run-in period with MK-8189 is incorporated in the study to [redacted] A washout period of at least 72 hours is included between the MK-8189 oral run-in period (Period 1) and the MK-5720 IM administration (Period 2) to fully understand the release kinetics and pharmacokinetics of MK-8189 following IM injection of MK-5720 in the absence of circulating carry-over MK-8189 from the prior oral run-in-period.

The dosing regimen was determined based on the following: clinical safety experience with MK-8189, the presence of preclinical safety margins for both MK-5720 and MK-8189, the inclusion of extensive safety monitoring in the clinic, and the fact that MK-5720 is not considered a compound with a high potential for risk of harm. There will be frequent, careful assessments of AEs throughout the postdose period. This recommendation is in keeping with the projected safety profile and the ability of the Phase 1 unit to monitor each participant closely. Safety data will be reviewed for at least up to 14 days post dose for dose escalation to Panel B and up to 28 days postdose for all subsequent panels before dose escalation between panels to allow for review of key safety parameters. The 14-day safety review period will allow for peak plasma concentrations of MK-8189 to be achieved from the MK-5720 LAI. Participants will be followed for at least 55 days allowing for collection of ~ 5 half-lives of MK-8189 based on estimated half-life of ~ 10 days in humans for MK-8189 from MK-5720 LAI.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section

7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

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

4.4.1 Clinical Criteria for Early Study Termination

A primary objective of this early Phase 1 study is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Meets diagnostic criteria for schizophrenia or schizoaffective disorder according to the DSM-5 criteria with the onset of the first episode being no less than 2 years prior to screening and monotherapy with antipsychotics for treatment should be indicated.
2. Has a total BPRS score of less than 48 with a BPRS score less than 4 for #10 (hostility) and #14 (uncooperativeness) at the Screening Visit.
3. Is in the nonacute phase of their illness and clinically stable for 3 months prior to screening as demonstrated by:
    a. no clinically significant change in dose of prescribed antipsychotic medication, or clinically significant change in antipsychotics medication to treat symptoms of schizophrenia for two months prior to screening. Determination of clinical significance of dose change is at the discretion of the investigator.
    b. no increase in level of psychiatric care due to worsening of symptoms of schizophrenia for three months prior to screening.

    Note: Participants that are stable but not currently taking antipsychotic medications are eligible.
4. Is in good health based on medical history, physical examination, VS measurements, and ECGs performed at the Screening Visit and/or prior to randomization. The assessment prior to randomization is based on the mean of triplicate measures. Note: The QTcF-duration must be less than or equal to 450 msec. Repeat 12-lead safety ECGs may be performed in participants whose parameters are, per investigator discretion, minimally outside the designated range.
5. 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.
6. Has a history of receiving and tolerating antipsychotics medication within the usual dose range employed for schizophrenia.

7. Has a stable living situation in which the participant or contact person can be reached by the investigator if there is a need for follow up.
8. Participants with hypothyroidism, diabetes, high blood pressure, chronic respiratory conditions or other medical conditions could be considered as a candidate for study enrollment if their condition is stable and the prescribed dose and regimen of medication is stable for at least 3 months prior to screening and there are no expected changes in co-medication during the study.
9. Participants is able to discontinue the use of all antipsychotic medication at least 5 days or 3 half-lives (which ever in longer) prior to the start of the treatment period and during the study.
10. Have a normal resting BP (systolic BP is greater than or equal to 90 mm Hg and less than or equal to 140 mmHg; diastolic BP is greater than or equal to 60 mmHg and less than or equal to 90 mmHg) and normal resting HR (greater than or equal to 45 bpm and less than or equal to 100 bpm) in the supine position at the pre-trial (screening) visit and/or prior to randomization. Repeat evaluations may be done if the values for a participant are, per investigator discretion, minimally outside the designated range. The assessment prior to randomization is based on the mean of the triplicate measures. Participants may be included if values are outside the normal range but considered not clinically significant per investigator discretion.
11. Has regular bowel movements and, in the opinion of the investigator, no clinically significant diarrhea or constipation.

Demographics

12. Is an individual of any sex/gender, from 18 years to 60 years of age inclusive, at the time of providing the informed consent.
13. The participant has a BMI greater than or equal to 18 and less than or equal to 40 kg/m^2 and total body weight of greater than 50 kg (110 pounds) at the Screening Visit. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight $(kg)/height\ (m)^2$.

Male Participants

14. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is:
    - MK-5720: at least 55 days

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
    - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant and should also

be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.
Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

- Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

15. A participant assigned female sex at birth is eligible to participate if:

She is a PONCBP, as defined in Appendix 5.

Informed Consent

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

Additional Categories

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

5.2 Exclusion Criteria

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

Medical Conditions

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

3. 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.
4. Has a tattoo, scar, or other physical finding at the area of the injection site that would interfere with the evaluation of local tolerability or integrity of the injection site.
5. Has a history of cancer (malignancy).

   Exceptions: (1) Participants with adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the study; (2) Participants with other malignancies which have been successfully treated greater than or equal to 10 years prior to the prestudy (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the prestudy (screening) visit (except those cancers identified at the beginning of this exclusion criteria); or (3) Participants, who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study.

6. Has evidence or history of a primary DSM-5 axis I psychiatric diagnosis other than schizophrenia or schizoaffective disorder per the allowed DSM-5 criteria within one month of screening.
7. Has evidence or history of mental retardation, borderline personality disorder, or organic brain syndrome.
8. Has a history of neuroleptic malignant syndrome or moderate to severe tardive dyskinesia.
9. Has a substance-induced psychotic disorder or behavioral disturbance thought to be due to substance abuse.
10. Has a DSM-5 defined substance use disorder (excluding nicotine and caffeine) within 3 months of screening.
11. Has a history of seizure disorder beyond childhood or is receiving treatment with any anticonvulsant to prevent seizures.
12. 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.
13. Has history of repeated or frequent syncope, vasovagal episodes, or epileptic seizures.
14. Has a family history of sudden death.
15. Has claustrophobia to a degree that prevents tolerance of MRI scanning procedure.

    Note: This is only applicable to panels receiving MRIs.
16. Has a metallic implant of any sort that prevents MRI examination including, but not limited to, aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, metallic tattoo, body piercing that cannot be removed, cochlear implant, or any other contraindication to MRI examination.

    Note: This is only applicable to panels receiving MRIs.

17. 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.
18. Has been in incarceration or imprisonment within 3 months prior to screening.
19. 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.
20. Participant has an estimated CrCl less than or equal to 80 mL/min based on the Cockcroft-Gault Equation.

    Cockcroft-Gault Equation:

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

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

    For females, multiply the result by 0.85.

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

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

21. History of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
22. Positive test(s) for HBsAg, hepatitis C antibodies or HIV.
23. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

24. Has received or is currently receiving treatment with clozapine for any length of time. Has received treatment with monoamine oxidase inhibitors within 3 months of screening or cariprazine within 2 months of screening.
25. Is unable to be washed off their parenteral depot antipsychotic medication prior to screening or requires a dose of a parenteral depot antipsychotic medication during the study.
26. Is unable to refrain from the use of co-medication that is a moderate or strong inhibitor or inducer of CYP3A beginning approximately 2 weeks or 5 half-lives, whichever is longer, prior to administration of the initial dose of trial drug and throughout the trial (Section 6.5).

27. Has received any nonlive vaccine starting from 14 days prior to study intervention or is scheduled to receive any nonlive vaccine through 30 days following study intervention. Exception: COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination. Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
28. Has received any live vaccines within 30 days prior to the first dose of study intervention or is scheduled to receive any live vaccine through 60 days following study intervention.

    Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

Prior/Concurrent Clinical Study Experience

29. 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

30. Under the age of legal consent.
31. Does not agree to follow the smoking restrictions as defined by the CRU.
32. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
33. 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.
34. Is a regular user (in the opinion of the investigator and Sponsor) of cannabis, a user of 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 prescribed medications permitted at the discretion of the investigator and Sponsor and/or cannabis) prior to randomization.
35. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions). Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

36. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.
37. 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

Period 1

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

Period 2

During the domiciling period, scheduled meals and snack(s) will be provided by the investigator per the site's standard procedures.

All Periods

Additionally, all laboratory safety assessments will be performed after an 8 hour fast as specified in Appendix 2.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention in Period 1, throughout the study and until the poststudy visit.

Participants also will refrain from the consumption of all fruit juices 24 hours before and after study intervention administration. On all other days during the study, consumption of 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 are advised to refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the Screening Visit. A recheck may be needed if

participants did not refrain from consuming caffeinated beverages or xanthine-containing products 12 hours prior to the Screening Visit.

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from:

- 12 hours before and after study intervention administration in each treatment period.
- 12 hours before poststudy visit.

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

5.3.2.2 Alcohol Restrictions

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

5.3.2.3 Tobacco Restrictions

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

5.3.3 Activity Restrictions

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

If a participant withdraws or discontinues 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.

6 STUDY INTERVENTION

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

Clinical supplies, MK-8189, MK-5720, placebo, and diluent, will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in [Table 6].

Table 6 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel A	Experimental	MK-8189	Drug	Tablet	4 mg	4 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsor
Panel A	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided centrally by the Sponsor
Panel A	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	35 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the Sponsor
Panel A	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel B	Experimental	MK-8189	Drug	Tablet	4 mg	8 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsor
Panel B	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided Centrally by the Sponsor
Panel B	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	70 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the Sponsor
Panel B	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor
Panel C	Experimental	MK-8189	Drug	Tablet	4 mg 12 mg	16 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsor
Panel C	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided centrally by the Sponsosr

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel C	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	140 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the Sponsor
Panel C	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor
Panel D	Experimental	MK-8189	Drug	Tablet	12 mg	24 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsosr
Panel D	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided centrally by the Sponsosr
Panel D	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	280 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the sponsor
Panel D	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel E	Experimental	MK-8189	Drug	Tablet	12 mg	48 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsor
Panel E	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided centrally by the Sponsor
Panel E	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	≤560 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the Sponsor
Panel E	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor
Panel F	Experimental	MK-8189	Drug	Tablet	12 mg	48 mg	Oral	Period 1	Test Product	IMP	Provided centrally by the Sponsor
Panel F	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg	Oral	Period 1	Placebo	IMP	Provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel F	Experimental	MK-5720	Drug	Injection, Powder, For Suspension	350 mg/mL	≤560 mg	IM	Period 2	Test Product	IMP	API and excipients provided centrally by the Sponsor
Panel F	Placebo Comparator	Placebo	Drug	Injection, Powder, For Suspension	0 mg	0 mg	IM	Period 2	Placebo	IMP	API and excipients provided centrally by the Sponsor

API=active pharmaceutical ingredient; EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; N/A= not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product

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

In this protocol, placebo for MK-5720 is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients.

Those who receive placebo in Period 1 will receive placebo in Period 2. Those receiving MK-8189 in Period 1 will receive MK-5720 in Period 2.

All supplies indicated in [Table 6] will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

MK-8189

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant.

MK-5720

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

MK-5720 and placebo dosage form will be prepared and dosed per the instructions outlined in the Method of Preparation Document and Study Operations Manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

A sample allocation table is provided below in [Table 7].

Table 7 Allocation of Participants to Treatment

Panel	N	MK-8189 Treatment Period 1	MK-5720 Treatment Period 2
Panel A	6	4 mg	35 mg
	2	Placebo	Placebo
Panel B	6	8 mg	70 mg
	2	Placebo	Placebo
Panel C	9	Less than or equal to 16 mg	Less than or equal to 140 mg
	3	Placebo	Placebo
Panel D	9	Less than or equal to 24 mg	Less than or equal to 280 mg
	3	Placebo	Placebo
Panel E	9	Less than or equal to 48 mg	Less than or equal to 560 mg
	3	Placebo	Placebo
Panel F	9	Less than or equal to 48 mg	Less than or equal to 560 mg
	3	Placebo	Placebo
The suggested doses may be adjusted downward based on evaluation of safety, tolerability and/or pharmacokinetic data observed in previous treatment periods/panels.			

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique will be used. MK-8189, MK-5720 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 participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

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

Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 60 days after the last dose of study intervention.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

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

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

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

Reason for use

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

Paracetamol/acetaminophen (up to 4 g per day), ibuprofen (up to 1.2 g per day) and antacids (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 are stable for at least 3 months prior to screening and there are no expected changes in co-medication during the study. Inclusion of participants being administered concomitant medications that have not been stable for 3 months must be discussed with the Sponsor. Moderate to strong inhibitors or inducers of CYP3A are not allowed as MK-8189 is being metabolized by these CYP enzymes and co-administration of inhibitors or inducers may potentially alter the metabolism and PK of MK-8189.The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

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

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

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

Participants will be washed off from their antipsychotic treatment (Section 8.1.5.1). The duration of washout period should be at least 5 days or cover at least 3 half-lives of the drug (whichever is longer) prior to Day -1 assessments in Period 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.

In the event that the patient must be discontinued due to worsening of psychosis while on MK-5720, standard of care practice should be initiated, utilizing the lowest dose of an oral antipsychotic required to control symptoms during washout of MK-5720. Approved oral antipsychotic medications for this study are outlined in [Table 8] based on prior clinical experience with addition of oral MK-8189 to the antipsychotic medications at the dose range mentioned below and that were generally well tolerated in 2 clinical studies conducted with

oral MK-8189 (P003 and P007). The medications listed below or use of any other standard of care oral antipsychotic medications may be used following prior consultation of the PI with the Sponsor.

Table 8 Approved Oral Antipsychotic Medications

Medication Name	Total Daily Dose Range Coadministered with MK-8189	Target Daily Dose Range for Schizophrenia in Adults
Quetiapine	50 to 600 mg	50 to 750 mg[a]
Aripiprazole	7.5 to 30 mg	10 to 15 mg[b]
Risperidone	0.5 to 8 mg	2 to 8 mg[c]
Olanzapine	10 to 40 mg	5 to 20 mg[d]
Ziprasidone	60 to 80 mg	40 to 200 mg[e]
Lurasidone	60 to 80 mg	40 to 160 mg[f]

[a] [U.S. Prescribing Information 2020]
[b] [U.S. Prescribing Information 2017]
[c] [U.S. Prescribing Information 1993]
[d] [U.S. Prescribing Information 2011]
[e] [U.S. Prescribing Information 2010]
[f] [U.S. Prescribing Information 2013]

For patients who may experience anxiety during an MRI scan and require prophylaxis, the investigator may use a short to intermediate duration benzodiazepine, such as lorazepam, if deemed necessary and after prior consultation with the Sponsor.

6.6 Dose Modification (Escalation)

All dose-escalation decisions will be made jointly by the investigator and the Sponsor. Members of the Sponsor safety review team will include: the trial clinical director, trial clinical scientist, senior level clinical director and trial biostatistician. Additional Sponsor attendees may include a clinical research associate and a pharmacologist. The Sponsor safety review team will obtain input from the investigator regarding his/her evaluation of safety and tolerability from the previous dosing period and his/her recommendation to dose escalate in the next panel.

Each dose-escalation decision will occur after at least 8 (Panels A and B) and 12 (Panels C through F) evaluable participants have completed the previous dose level (participants will be randomized to receive MK-5720 or placebo in a 3:1 ratio, respectively).

Dose-escalation decisions will be based on blinded key safety variables, with summary statistics as needed. Safety variables will include, vital signs, 12-lead ECG, laboratory safety tests, AE, and neurological assessments from the previous dose levels up to at least 14 days postdose. PK data may be included in the dose-escalation decisions (Section 2.1 and Section 2.2).

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

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

Participant discontinuation criteria are outlined in Section 7.

6.6.1 Stopping Rules

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

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

1. An individual participant reports an SAE considered related to the study intervention by the investigator.
2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

If any of the above stopping rules are met, subsequent higher doses will be lowered based on joint agreement of the Sponsor and investigator in order for the study to continue.

3. Should the emerging PK (mean) data indicate that the maximum clinical exposure (C_{max} or AUC), as defined in Section 4.3 will be exceeded, subsequent higher doses will be adjusted based on joint agreement of the Sponsor and investigator.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

The emergency unblinding call center will use the intervention randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10).

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

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

- Procedures conducted as part of a site generic screening (with an ERC/IRB approved site generic screening consent) on potential participants (eg, blood count, vital signs, ECG, etc) and obtained before signing of study ICF may be used for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the screening window defined in this protocol.

The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in the Study Operations manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally

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

8.1.1.1 General Informed Consent

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

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

Washout From Antipsychotics:

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

Participants may restart their antipsychotics therapy following completion of the last study procedures on Day 55 in Period 2.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant

will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of 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 reassigned to another participant.

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

8.1.8 Study Intervention Administration

Period 1

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

Period 2

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee according to the specifications within the pharmacy manual.

In Panels A to C, participants will receive an IM injection in the deltoid. For Panels D to F, participants will receive an IM injection in the deltoid or in their gluteal muscle as directed by the Sponsor.

Study intervention and placebo will be provided to the study staff will require reconstitution by site staff according to the directions in the Method of Preparation. Study intervention(s) will be provided to the study staff in prefilled syringes from the pharmacy. Syringes will be covered with a blinding label. However, there is a significant visual difference between the active and placebo formulations, the unit staff who are involved in study drug administration cannot be involved in other areas of study conduct to maintain blinding. Site staff should use the appropriate needle length and gauge for administering study intervention based on the BMI of the participants.

8.1.8.1 Timing of Dose Administration

Period 1

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

Period 2

Study drug administration will occur according to the SoA and Method of Preparation document. Once the study intervention(s) are filled into syringes, it may be stored at ambient conditions as directed in the Method of Preparation document.

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. If a participant discontinues for any reason at any time during the course of the study, 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 1.3 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone

and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

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

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

8.1.11 Domiciling

Participants currently treated with antipsychotic medication will be domiciled in the CRU from up to Day -6 prior to dose administration (to start the washout period of current antipsychotic medication) in Period 1 and will remain in the CRU until all 28 days postdose procedures have been completed in Period 2. Participants not currently being treated with antipsychotic medication may be domiciled minimally starting on Day -2 in Period 1. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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 over the course of the study (from prestudy

to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in the Study Operations Manual.

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

8.3.1 Physical Examinations

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

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

BMI

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

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

8.3.2 Vital Signs

- Body temperature, heart rate, respiratory rate, and blood pressure will be assessed at prespecified timepoints noted in the SoA (Section1.3).
- Blood pressure and heart rate measurements will be assessed in a supine position as well as orthostatic positions with a completely automated device. Manual techniques will be used only if an automated device is not available.
- VS measurements should be taken before blood collection for laboratory tests.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-8189/placebo in Period 1 (Day 1 only) MK-5720/placebo in Period 2. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements in both Periods.

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

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

8.3.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.
- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.

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

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

The correction formula to be used for QTc is Fridericia.

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

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

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

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

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

8.3.5 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, before their assessment of the participant and to further inform their evaluation.

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

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). After that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety. In addition, all AEs of suicidal ideation or behavior must be recorded as an ECI (see Section 8.4.7). Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

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.

8.3.7 Assessment of Neuropsychological Effects

A general (full) Neurological Exam will be performed at the Screening visit, predose in Period 1 and 2, prior to discharge in Period 2, and at the Day 56 outpatient visit. A targeted Neurological Exam will be administered at times specified in the SoA.

A BPRS evaluation will be performed at Screening, Baseline in Period 1 and will also be completed at times specified in the SoA.

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

8.3.8 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

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

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

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

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

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

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

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

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

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

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 9].

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

Table 9 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

Not applicable

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an

additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

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

8.5 Treatment of Overdose

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

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

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-5720 and MK-8189

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

8.7 Pharmacodynamics

Not applicable

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

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

- Leftover samples listed in Section 8.8

8.10 Visit Requirements

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

8.10.1 Screening

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

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 Visit

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8).

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

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

8.10.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last study procedure for the poststudy visit in Period 2. If the poststudy visit occurs less than 14 days after the last study procedure, a subsequent follow-up telephone call should be made at 14 days post the last study procedure 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-5720 is the critical procedure.

At any postdose time point, the blood sample for MK-5720 must be collected as close to the exact time point as possible. All other procedures should be completed as close to the scheduled time as possible. Study procedures can be performed before or after the scheduled time.

1. 12-Lead Safety ECG
2. Vital signs

a. Resting BP and HR
b. Orthostatic BP and HR

3. Laboratory safety tests
4. Neurological exams: C-CSSRS, BPRS, BARS, AIM, SAS

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

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

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in [Table 10].

Table 10 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
Predose	- 3 hours
0 to <12 h	5 min
12 to <24 h	15 min
24 to <48 h	30 min
48 to <672 h	2 h
>672 h	48 h

- Predose standard safety evaluations: VS and ECG at 3 hours; laboratory safety tests and physical examination at 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical examination
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to 168-hours postdose may be obtained within 2 hours of the theoretical sampling time

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

This is a Phase 1 assessment of MK-5720 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Repeat of or decrease in the dose of the study intervention administered in any given panel
- Interchange of doses between panels
- Entire panel(s) may be omitted
- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose

- Addition of PK pause
- Modification of the PK sample processing and shipping details based on newly available data

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

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

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

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

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Responsibility for Analyses

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

9.2 Hypotheses/Estimation

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

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[redacted]

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Safety: Primary safety endpoints will include all types of adverse events and discontinuation of study intervention due to adverse event(s), in addition to laboratory safety tests, ECGs, and vital signs. Baseline is defined as measurements obtained pre-dose Day 1. These endpoints will be calculated for both periods (oral run-in doses of MK-8189 and IM single-ascending doses of MK-5720).

Pharmacokinetics: The pharmacokinetic variables of plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2 will be evaluated along with the plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2. These PK endpoints apply to Period 2 (IM single-ascending doses of MK-5720).

9.3.2 Secondary Endpoints

Pharmacokinetics: The following PK endpoints apply to Period 2 (IM single-ascending doses of MK-5720).

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[redacted]

For each site of administration, the pharmacokinetic variables of plasma MK-5720 AUC0-last, AUC0-inf, Cmax, Tmax, CL/F, Vz/F and apparent terminal t1/2 will be evaluated along

with the plasma MK-8189 AUC0-28d, AUC0-inf, Cmax, Tmax, C28d, CL/F, Vz/F and apparent terminal t1/2.

9.3.3 Exploratory Endpoints

Pharmacokinetic: Following oral run-in doses of MK-8189 (Period 1), the pharmacokinetic variables of plasma MK-8189 AUC0-24, Cmax, Tmax, C24 and apparent terminal t1/2 will be evaluated.

Following IM single-ascending doses of MK-5720 (Period 2), the depot volume and surface area calculated via intensity threshold-based segmentation of the MRI images will be evaluated to better understand any differences in pharmacokinetics between patients.

9.4 Analysis Populations

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

9.4.1 All Participants As Treated Population

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

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

9.4.2 Per-Protocol (PP) Population

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

9.5 Statistical Methods

9.5.1 Statistical Methods for Safety Analyses

Safety will be summarized separately for the oral run-in doses of MK-8189 [Period 1] and IM single-ascending doses of MK-5720 [Period 2]. The following will be done for both periods.

Incidence of AEs will be descriptively summarized. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and 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).

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

9.5.2 Statistical Methods for Pharmacokinetic Analyses

The following analyses are for Period 1 of the protocol (oral run-in doses of MK-8189).

Individual values will be listed for each PK parameter, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV, calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

The following analyses are for Period 2 of the protocol (IM single-ascending doses of MK-5720).

Model-based PK summary

Separately for each PK parameter, individual values of plasma MK-5720 (AUC0-last, AUC-inf, and Cmax) and plasma MK-8189 (AUC0-28d, AUC0-inf, Cmax, and C28d), after administration of a single dose of MK-5720 from Panels A through F will be natural log-transformed and evaluated with a linear effects model containing a fixed effect for treatment. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent CIs for the least squares means for each treatment will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these CIs will yield estimates for the population GMs and CIs about the GMs on the original scale. A sample code is as follows:

```
proc mixed data=adpp;
class treatment;
model lnpk=treatment/ddfm=kr;
lsmeans treatment/alpha=0.05 cl;
run;
```

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PK Comparison of Deltoid vs Gluteal Muscle

A comparison between Deltoid and Gluteal Muscle will be evaluated using the above linear model at a common dose level for plasma MK-5720 and plasma MK-8189. If appropriate, dose normalization prior to construct of comparison and subsequent calculation of the geometric mean ratios and corresponding 90% confidence interval will be implemented.

Descriptive Statistics

Individual values will be listed for each PK parameter by treatment (for MK-5720 and MK-8189), and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV, calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

QTc Analysis

QTc will be evaluated through development of a model describing the relationship between QTc change from baseline and MK-5720 plasma concentrations and the relationship between QTc change from baseline and MK-8189 plasma concentrations. Details of the concentration-QTc analysis will be specified in a separate modeling analysis plan (MAP). This MAP will be completed prior to unblinding and database lock. The planned analysis will be aligned with the Scientific White Paper on Concentration-QTc modeling - A Review [Garnett, C., et al 2017]. Results of this analysis will be reported separately from the CSR.

Counts will be provided by dose and time point for QTc values falling in the following ranges: ≤450, >450, >480 and >500 msec. Counts will also be provided by dose and time point for QTc change from baseline values falling in the following ranges: <30, ≥30 and ≥60 msec. Means and 90% confidence intervals for QTc and QTc change from baseline will be provided for each dose.

Exploratory Analysis

The depot volume and surface area from the MRI images will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum, by deltoid muscle and gluteal muscle.

9.6 Interim Analyses

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

9.7 Multiplicity

The hypothesis related to target PK will be addressed using posterior probabilities, therefore, there is no need for a multiplicity adjustment.

9.8 Sample Size and Power Calculations

The following power applies to Period 2 of the protocol (IM single-ascending doses of MK-5720).

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10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.6 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 11] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.3 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11 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	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (as needed in PONCBP only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) or specify other tests if applicable			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PONCBP=person of nonchildbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

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

Assessment of intensity/toxicity

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

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

Assessment of causality

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Nonchildbearing Potential (PONCBP)

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

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

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

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

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

Nonparticipant of Childbearing Potential

A nonparticipant assigned female sex at birth is considered fertile and capable of becoming pregnant following menarche until becoming postmenopausal unless permanently sterile (see below):

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

- Premenarchal
- Premenopausal with 1 of the following:
  - Hysterectomy
  - Bilateral salpingectomy

- Bilateral oophorectomy
- Permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity).

- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

10.5.2 Contraceptive Requirements

Not applicable

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2 Scope of Future Biomedical Research[3, 4]

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

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

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

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

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Blood Volume Table

Please refer to the Study Operations Manual for Blood Volume Table.

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥200 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥120 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (F)		
Male	QTc ≥450 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥450 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P. Mitrale or P. Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All

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

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate;; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1.

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

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

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

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

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

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

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

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

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

10.11 Appendix 11: General and Targeted Neurological Examinations

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

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

10.11.1 The General Neurological Examination

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

10.11.1.1 Module 1 – Mental Status Examination

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

B. Thought Processes and Language (generally assess logic, relevance, organization, and coherence of participant's use of language throughout the interview).

C. Orientation (time, place, person).

D. Attention/Concentration.
Ask the participant to count backwards from 100 by 7's ("Serial 7's") or ask to recite months backwards or spell a 5 unique letter word (eg, "WORLD") backwards.
Note: To avoid learning effects, switch between tests throughout the study.

E. Memory (test registration of 3 objects; then test immediate recall 5 minutes later).
Grade: NORMAL or IMPAIRED and describe abnormality (for each, A to E, above).
Normal performance on Serial 7's is getting to 65 with no more than 1 error.

10.11.1.2 Module 2 – Cranial Nerve Assessment

A. II – Visual Fields and acuity

B. II, III – Pupil Size and Reactivity

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

D. V – Facial Sensation, Jaw Strength

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

F. VIII – Auditory Acuity (assessed using a bed-side screening test [eg, by rubbing fingers on each side of participant's head or by whispering numbers])

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

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

10.11.1.3 Module 3 – Motor System

A. Muscle Tone

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

Score: left and right

Grade: NORMAL, INCREASED or DECREASED

B. Muscle Strength

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

Grade: NORMAL, IMPAIRED and describe abnormality

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

Score: left and right

Grade:

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

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

Score: left and right

Grade:

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

C. Pronator Drift

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

Score: left and right

Grade: NORMAL or IMPAIRED and describe abnormality

10.11.1.4 Module 4 – Reflexes

A. Biceps

B. Knee

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

Score: left and right

Grade: NORMAL, INCREASED, DECREASED, or ABSENT

C. Babinski

Score: left and right

Grade: NORMAL or ABNORMAL

10.11.1.5 Module 5 – Coordination and Gait

A. Rapid, Rhythmic Alternating Movements

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

Score: left and right

Grade: NORMAL or IMPAIRED

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

B. Point-to-Point Movements

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

Score: left and right

Grade: NORMAL or IMPAIRED

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

C. Romberg

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

Be prepared to catch the participant if they are unstable.

Grade: NORMAL or IMPAIRED

D. Gait

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

Grade: NORMAL or IMPAIRED and describe abnormality

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

Grade: NORMAL or IMPAIRED and describe abnormality

10.11.1.6 Module 6 – Sensory

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

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

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

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

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

F. Stereognosis: (identify common objects placed in hand, [eg, coin, key, etc]).

Score: left and right

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

10.11.2 The Targeted Neurological Examination

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

10.11.2.1 Module 1 – Mental Status Examination

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

10.11.2.2 Module 2 – Cranial Nerve Assessment

B. II, III – Pupil Size and Reactivity

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

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

10.11.2.3 Module 3 – Motor System

B. Muscle Strength

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

Grade: NORMAL or IMPAIRED and describe abnormality

10.11.2.4 Module 5 – Coordination and Gait

D. Gait

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

Grade: NORMAL or IMPAIRED and describe abnormality

10.11.2.5 Module 6 – Sensory

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

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
A2M	alpha-2-macroglobulin
AAP	atypical antipsychotics
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AGP	alpha-1-acid glycoprotein
AIMS	abnormal involuntary movement scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
API	active pharmaceutical ingredient
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-28d	area under the concentration-time curve from 0 to 28 days
AUC0-inf	area under the concentration-time curve from 0 to infinity
AUC0-last	area under the concentration-time curve from 0 to last measurable concentration
AV	atrioventricular
BARS	Barnes Akathisia Rating Scale
BDS	blood drug screen
BLA	biologics license application
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BPRS	Brief Psychiatric Rating Scale
C28d	concentration at Day 28
cAMP	cyclic adenosine monophosphate
CCU	cardiac care unit
cGMP	cyclic guanosine monophosphate

Abbreviation	Expanded Term
CI	confidence interval
Cmax	maximum plasma concentration
CNS	central nervous system
CL	clearance
CL/F	apparent clearance
COVID-19	coronavirus disease of 2019
CR	controlled-release
CRF	case report form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctrough	trough concentration
CV	coefficient of variation
CYP	cytochrome p450
CYP2C9	cytochrome p450 2c9
CYP3A	cytochrome p4503a
DDI	drug-drug interaction
DFC	dry fill capsule
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
eGFR	estimated glomerular filtration rate
EM	exposure multiple
EMA	European Medicines Agency
EO	enzyme occupancy
EPS	extrapyramidal symptoms

Abbreviation	Expanded Term
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	full analysis set
FIH	first in human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GLP	good laboratory practice
GM	geometric mean
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IM	intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	immediate release
IRB	Institutional Review Board

Abbreviation	Expanded Term
IV	intravenous
IWG	International Working Group
LAI	long acting injectable
LLN	lower limit of normal
MAD	maximum administered dose
MDRD	modification of diet in renal disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRSD	maximum recommended starting dose
NCS	not clinically significant
NDA	New Drug Application
NHP	nonhuman primate
NOAEL	no observed adverse effect level
NR	normal range
OTC	over the counter
P	protocol (number)
PANSS	Positive and Negative Syndrome Scale
PCL	protocol clarification letter
PCP	primary care physician
PDE	phosphodiesterase
PDE10A	phosphodiesterase 10A
PET	positron emission tomography
PK	pharmacokinetic
po	orally
POC	proof of concept
PONCBP	person of nonchildbearing potential
PP	per-protocol
PQC	product quality complaint
PR	pulse rate
QD	once daily

Abbreviation	Expanded Term
QM	once monthly
QP2	Department of Quantitative Pharmacology and Pharmacometrics
QTc	QT corrected using Fridericia's formula
RNA	ribonucleic acid
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SD	standard deviation
SGA	second generation antipsychotic
SIM	site imaging manual
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOP	standard operating procedures
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TK	toxicokinetics
Tmax	time to maximum plasma concentration
t1/2	half life
UDS	urine drug screen
ULN	upper limit of normal
Vd	volume of distribution
Vz/F	apparent volume of distribution
VS	vital signs

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