Official Protocol Title:	A Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics and Sleep Latency Effects of MK-6552 in Participants with Narcolepsy Type 1
NCT number:	NCT06179407
Document Date:	05-Sep-2024

TITLE PAGE

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Protocol Title: A Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics and Sleep Latency Effects of MK-6552 in Participants with Narcolepsy Type 1

Protocol Number: 004-05

Compound Number: MK-6552

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

Legal Registered Address:

126 East Lincoln Avenue
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Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	Not applicable
EudraCT	Not applicable
jRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	164999

Approval Date: 05 September 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	05-Sep-2024	CCI [redacted]
Amendment 4	21-Aug-2024	This amendment is to include an additional Panel (Panel B) to assess safety, tolerability, CCI [redacted]
Amendment 3	17-Apr-2024	This amendment is to provide additional clarification for inclusion criterion #8 around POCBP.
Amendment 2	02-Apr-2024	This amendment is to clarify the inclusion criterion (#8) around conditions and contraceptive requirements for participants assigned female sex at birth.
Amendment 1	04-Mar-2024	This amendment is to update/add a inclusion criterion and exclusion criteria to increase participant's safety during study conduct.
Original Protocol	06-NOV-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendment:

This amendment is to add a safety laboratory assessment timepoint in each period of Part 2 for participants in Panel B to monitor liver enzymes function after multiple days of dosing.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.3.3 Schedule of Activities Part 2 Panel B	Addition of a safety laboratory assessment time-point for Panel B in each period of Part 2.	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1 Synopsis	Addition of Panel B (approximately 12 participants) at MK-6552 dose levels of 1 mg to 4 mg.	CCI [redacted]
Section 1.1 Synopsis	Changes to the primary safety objective.	To add the safety assessment of multiple day dosing when MK-6552 CCI [redacted]
Section 1.1 Synopsis	Changes to the primary PD objective.	CCI [redacted]
Section 1.1 Synopsis	Updated the estimated duration of study from 11 to 17 months	To account for the additional 12 participants in Panel B.
Section 1.1 Synopsis	Updated the approximate number of participants in the study from 12 to 24.	To account for the additional Panel B.
Section 1.1 Synopsis	Updated the Intervention Groups and Duration table.	To add the new dosage levels and corresponding treatment periods of Panel B.
Section 1.1 Synopsis	Updated the Total Number of Intervention Groups/Arms from 4 to 7.	To add the new dosage levels of Panel B.
Section 1.1 Synopsis	Updated overall Duration of Participation from 11 to 14 weeks.	To account for the updated screening period of 5 weeks and number of intervention weeks from 5 to 7 due to natural scheduling of treatment period every ~7 days by the sites.
Section 1.2 Schema	Addition of Panel B with corresponding 4 sequential treatment periods of 1 mg to 4 mg.	To account for the additional Panel B at the higher dose levels.
Section 1.2 Schema	Study Diagram figure was updated to reflect the dose levels in Panels A and B	To account for the additional Panel B at the higher dose levels.
Section 1.3.1 Schedule of Activities Part 1	Removed the specific number of days for the EDS SOC Washout Period	To provide more flexibility in the washout duration requirements due to different prior medications taken by the participants.
Section 1.3.1 Schedule of Activities Part 1	Added the screening period window of +/- 7 days.	To clarify previous language stating “approximately 28 days”.
Section 1.3.1 Schedule of Activities Part 1	Added “All Panels” to the first row of the SoA Part 1 table	To clarify that the Part 1 SoA is applicable to Panel A and Panel B.
Section 1.3.1 Schedule of Activities Part 1	Added fasting requirements on the “Standard Meals” row of the table.	To clarify the requirement for fasting in the SoA Part 1 Table.
Section 1.3.1 Schedule of Activities Part 1	Removed note that allowed the predose safety lab assessment to be collected the evening before planned dosing.	To address a discrepancy with the fasting requirement. Since fasting is required before safety lab blood collection, operationally, the procedure cannot be completed the evening before dosing.
Section 1.3.2 Schedule of Activities Part 2 Panel A	Added “Panel A” to the first row of the SoA Part 2 Panel A table	To clarify that this SoA table is applicable only to Panel A.
Section 1.3.2 Schedule of Activities Part 2 Panel A	Removed 16h time-point from the SoA Part 2 Panel A table.	To address a typo. There are no procedures performed at the 16h time-point in the study.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.2 Schedule of Activities Part 2 Panel A	Added fasting requirements on the "Standard Meals" row of the table.	To clarify the requirement for fasting in Part 2 Panel A.
Section 1.3.2 Schedule of Activities Part 2 Panel A	Removed note that allowed the predose safety lab assessment to be collected the evening before planned dosing.	To address a discrepancy with the fasting requirement. Since fasting is required before safety lab blood collection, operationally, the procedure cannot be completed the evening before dosing.
Section 1.3.2 Schedule of Activities Part 2 Panel A	Removed the "predose" mention in the note column for the standard meals row.	To clarify that fasting is needed before all safety time-points including predose and 24 hours postdose unless mentioned otherwise.
Section 1.3.3 Schedule of Activities Part 2 Panel B	Added SoA Part 2 Panel B table	To account for the added Panel B in the study where some of the procedures have been modified.
Section 1.3.3 Schedule of Activities Part 2 Panel B	Added detail in Notes field for "Standard Meals" row around fasting requirement on Day 4 of each period.	To clarify that although there is a safety lab blood collection on Day 4 of each period, participants do not need to fast on that day.
Section 1.3.3 Schedule of Activities Part 2 Panel B	Added Day 4 safety lab assessment blood collection.	CCI [redacted]
Section 2.1 Study Rational	Rationale to assess higher dose range of MK-6552 was added	To account for the additional Panel B at the higher dose levels.
Section 2.2.2 Preclinical and Clinical Studies	Updated PN001 and PN005 completed study summaries.	To further clarify the design of PN001and provide the updated study status of PN005.
Section 2.2.2 Preclinical and Clinical Studies	Added PK data from PN005.	To add the final PK data from PN005 that is now completed.
Section 2.2.3 Ongoing Clinical studies	Added clinical summary from ongoing PN002, 003 and 007.	To provide an update on the ongoing clinical conduct and available preliminary safety data.
Section 2.2.3 Ongoing Clinical studies	CCI [redacted]	CCI [redacted]
Section 3 Hypotheses, Objectives and Endpoints	Changes to the primary safety objective.	To add the safety assessment of multiple day dosing when MK-6552 is administered bid 6 hours apart.
Section 3 Hypotheses, Objectives and Endpoints	Changes to the primary PD objective.	To add the PD assessment of multiple day dosing when MK-6552 is administered C CI [redacted]
Section 3 Hypotheses, Objectives and Endpoints	Changes to the exploratory PD objective	To add the PD assessment of a single day dosing when MK-6552 is administered C CI [redacted]
Section 4.1 Overall Design	Updated the study design with the additional Panel B participants and corresponding doses.	To account for the assessment of higher doses of MK-6552 on safety, PK and PD in an additional 12 participants.
Section 4.1 Overall Design	CCI [redacted]	CCI [redacted]
Section 4.1 Overall Design	Added the additional visit to the site on Day 4 site for Panel B participants for safety lab assessment blood collection.	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Section 4.2 Scientific Rational for Study Design	Added the rationale for study design of Panel B.	To account for the additional Panel B at the higher dose levels.
Section 4.2 Scientific Rational for Study Design	Updated clinical half-life of MK-6552	To provide an updated half-life based on the totality of the data acquired in HV.
Section 4.2.1.1 Safety Endpoints	Doses and dosing duration were updated from ongoing clinical studies and current study.	To provide the updated doses and dosing durations that are investigated in HV or will be investigated in NT1 participants
Section 4.2.1.1 Safety Endpoints	CCI [redacted]	To monitor participant safety labs as participants receive multiple higher doses of MK-6552.
Section 4.3 Justification for Dose	Justification to assess higher dose range in Panel B was added.	To account for the additional Panel B at the higher dose levels.
Section 4.3 Justification for Dose	CCI [redacted]	CCI [redacted]
Section 4.3 Justification for Dose	Table 2 was added to summarize CCI [redacted]	To provide supporting data justifying the assessment of higher dose range in Panel B.
Section 4.3.1 Starting Dose for This Study	CCI [redacted]	CCI [redacted]
Section 4.3.2 Maximum Dose Exposure for This Study	Projected CCI [redacted]	To account for the additional Panel B at the higher dose levels.
Section 4.3.2 Maximum Dose Exposure for This Study	Added summary of PK and safety from ongoing PN002.	CCI [redacted]
Section 4.3.2 Maximum Dose Exposure for This Study	CCI [redacted]	To provide an update on latest safety data obtained in PN002 study.
Section 4.3.3 Rationale for Dose Interval and Study Design	Updated with the Panel B dose levels and study design.	To account for the additional Panel B at the higher dose levels.
Section 5.2 Exclusion Criteria	Removed CrCl wording from EC#5.	To correct a typo. Only eGFR criteria is to be used to assess kidney function.
Section 5.3.1.1 Diet Restrictions	Added fasting requirements before safety lab assessment blood collection.	To clarify on which days participants must fast due to safety lab assessments.
Section 5.3.3 Activity Restrictions	Added the activity restriction requirements for participants that don't need to washout from EDS SOC.	To clarify that participants that don't required a washout from EDS SOC must also avoid activities requiring high degree of attention such as driving a car.
Section 6.1 Study Intervention(s) Administered	Updated the Study Intervention Table with Panel B dosage levels and corresponding Treatment Periods.	To account for the addition of Panel B to the study.
Section 6.3.1 Intervention Assignment	Updated Allocation of Participants to Treatment Table with Panel B information.	To account for the addition of Panel B 4 sequential Treatment Periods in Part 1 and 2-period cross-over in Part 2.

Section Number and Name	Description of Change	Brief Rationale
Section 7.1.1 Individual Stopping Criteria	CCI [redacted]	CCI [redacted]
Section 8.1.5.1 Prior Medications	Added study restrictions period for participants that don't required a EDS SOC washout.	To clarify the study restriction period for participants that don't require a Washout Period before randomization.
Section 8.1.8.1Timing of Dose Administration	Added information around timing of dose administration for participants in Panel B.	To account CCI [redacted]
Section 8.3.10.1 Safety Phone Calls During the Screening Period	Modified the language around a specific number of days for the safety phone calls.	To add flexibility for participants on concomitant medications that require a different number of safety phone calls based on washout requirement that may differ from EDS SOC listed.
Section 8.3.10.2 Compliance and Safety Phone Calls in Part 2 Days 2 to 6	Added frequency of dosing for participants in Panel B.	To account for the participants in Panel B that must take their study medication at home 6 hours apart.
Section 8.4.4 Regulatory Reporting Requirements for SAE	Added a note to specify that the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.	For completeness, for applicable studies, the process to report SUSARs to the Eudravigilance database has been added.
Section 8.11.1 Screening	Added the screening period window of 1 week (+/- 7 days).	To clarify previous language stating, "approximately 4 weeks".
Section 8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure	Remove safety lab tests from the procedures list that can be completed within 24 hours of dosing.	To address a discrepancy with the fasting requirement. Since fasting is required before safety lab blood collection, operationally, the procedure can't be completed the evening before planning dosing.
Section 8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure	Added safety lab tests procedure window.	To provide flexibility around the Part 2 Day 4 visit needed for the participant in Panel B.
Section 9.5.2	Added the new panel to the pharmacodynamic models.	To be more explicit that separate models are run for each panel and each of the two timepoints.
Section 9.5.3	Minor adjustment for dose proportionality subjection for language about new panel.	To be more explicit that analysis may be done for each panel separately since completely different subjects at two different dose ranges between the two panels
Section 10.1.1 Code of Conduct for Interventional Clinical Trials	Added Regulation (EU) 536/2014 to the list of regulations that MSD clinical trials is in compliance with.	To clarify that the Sponsor is in compliance with EU CTR 536/2014.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added a footnote to Table 8 around Part 2 Day 4 fasting requirement for Panel B.	To clarify that although there is a safety lab blood collection on Day 4 of each period, participants don't need to be fasted on that day.

Section Number and Name	Description of Change	Brief Rationale
Section 10.8 Appendix 8	Added abbreviations as applicable for updated text.	To capture newly added abbreviations for revised text.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Two-Part Study to Assess the Safety, Tolerability, Pharmacokinetics and Sleep Latency Effects of MK-6552 in Participants with Narcolepsy Type 1

Short Title: A Safety, Pharmacokinetic and Pharmacodynamic Study of MK-6552 in Participants with Narcolepsy Type 1

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

Participants with NT1 18 to 55 years of age inclusive.

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of a single-day CCI and multiple-day CCI administration of MK-6552 in participants with Narcolepsy Type 1.	Adverse events, discontinuation of study intervention due to adverse events
To assess the pharmacodynamic profile of MK-6552 bid CCI after multiple-day administration in participants with Narcolepsy Type 1. CCI	Maintenance of wakefulness test trial conducted one hour after each dose on CCI
Secondary Objectives	**Secondary Endpoints**
CCI CCI	CCI

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Narcolepsy
Population	Participants with narcolepsy type 1
Study Type	Interventional
Intervention Model	Sequential This is a multi site study.
Type of Control	Placebo
Study Blinding	Unblinded open-label study Part 1 Double-blind study Part 2
Blinding Roles	No blinding for study Part 1 Participants or Subjects for study Part 2
	Investigator for study Part 2
	Sponsor for study Part 2
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 17 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 24 participants will be randomized in the study in order to provide evaluable data on 16 participants (minimum of n=8 per panel).

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Active	MK-6552	CCI [redacted]	CCI [redacted]	Oral	Part 1 Panels A and B: Period 1 Period 2 Period 3 Period 4 Part 2 Panels A and B: Days 1 to 7 in Periods 1 and 2	Test Product
Placebo	Placebo	0 mg	Part 2 Panel A: 0 mg bid q8h Panel B: 0 mg bid q6h	Oral	Part 2 Panels A and B: Days 1 to 7 in Periods 1 and 2	Placebo

Total Number of Intervention Groups/Arms	7
Duration of Participation	Each participant will participate in the study for approximately 14 weeks, from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 5 weeks, each participant will receive assigned intervention for approximately 7 weeks. After the end of treatment each participant will be followed for 2 weeks.

Study Governance Committees:

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

There are no governance committees in this study. Regulatory, ethical and study oversight 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 Study Schema

Part 1- Panel A[a,b,c]			
Period 1[d]	**Period 2[d]**	**Period 3[d]**	**Period 4[d]**
CCI	CCI	CCI mg	CCI
Part 1- Panel B[a,b,c]			
Period 1[d]	**Period 2[d]**	**Period 3[d]**	**Period 4[d]**
CCI	CCI	CCI mg	CCI
Part 2- Panel A[e,f,g]			
Period 1[i]		**Period 2**	
CCI MK-6552/PBO		CCI MK-6552/PBO	
Part 2- Panel B[f,g,h]			
Period 1[i]		**Period 2**	
CCI MK-6552/PBO		CCI MK-6552/PBO	

a The suggested doses (with the exception of the starting dose) may be adjusted downward based on evaluation of safety, tolerability, and pharmacokinetic data observed in previous intervention periods. Refer to Section 6.6 (Dose Modification) and Section 7.1.1 (Individual Stopping Criteria) for the safety data that will be reviewed prior to dose escalation.

b Part 1 of the study will be open label in which all participants will receive MK-6552.

c. In Part 1, MK-6552 will be administered CCI in each treatment period.

d. At least 4 days will separate study drug administration in between periods of Part 1.

e. In Part 2 Panel A, MK-6552/PBO will be administered CCI in each treatment period.

f. The suggested dose may be adjusted downward based on evaluation of safety, tolerability, and available pharmacokinetic data from Part 1.

g. At least 4 days will separate study drug administration in between Part 1 and Part 2 of the study.

h. In Part 2 Panel B, MK-6552/PBO will be administered CCI

i. At least 2 days will separate study drug administration between periods of Part 2.

PBO=placebo, bid=twice a day.

Figure 1 Study Diagram

1.3 Schedule of Activities

1.3.1 Part 1

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																
Study Period:	**Screening**		**Intervention**													**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**												**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI													
Administrative/Study 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		X													**Sec. 8.1.3**
Inclusion/Exclusion Criteria	X		X													**Sec 5, 1, 5.2, 8.1.2** Review of inclusion/exclusion criteria will occur at Screening and after predose procedures (if applicable) in Period 1 only. Based on IC/EC, only specific criteria will be reviewed at predose (Period 1 only) prior to randomization.
Medical History	X	X	X													**Sec. 8.1.4** Substances: Includes substance usage (drugs, alcohol, tobacco, and caffeine).
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec. 5.2, 6.5, 8.1.5**

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																
Study Period:	**Screening**		**Intervention**													**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**												**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI													
Assignment of Screening Number	X															**Sec. 8.1.6** Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit.
Assignment of Randomization Number			X													**Sec. 5.5, 8.1.7**
MK-6552 Administration				X								X				**Sec. 8.1.8.1** In each treatment period, a second dose of study intervention ~ 6 hours (+/- 30 mins) following the first dose will be administered to participants
Domiciling			X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec. 8.1.11** In each treatment period, participants will report to the CRU the day before (Day -1) the first scheduled day of study intervention administration and remain in the unit at least up to 24-hours postdose #2

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																	
Study Period:	**Screening**		**Intervention**														**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**													**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI														
Standard Meals								X	X	X	X						CCI

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																	
Study Period:	**Screening**		**Intervention**														**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**													**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI														
Safety Procedures																	
C-SSRS Baseline/Screening	X																**Sec. 8.3.8.1**
Full physical examination	X		X													X	**Sec. 8.3.1** In each treatment period full PE will be conducted as follows: Dose 1: Predose, and 24-hour postdose 1 Dose 2: 24-hour postdose 2 Predose physical exam may be conducted upon admission within 24 hours of dosing.
General neurological examination	X		X														**Sec. 8.3.2, Appendix 10 (Sec 10.10.1)** Applicable at Screening and at each treatment period at Predose #1 only Predose #1 general NE, may be conducted upon admission within 24 hours of dosing

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																
Study Period:	**Screening**		**Intervention**													**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**												**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI													
Targeted neurological examination							X				X				X	**Sec. 8.3.2, Appendix 10 (Sec 10.10.2)** In each treatment period, targeted NE will be conducted as follows: CCI
Height	X															**Sec. 8.3.1**
Weight	X															**Sec. 8.3.1, 8.3.3** BMI to be taken only at Screening
Resting VS (HR, BP)	X		X		X	X	X	X	X	X	X				X	CCI

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																	
Study Period:	**Screening**		**Intervention**														**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**													**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI														
Orthostatic VS (HR, BP)	X		X				X		X		X					X	**Sec 8.3.4.2** In each treatment period orthostatic VS will be measured as follow: CCI
RR and BT	X		X				X				X					X	**Sec. 8.3.4.1** In each treatment period RR and BT will be measured as follow: CCI
12-lead ECG	X		X			X	X	X		X	X					X	**Sec. 8.3.5, Appendix 8** In each treatment period all ECGs are to be conducted in triplicate. At screening and poststudy, ECG will be conducted as single measurements. CCI

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																	
Study Period:	**Screening**		**Intervention**														**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**													**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI														
																	CCI
Serum (hCG; POCBP only)	X																**Sec. 8.3.6, Appendix 2**
Urine Pregnancy Test (POCBP only)			X														**Sec. 5.1, 8.3.7** Urine pregnancy test to be completed in each treatment period
Serum FSH - (POCBP only)	X																**Appendices 2 and 5**
HIV, hepatitis B and C screen (per site SOP)	X																**Sec. 5.2, Appendix 2**
Drug screen (per site SOP)	X		X														**Appendix 2** Screening drug screen is mandatory, any additional drug screens are conducted per site SOP. Alcohol test will be conducted using a breathalyzer. To be collected in Period 1 only Predose drug screen and alcohol test may be collected upon admission within 24 hours of dosing.

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																
Study Period:	**Screening**		**Intervention**													**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**												**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI													
Hematology, Chemistry, Urinalysis	X		X													**Sec, 8.3.6, Appendix 2** In Period 1 only, blood for safety laboratory tests will be collected as follow: Dose 1: Predose
Safety Phone Calls		X														**Sec. 8.3.10.1, 8.1.5.1** Washout period may vary based on the EDS SOC
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec. 8.4, Appendix 3**
Pharmacokinetics																
Blood for Plasma MK-6552 and or Metabolites Assay			X		X	X	X	X	X	X	X	X	X	X	X	**Sec. 8.6.1, 8.11.5** In each treatment period, PK blood collection will be as follow: CCI

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																
Study Period:	**Screening**		**Intervention**													**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**												**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI													
Pharmacodynamics																
PSG	X															**Sec. 8.7.1**
CCI	X		X				X				X	X				**Sec. 8.7.3** In each treatment period completed at: CCI
CCI			X												X	**Sec. 8.7.4** CCI

Part 1/All Panels/All Periods/Dose 1 and Dose 2[a]																	
Study Period:	**Screening**		**Intervention**														**Notes:**
Scheduled Day	**Screening/Rescreening[b]**	**EDS SOC Washout Before Randomization (Remote Visit Through Phone Call)**	**D1**													**D2**	**Screening procedures to be completed within approximately 28 days ± 7 days from randomization**
CCI			CCI														
Biomarkers																	
Blood for Planned Genetic Analysis			X														**Sec. 8.8.1** Collected from enrolled participant in Period 1 only.
Blood for HLA DQB1*0602 Genotyping	X																**Sec. 8.8**

AE=adverse event; BDS=blood drug screen; BMI=body mass index; BP=blood pressure; BT=body temperature; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; D=day; EC=exclusion criteria; ECG=electrocardiogram; EDS=excessive daytime sleepiness; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HLA-DQB1=human leukocyte antigen DQ Beta 1; HR=heart rate; IC=inclusion criteria; ID=identification; CCI; NE=neurological examination; PE=physical examination; PGA=planned genetic analysis; PK=pharmacokinetic; POCBP=participant of childbearing potential; CCI; RR=respiratory rate; SAE=serious adverse event; SOC=standard of care; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

a. Predose time-point is applicable to Dose #1 only.

b. Rescreening is defined as a separate screening period. All activities conducted during Screening must be completed as part of Rescreening. See Section 8.11.1.

1.3.2 Part 2 Panel A

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI					CCI					CCI				
CCI	CCI													
Administrative/Study Procedures														
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec. 5.2, 6.5, 8.1.5**
Study Intervention (MK-6552 or Placebo) Administration		X								X	X	X		**Sec 8.1.8.1** CCI [redacted] administration should be taken around the same time every day.

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Study Medication Diary Dispensing/Review		X									X	X		**Sec. 6.4, 8.1.8** In each treatment period, Study Medication Diary will be dispensed to participants on Day -1. CCI [redacted]
Domiciling	X	X	X	X	X	X	X	X	X	X	X			**Sec 8.1.11** CCI [redacted] day and remain in the unit up to 24 hours postdose #1.

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI [redacted]														
Standard Meals					X	X	X	X	X	X				**Sec 5.3.1** CCI [redacted]

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]	[redacted]													
[redacted]	[redacted]													
Safety Procedures														
Full physical examination	X										X		X	**Sec 8.3.1** Not applicable for predose #2 CCI [redacted]
General neurological examination	X												X	**Sec. 8.3.2, Appendix 10 (Sec 10.10.1)** CCI [redacted]

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Targeted neurological examination					X			X			X			**Sec. 8.3.2, Appendix 10 (Sec 10.10.2)** In each treatment period targeted NE will be conducted as follows: CCI [redacted]
VS (HR, BP)	X				X			X					X	**Sec 8.3.4.1** In each treatment period predose (baseline) will be in triplicate measurements. Postdose time-points will be in single measurement. Dose1: Predose, 2-, 6-hours postdose 1 Dose 2: 2 hour postdose 2
12-lead ECG	X						X						X	**Sec 8.3.5, Appendix 8** In each treatment period ECG at Predose (baseline) will be in triplicate measurements. Postdose ECG time-points will be in single measurement. CCI [redacted] [redacted]

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI [redacted]														
Urine Pregnancy Test (POCBP only)	X												X	Sec. 5.1, 8.3.7 In each treatment period urine pregnancy test to be completed on Day 1 only
Hematology, Chemistry, Urinalysis	X										X		X	**Sec. 8.3.6, Appendix 2** In each treatment period blood for safety laboratory tests will be collected as follow: CCI [redacted]
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec 8.4, Appendix 3**
Safety/Study Medication Compliance Phone Calls											X	X		**Sec 8.3.10.2** CCI [redacted]
C-SSRS Since Last Assessment	X						X							**Sec 8.3.8.1** CCI [redacted]

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Blood for Plasma MK-6552 and or Metabolites Assay	X				X		X	X			X	X		**Sec 8.6.1** In each treatment period, PK blood collection will CCI [redacted]
Pharmacodynamic														
CCI [redacted]														
MWT				X		X		X	X					**Sec 8.7.2, 8.11.5** CCI [redacted]

Part 2/Panel A/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI														
CCI	X		X			X								**Sec 8.7.3** CCI
CCI	X										X			**Sec 8.7.4** CCI

AE=adverse event; BDS=blood drug screen; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; CCI ; PE=physical examination; NE=neurological examination; PGA=planned genetic analysis; POCBP=participant of childbearing potential; CCI ; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

a. Predose time-point is applicable to Dose #1 only.

1.3.3 Part 2 Panel B

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Administrative/Study Procedures														
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec. 5.2, 6.5, 8.1.5**
Study Intervention (MK-6552 or Placebo) Administration		X						X			X	X		**Sec 8.1.8.1** CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Study Medication Diary Dispensing/Review		X									X	X		**Sec. 6.4, 8.1.8** In each treatment period, Study Medication Diary CCI [redacted]
Domiciling	X	X	X	X	X	X	X	X	X	X	X			**Sec 8.1.11** In each treatment period CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Standard Meals					X	--	--	--	---	--				Sec 5.3.1 CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI [redacted]														
Safety Procedures														
Full physical examination	X										X		X	**Sec 8.3.1** CCI [redacted]
General neurological examination	X												X	**Sec. 8.3.2, Appendix 10 (Sec 10.10.1)** CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI [redacted]														
Targeted neurological examination					X			X			X			**Sec. 8.3.2, Appendix 10 (Sec 10.10.2)** CCI [redacted]
Resting VS (HR, BP)	X				X			X					X	**Sec 8.3.4.1** CCI [redacted]
12-lead ECG	X						X						X	CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI [redacted]														
Urine Pregnancy Test (POCBP only)	X												X	Sec. 5.1, 8.3.7 In each treatment period urine pregnancy test to be completed on Day 1 only
Hematology, Chemistry, Urinalysis	X										X	X	X	**Sec. 8.3.6, Appendix 2** In each treatment period blood for safety laboratory tests will be collected as follow: CCI [redacted]
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sec 8.4, Appendix 3**
Safety/Study Medication Compliance Phone Calls											X	X		**Sec 8.3.10.2** CCI [redacted]
C-SSRS Since Last Assessment	X						X							**Sec 8.3.8.1** CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	Notes:
CCI [redacted]														
Pharmacokinetics														
Blood for Plasma MK-6552 and or Metabolites Assay	X				X		X	X			X	X		**Sec 8.6.1** CCI [redacted]
CCI [redacted]														
CCI [redacted]														
MWT				X		X		X						**Sec 8.7.2, 8.11.5** CCI [redacted]

Part 2/Panel B/All Periods/Dose 1 and Dose 2[a]														
													Poststudy	**Notes:**
CCI														
CCI	X		X			X								**Sec 8.7.3** CCI
LSEQ	X										X			**Sec 8.7.4** CCI

AE=adverse event; BDS=blood drug screen; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HR=heart rate; ID=identification; CCI PE=physical examination; NE=neurological examination; PGA=planned genetic analysis; POCBP=participant of childbearing potential; CCI; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

a. Predose time-point is applicable to Dose #1 only.

2 INTRODUCTION

2.1 Study Rationale

This study constitutes the first administration of MK-6552 to participants with NT1.

The primary objectives of Part 1 are to evaluate the safety, tolerability and PK of MK-6552 after administration of ascending oral doses (MK-6552 CCI) in a single day to participants with NT1. CCI

The primary objectives of Part 2 are to investigate the PD profile of MK-6552 CCI

This trial amendment to include administration of multiple oral doses of MK-6552 from CCI which will provide additional information on the relationships between MK-6552 and safety, tolerability, pharmacokinetics and potential alerting effects in NT1 patients. CCI

CCI

The number of participants (n≤24) 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 for detailed background information on MK-6552.

2.2.1 Pharmaceutical and Therapeutic Background

MK-6552 is a small molecule agonist of the OX2R being developed for the treatment of CCI [redacted]

MK-6552 is a selective agonist of the OX2R and is not considered a compound with a high potential risk of harm to participants (EMA 2007). MK-6552 is not a biological molecule, does not exhibit species-specific action, and is not directed towards immune system targets. CCI [redacted]

2.2.2 Preclinical and Clinical Studies

Refer to the IB for detailed preclinical studies for MK-6552.

MK-6552 has been investigated in two completed Phase 1 study in healthy male participants: MK-6552-001 (PN001), conducted in Belgium; and MK-6552-005 (PN005), conducted in the US.

PN001

MK-6552-001 (PN001) was a randomized, placebo-controlled, double-blind, single ascending dose study to evaluate the safety, tolerability, and PK of MK-6552 in healthy male participants, This study consisted of 2 alternating panels (A and B) followed by a third panel (Panel C) consisting of 8 participants each, all of whom were administered single-oral doses of MK-6552 or placebo (3:1 ratio) as an on-site formulation (oral suspension).. In this study, 24 healthy male participants were administered single oral doses of MK-6552 (0.5 to 4.5 mg), except in Panel C Periods 3 and 4, in which participants received 2 doses of MK-6552 1 mg on a single day, administered q6h and q8h, respectively.

CCI [redacted]

[redacted]

PN005

MK-6552-005 (PN005) was a single-panel, 3-period, open label study in healthy male participants to assess the potential PK interaction effect of MK-6552 with modafinil, a CYP3A4 inducer. PN005 evaluated the impact of the moderate CYP3A inducer modafinil on MK-6552 exposure. In humans, MK-6552 is anticipated to be predominately eliminated by CYP3A-mediated metabolism based on the in vitro reaction phenotyping experiments conducted with recombinant CYP enzymes. Therefore, MK-6552 has the potential to be a victim of DDIs through inhibition and induction of CYP3A. Approximately 11 healthy study participants were administered single oral doses of MK-6552 1.0 mg on 3 separate days during the study: once alone, once in combination with modafinil 200 mg daily dosed to steady-state plasma concentrations, and once in combination with modafinil 400 mg daily dosed to steady-state plasma concentrations. Single doses of MK-6552 1.0 mg were generally well tolerated in single dose administration when administered alone as well as when co-administered with modafinil 200 mg and modafinil 400 mg. CCI [redacted]

[redacted]

CCI [redacted]

2.2.3 Ongoing Clinical Studies

Ongoing clinical investigations of MK-6552 include MK-6552-002 (PN002); MK-6552-003 (PN003); and MK-6552-007 (PN007). PN003 is clinically complete; however, as of 21-AUG-2024, database lock has not been achieved and study data are still blinded. PN002 is being conducted at 1 site in Belgium in conformance with GCP. PN003 is being conducted at 2 sites in the US, and PN007 is being conducted in 1 site in the US, both under the MK-6552 IND.

PN002

MK-6552-002 (PN002) is a double-blind, placebo-controlled multiple ascending dose study to assess the safety and tolerability of multiple doses of MK-6552 in healthy participants. It includes 8 panels of n=8 study participants, assigned 6:2, active: placebo. Panels A-C will receive10 days of bid dose administration of MK-6552 at 0.25, 0.5 mg and 1.0 mg dose levels and Panels D, F, and G received 5 days of bid dose administration of MK-6552 at the 2.0 mg, 5.0 mg, and 7.0 mg dose levels. Additionally, 1 panel (Panel E) received 2 days of bid administration of MK-6552 4.0 mg followed by 3 days of bid administration of MK-6552 3.25 mg. Panel H will receive 5 days of bid administration of MK-6552 4.0 mg q3h. CCI [redacted]

As of 13-AUG-2024, PN002 has completed multiple dosing of MK-6552 up to 7.0 mg q6h BID and data remain blinded. Approximately 40 healthy male and female participants have been administered multiple daily oral doses of MK-6552/PBO 0.25 to 7.0 mg. CCI [redacted]

CCI

[redacted]

PN003

MK-6552-003 (PN003) is a randomized, double-blind, 3-period crossover study to assess the effects of MK-6552 on sleep latency in sleep-deprived healthy study participants with modafinil as a positive control. This study assessed the effect of MK-6552 on sleep latency as measured by the MWT in 18 healthy study participants who were allocated to receive either MK-6552, modafinil, or PBO to MK-6552 or modafinil in each of the 3 treatment

periods. All participants received all treatment allocations during the study in a double-dummy fashion, with period-specific treatment allocation being randomized for a given participant according to the randomized allocation schedule. Participants received a maximum of one active treatment (MK-6552 CCI [redacted] or modafinil 200 mg once) in any given treatment period. As of 13-AUG-2024, this study is clinically complete although database lock has not yet been achieved and study data are still blinded. Single day administration of MK-6552 2.0 mg q8h x 2 doses were generally well tolerated. The most frequently reported AEs (≥2 occurrences) in participants receiving MK-6552 2.0 mg, modafinil or PBO were headache (5) and nausea (2). All reported AEs have been mild to moderate in intensity. There have no SAEs or deaths in this study.

PN007

MK-6552-007 (PN007) is a study to evaluate the effects of coadministration of diltiazem on the plasma pharmacokinetics of a single dose of MK-6552 in healthy study participants. CCI [redacted] CCI

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Participants with NT1 18 to 55 years of age inclusive.

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of a single-day CCI and multiple-day CCI administration of M with Narcolepsy Type 1.	Adverse events, discontinuation of study intervention due to adverse events
To assess the pharmacodynamic profile of MK-6552 CCI after multiple-day administration in participants with Narcolepsy Type 1. CCI	CCI
Secondary Objectives	**Secondary Endpoints**
To characterize the plasma pharmacokinetics of MK-6552 following administration of single-day bid CCI oral doses in participants with Narcolepsy Type 1. CCI	CCI

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, 2-part, placebo-controlled (Part 2 only), double-blind (Part 2 only), multisite study to evaluate the safety, tolerability, PK and pharmacodynamics of MK-6552 in participants with NT1. The study is to be conducted in conformance with GCP.

CCI

CCI [redacted]

[redacted]

Because this is a Phase 1 assessment of MK-6552 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

This study constitutes the first administration of MK-6552 to participants with NT1. CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

CCI [redacted]

The safety and tolerability of MK-6552 will be assessed throughout the study by monitoring AEs/SAEs, 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 also taking into consideration the demonstrated clinical half-life of MK-6552 CCI [redacted]

4.2.1.2 Pharmacokinetic Endpoints

CCI [redacted]

4.2.1.3 Pharmacodynamic Endpoints

CCI [redacted]

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 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.

4.2.1.5 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Placebo

Part 1 will not include placebo in order to maximize collection of safety data supporting administration of MK-6552 in all participants at all dose levels. Part 2 will include placebo to allow for an appropriate assessment of pharmacodynamic data of MK-6552 and to maintain study blinding to reduce bias.

4.2.3 Rational 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

CCI [redacted]

CCI

[redacted]

Table 2 Preliminary PK for 4 NT1 participants from Part 1

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

As this is a Phase 1 assessment of MK-6552 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.1 Starting Dose for This Study

CCI

[redacted]

CCI

[redacted]

4.3.2 Maximum Dose Exposure for This Study

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

PN002 is an ongoing multiple ascending dose Phase 1 study to assess the safety and PK of multiple-day administration of twice daily oral doses of MK-6552 in healthy male and female participants.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.3.3 Rationale for Dose Interval and Study Design

CCI

[redacted]

CCI

[redacted]

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

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Has a diagnosis of NT1, including a valid PSG within the previous 5 years and a current diagnosis of NT1 for at least 6 months based on criteria established by the International Classification of Sleep Disorders- Third Edition. A current NT1 diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [American Psychiatric Association 2013] is also acceptable.

   Note: At the discretion of the investigator, a valid PSG within the past 10 years may be acceptable. Alternatively:

   A PSG including MSLT can be repeated at the site during the Screening period or,

   A CSF hypocretin A level < 110 pg/ml is also acceptable as confirmatory of a NT1 diagnosis in the absence of valid PSG data. If not available, a CSF sample can be collected for hypocretin A level assessment at the discretion of the investigator.
2. Is positive for HLA-DQB1*06:02 allele supporting a diagnosis of NT1

   Note: At the discretion of the investigator, participants with a negative HLA-DQB1*06:02 genotyping, but a PSG and/or a CSF hypocretin A level (per IC#1) supporting a diagnosis of NT1 may be enrolled in the study.
3. Has a baseline history of unequivocal cataplexy prior to initiation of anti-cataplexy medications.
4. Is free of any disease that in the opinion of the investigator would interfere with trial evaluations based on medical history, physical and targeted neurological examinations, VS measurements and ECG performed prior to enrollment (abnormal VSs and ECGs may be repeated once to confirm eligibility). Subjects with chronic medical conditions including but not limited to hyperlipidemia, and hypothyroidism which have been well-controlled on a stable dose of medication for the past two months, may be enrolled if clinically acceptable to the investigator and the Sponsor.

5. Has a BMI between 18 and 32 kg/m^2, inclusive. See Section 8.3.3 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

   Note: Participants who have a BMI up to 35.0 kg/m^2 may be enrolled at the discretion of the investigator.

Demographics

6. Is an individual of any sex/gender, from 18 years to 55 years of age inclusive, at the time of providing the informed consent.

Assigned Male Sex at Birth

7. 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:
   - CCI

Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

OR

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.

Assigned Female Sex at Birth

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

- Is not a POCBP

OR

- Is a POCBP and must meet all the bullet points below:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 7 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

Additional Categories

10. Is willing to forego operating a motor vehicle or heavy machinery from the EDS SOC washout period through Part 1 and Part 2 and until reinitiation of EDS SOC after completion of all study procedures in the last treatment period of Part 2.
11. Reports a total sleep time of > 6 hours on at least 4 out of 7 nights each week within the 4 weeks prior to screening visit.
12. Has regular sleep initiation times no later than midnight.
13. Agrees not to engage in night shift work, and not to cross more 3 times zones during the 2 weeks prior to randomization and throughout the course of the study.
14. 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. History of or current hypertension defined as a SBP ≥140 mm Hg and a DBP ≥90 mm Hg.
2. Has underlying cardiovascular or cerebrovascular conditions in which an acute rise in blood pressure would pose a clinical concern, including but not limited to aneurysms or arteriovenous malformations.
3. Has a history of renal or hepatic impairment.
4. Has screening safety laboratory findings consistent with moderate or severe hepatic impairment, including but not limited to clinically significant elevations in AST, ALT, alkaline phosphatase, or bilirubin above normal range; clinically significant decreases in albumin below normal range; clinical significant decreases in platelet count below normal range.
5. Has an estimated eGFR ≤80 mL/min/1.73 m^2 based on the 2021 CKD-EPI.

CKD-EPI Equation:

$$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa,1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.994^{Age} \times 1.012 \text{ [if female]}$$

Where Scr is serum creatinine, K is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/K or 1, max indicates the maximum of Scr/K or 1

Participants who have an eGFR of up to10% below 80 mL/min/1.73 m^2 may be enrolled in the study at the discretion of the investigator.

6. Has a history of cardiac ischemia or cerebral ischemia including but not limited to history of stroke, transient ischemic attack, or transient global amnesia.
7. Based on clinical interview and responses on the C-SSRS, is at imminent risk of self-harm or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the *past 5 years* or suicidal behavior in *their lifetime*.
8. Mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.
9. History of cancer (malignancy). Participants with definitively treated disease who, in the opinion of the study investigator, are highly unlikely to have a recurrence for the duration of the study may be enrolled at the discretion of the investigator.

10. Has a history of any of the following sleep disorders:
    - obstructive sleep apnea (OSA) defined as an Apnea Hypopnea Index > 15 per hour per the AASM alternate criteria,
    - primary insomnia (within the past 6 months),
    - circadian rhythm sleep disorder,
    - shift work sleep disorder (within the past 6 months),
    - clinically significant parasomnia at the discretion of the investigator.
11. Has a medical condition that in the opinion of the investigator, may account for the patient's excessive daytime sleepiness, e.g., pain, cardiac disease, nocturia (>3 times/night), or hot flashes.
12. For participants requiring lumbar puncture to determine study eligibility: Has a medical condition that in the opinion of the investigator may increase the risks associated with a lumbar puncture (eg, individuals with increased intracranial pressure, bleeding diathesis).
13. Has a history of seizure disorder, clinically significant head trauma, or past invasive intracranial surgery or clinically significant dementia.
14. Participants has, in the opinion of the investigator, a confounding psychiatric disorder such as any history of a psychotic disorder (e.g. schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder) or currently has active, inadequately-treated depression, post-traumatic stress disorder, or other anxiety disorder.
15. 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.
16. Positive test(s) for HBsAg, hepatitis C antibodies or HIV. Note: Participants with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included upon consultation with the Sponsor.
17. 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.
18. Participants, in the opinion of the investigator, has a history or current evidence of any condition, therapy, lab abnormality or other circumstances that might confound the results of the study, or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate.

Prior/Concomitant Therapy

19. Unable to refrain from or anticipates the use of CYP3A4 inhibitor and/or inducer drugs and food, drug, supplements or other products with known stimulating or sedating properties beginning ~ 2 weeks (or 5 half-lives) prior to administration of the first dose of the study intervention, throughout the study (including washout intervals between treatment periods and study parts), and until the poststudy visit: TCAs, amphetamine, hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants, clonidine, pemoline, melatonin, guarana, ma huang, kava-kava, valerian, hoodia, St. Johns wort and any other stimulants and alerting agents prescribed for use on a daily basis. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

20. 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

21. QTc interval ≥450 msec.

Other Exclusions

22. Is under the age of legal consent.
23. Has a history of substance abuse or dependence within the past two years (except if currently in sustained full remission for at least one year or meets criteria for early full remission, according to DSM-IV-TR). Substances include alcohol, hypnotics, cannabis, nicotine (only if the nicotine dependence is affecting sleep) and any illicit drugs of abuse. Participants must have a negative drug screen prior to randomization.
24. Consumes the equivalent of more than 10 cigarettes a day or routinely smokes during the night.
25. Has history of tobacco use associated with maintaining wakefulness (i.e., participants who smoke or use tobacco products to stay awake) or a need for a cigarette within 30 minutes of waking in the morning.
26. Does not agree to follow the smoking restrictions as defined by the CRU.
27. Unable to refrain from alcohol intake from the EDS SOC washout period through Part 1 and Part 2 and until reinitiation of EDS SOC after completion of all study procedures in the last treatment period of Part 2 or until return to baseline at the discretion of the investigator.
28. Participant is, in the opinion of the investigator, at risk for alcohol withdrawal.
29. Consumes greater than 3 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.
30. A POCBP who has a positive urine pregnancy test within 24 hours before first dose of study intervention (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
31. 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

In Part 1, in each treatment period, and in Part 2 on Days 1 and 7, participants will fast from all food and drinks, except water, for at least 8 hours before the first dose of study intervention administration. Participants will fast from all food and drinks, except water, between first dose of study intervention administration and the first scheduled meal. Meals and snack(s) will be provided by the site staff at time points indicated in the study flowchart. Participants will fast from all food and drinks, except water, between meals and snacks. The overall composition of the meals will be at the discretion of the investigator however the meal content must be in compliance with the caffeine and the alcohol restrictions (see Section 5.3.2).

After the 24-hour postdose #2 procedures (for Part 1) or 24-hour postdose #1 procedures (for Part 2) have been completed, subsequent meals and snacks will be unrestricted in composition, and timing.

Approximately 240 mL of water will be provided during study intervention administration. Additional water may be provided in 50-mL increments if desired. Water will be restricted 1 hour before and 1 hour after study intervention administration.

Participants will also fast before laboratory safety evaluations in Part 1 Day 1 (Period 1 only) and in CCI Fasting requirements for laboratory safety evaluations are at least 8 hours prior to collection.

Although there will be no diet composition and timing restrictions while the participants are taking the study intervention at home on Day 2 to Day 6, the meal content must be in compliance with the caffeine and the alcohol restrictions (see Section 5.3.2).

Instructions on whether to take MK-6552 with or without food and/or drink may be modified during the study based on newly available data.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention, throughout the study including the washout interval between treatment periods and Parts 1 and 2 and until the poststudy visit.

Participants also will refrain from the consumption of all fruit juices 24 hours before and after study intervention administration in each treatment periods (Part 1) and on Days 1 and 7 (Part 2). 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 of Part 1 and on Days 1 and 7 of Part 2
- 12 hours before poststudy visit.

At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 3 units per day (1 unit = 120 mg of caffeine).

A list of common caffeine-containing products and their caffeine content is provided in Appendix 11.

5.3.2.2 Alcohol Restrictions

Participants are advised to refrain from consumption of alcohol 24 hours prior to the screening visit. A recheck may be needed if participants did not refrain from consuming alcohol 24 hours prior to the Screening Visit.

Participants will refrain from consumption of alcohol from:

- The EDS SOC washout period through Part 1 and Part 2 and until reinitiation of EDS SOC after completion of all study procedures in the last treatment period of Part 2 or until return to baseline at the discretion of the investigator.
- 24 hours before poststudy visit.

At all other times, alcohol consumption is limited to no more than approximately 2 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.

During the study, if the participant is a smoker, they will limit the number of cigarettes (including ecigarettes/vaping) to 10 per day.

5.3.3 Activity Restrictions

Parts 1 and 2

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 study parts), and until the poststudy visit.

Participants will avoid activities requiring high degree of attention such as driving a car from EDS SOC Washout Period until reinitiation of EDS SOC after completion of all study procedures in Part 2, Period 2.

Participants not on EDS SOC will also avoid activities requiring high degree of attention such as driving a car from participant randomization in Part 1 Period 1 Day 1 until completion of all study procedures in Part 2, Period 2.

Participant transportation needs will be covered by the Sponsor from the time driving restriction is in effect (EDS SOC Washout Period or randomization in Part 1 Period 1 Day 1) until completion of all study procedures in study Part 2, Period 2. Transportation options covered may include public transportation, family member, taxi, Uber, Lyft share rides, etc.

Part 2

Participants will avoid vigorous physical activity (ie, strength training, running, hiking or biking uphill, etc.) up to 4hours after study medication administration from Day 1, Period 1 until reinitiation of EDS SOC after completion of all study procedures in Period 2.

5.3.4 Bedtime

Throughout the study, participants should go to bed at their usual bedtime. To ensure at least 6 hours of sleep per night, starting in the first treatment period of Part 1 and throughout the study until reinitiation of EDS SOC treatment (after completion of all study procedures in Part 2 Period 2), participants will avoid going to bed pass midnight time.

5.3.5 Other

Participants will NOT engage in the following activities from the EDS SOC washout period, throughout the study (including washout intervals between treatment periods and study parts) and until reinitiation of EDS SOC treatment after completion of all study procedures in Part 2, Period 2).

- nighttime shift work
- travel across >3 time zones

5.4 Screen Failures

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

Participants may be rescreened as appropriate per Section 8.11.1.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

Country-specific requirements are noted in Appendix 7.

Table 4 Study Interventions

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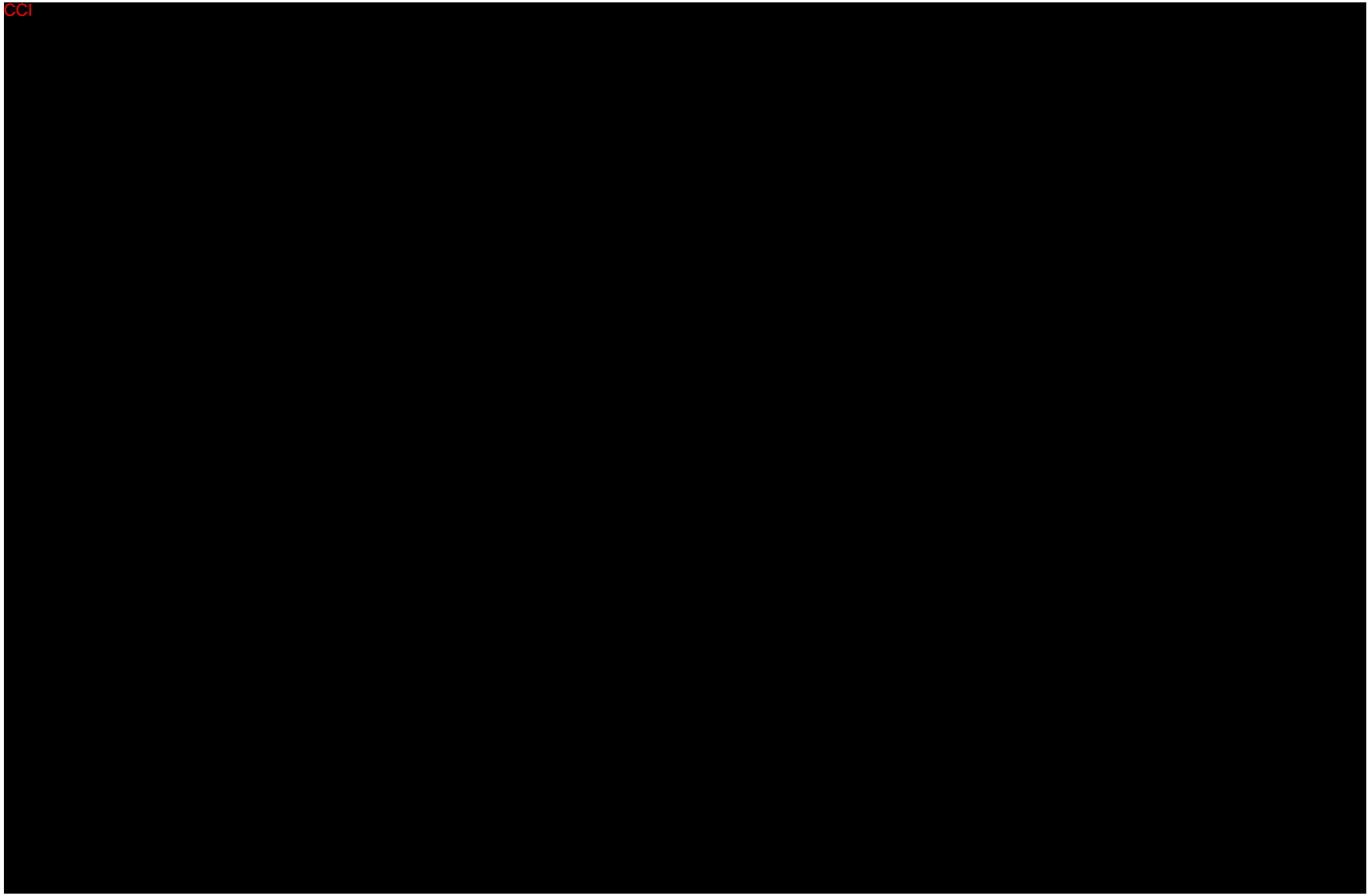

CCI [redacted]

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; CCI [redacted]

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

All supplies indicated in Table 4 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

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.

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 5.

Table 5 Allocation of Participants to Treatment

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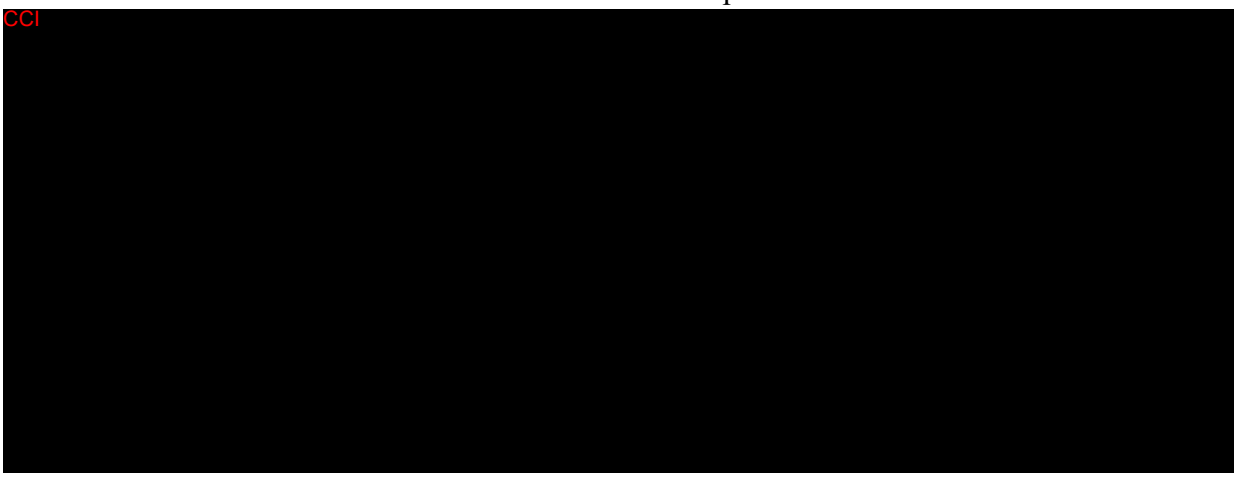

6.3.2 Stratification

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

6.3.3 Blinding

Part 1 of this study is conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

In Part 2 of this study, a double-blinding technique will be used. MK-6552 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.

See Section 8.1.10 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

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

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

In Part 1 when participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention. Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

In Part 2 (Day 2 [afternoon dose only] and Days 3 to 6) when participants self-administer the study intervention at home, daily phone calls will be made to check study intervention administration compliance. Compliance with study intervention will also be assessed at the next on-site visit by direct questioning and site review of the completed study intervention dosing diary as captured by the participant. Compliance will also be assessed by counting returned capsules during the next on-site visit and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of MK-6552/placebo capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

When participants are dosed at the site CCI [redacted], study intervention administration will be witnessed by the CRU staff. The staff will witness the participant record the dosing in the study medication diary.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during time periods specified by this protocol for that medication must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

COVID-19 and flu vaccines 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 (ie, those not licensed or approved for Emergency Use) are not allowed.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications are permitted:

Medications for treatment of cataplexy may be continued for the duration of the trial include selective serotonin reuptake inhibitors (SSRIs) and/or serotonin noradrenaline reuptake inhibitors (SNRIs).

Systemic contraceptives and hormone replacement therapy are permitted for POCBP participants.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

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

6.6 Dose Modification (Escalation)

Dose escalation decisions are applicable only to Part 1.

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(s), 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 their evaluation of safety and tolerability from the previous dosing period and their recommendation to dose escalate in the next period.

Each dose-escalation decision will occur on an individual basis as the study enrollment of participants will be progressive and on-going throughout the study.

Dose-escalation decisions will be based on key safety variables, including VS, 12-lead ECG, laboratory safety tests, PE, NE, and AEs/SAEs from the previous dose levels up to at least 24 hours postdose #2. Additionally, individual stopping rules (Section 7.1.1) will be reviewed to confirm none of the rules are met. Pharmacokinetic 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, individual 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),

Dosing in Part 1 may be stopped and participants may proceed to Part 2 at a dose up to the maximum safe and well tolerated dose reached in Part 1.

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), an 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 below stopping rules are met, subsequent higher doses in Part 1will 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 4.3.2 will be exceeded, subsequent higher doses will be adjusted based on joint agreement of the Sponsor and investigator.
4. CCI
5. CCI
6. CCI

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 in Part 1 supplies are provided open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

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

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

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

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

The participant or participant's legally acceptable representative requests to discontinue study intervention.

The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.

The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

The participant has a confirmed positive serum pregnancy test.

The participant has a positive drug screen at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

The participant meets any of the individual stopping rules described is Section 7.1.1.

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

7.1.1 Individual Stopping Criteria

CCI

[redacted]

CCI

[redacted]

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 providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent 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 Appendix 8.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information

provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

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

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

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

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

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all 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 2 months before starting the study.

CCI

[redacted]

CCI [redacted]

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Part 1

Study intervention will be administered by the investigator and/or an appropriately qualified designee at the site.

Part 2

Participants will be instructed on how to administer at home study intervention by the site staff.

While participants are at the site, the study medication will be taken by the participant under supervision from the site staff. Following study administration, the participant will complete the Study Medication Diary followed by site staff verification that the diary has been completed properly.

In each treatment period, on Day 2 before being discharged from the site, participants will receive their assigned bottle of study intervention for unsupervised administration at home for Day 2 afternoon dose and for Days 3 to 6. Upon participants return to the site on Day 6, the study intervention bottle will be collected by the site staff in preparation for Day 7 treatment administration at the site.

8.1.8.1 Timing of Dose Administration

CCI

[redacted]

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11.4. to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or

as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, 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

CCI

[redacted]

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 below. 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 Central Laboratory Services 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 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.

8.3.2 Neurological Examinations

General and targeted neurological examinations will be conducted according to the procedures outlined in Appendix 10.

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

8.3.4 Vital Signs

Body temperature, PR, RR, and BP will be assessed. **The same method must be used for all measurements for each individual participant and should be the same for all participants at a given site.**

Resting and orthostatic BP and HR will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Resting BP and HR position can be seated or semi-recumbent. The same position must be used for all measurements for each individual participant and should be the same for all participants at a given site.

VS will be measured after at least 10 minutes rest for the participant in a quiet setting without distractions and will include temperature, systolic and diastolic BP, HR and RR.

8.3.4.1 Resting Vital Signs

<u>Vital Sign Measurements (Heart Rate and Blood Pressure)</u>

Participants should be resting in a quiet setting without distractions for at least 10 minutes before having VS measurements obtained. 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.

At screening, HR and BP will be in triplicate measurements, obtained at least 1 minute apart (all 3 sets completed within 6 minutes). The median of the three measurements will be used to assess for participants eligibility.

Part 1

In each treatment period, the predose (baseline) HR and BP will be in triplicate measurements, obtained at least 1 minute apart (all 3 sets completed within 6 minutes) within 3 hours of dosing MK-6552. The median 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 also be measured in triplicate measurements.

Part 2

In each treatment period, on Days 1 and 7, the predose (baseline) HR and BP will be in triplicate measurements, obtained at least 1 minute apart (all 3 sets completed within 6 minutes) within 3 hours of dosing MK-6552/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). All postdose VS measurements will be single measurements.

Poststudy visit HR and BP will be in triplicate measurements, obtained at least 1 minute apart (all 3 sets completed within 6 minutes).

Participants will continue to rest from dosing until 1 hour postdose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure.

Body Temperature

Body temperature will be measured in Part 1 only. The same method must be used for all measurements for each individual participant and should be the same for all participants at a given site.

8.3.4.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained for Part 1 only. Participants should be resting for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.

8.3.5 Electrocardiograms

All 12-lead ECGs 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 8 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. Participants may need to remove interfering garments.

Participants should be resting for at least 10 minutes before each ECG measurement. The resting position may include seated, semi-recumbent or supine, but the same position must be used for all measurements for each individual participant and should be the same for all participants at a given site.

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.

For all participants, screening and poststudy ECG recordings are to be obtained in single measurements.

Part 1

Before each treatment period, predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing MK-6552. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

In all treatment periods, postdose ECG will be in triplicate measurements at the time-points specified in the SoA.

Part 2

Before each treatment period, on Days 1 and 7, predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing MK-6552. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

All postdose ECG will be obtained as single measurements at the time-points specified in the SoA.

For both study parts

During each treatment period, if a participant demonstrates a median increase in QTc interval ≥60 msec, or ≥ 25% compared to the median predose baseline measurement, the participant will continue to be monitored by triplicate repeat ECGs every 30 minutes for at least 2 hours or until the abnormality is resolved. If prolongation of the QTc interval ≥60 msec persists over 120 minutes, a consultation with a cardiologist may be appropriate and the Sponsor should be notified (see Section 7.1.1).

During each treatment period, if the median QTc interval is ≥500 msec for postdose measurements and sustained for 120 minutes (see Section 7.1.1), the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the median increase in QTc interval ≥60 msec, or ≥ 25% compared to the median predose baseline measurement or median QTc interval is ≥500 msec for postdose measurements and these changes are sustained for 120 mins, the QTc individual stopping rule will be met and dosing to the particular participant should be halted and the Sponsor's clinical director informed within 24 hours:

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

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

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

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

8.3.6 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 Central Laboratory Services 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.

8.3.7 Pregnancy Testing

Pregnancy testing:

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

8.3.8 Suicidal Ideation and Behavior Monitoring

8.3.8.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

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

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

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

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

designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

8.3.9 Photograph of Rash

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

8.3.10 Safety/Compliance Phone Calls

8.3.10.1 Safety Phone Calls During the Screening Period

During the EDS SOC washout period, safety phone calls will be performed every day for the duration of the required EDS SOC washout period before study intervention randomization to confirm EDS SOC washout and collect any AEs/SAEs. The safety phone calls start day may be adjusted based on the specific EDS SOC washout requirements.

For participants on EDS SOC modafinil, armodafinil and/or pitolisant: safety phone calls will be completed from Day -7 to Day -1

For participants on EDS SOC solriamfetol, Xyrem or methylphenidate: safety phone calls will be completed on Day -1.

8.3.10.2 Compliance and Safety Phone Calls CCI

CCI [redacted]

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators 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 6.

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

Table 6 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
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

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

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

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

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

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

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

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

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

Disease-related events and /or disease-related outcomes not qualifying as AEs or SAEs are not applicable to this study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

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

3. Suicidal ideation, suicidal behavior.
4. Events associated with potential for abuse (the Operations Manual will contain a list of specific terms associated with potential for abuse).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any study intervention administered that exceeds the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a non-study intervention dose (eg, rescue or concomitant medication) is to be considered an overdose, with notification of the Sponsor.

Sponsor does not recommend specific treatment for 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 samples 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-6552

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

8.7 Pharmacodynamics

8.7.1 CCI

[redacted]

8.7.2 CCI

[redacted]

8.7.3 CCI

[redacted]

8.7.4 CCI [redacted]

[redacted]

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 (DNA) for genetic analysis
- Blood for HLA-DQB1*06:02 Genotyping

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.9 Future Biomedical Research Sample Collection

If the participant has provided documented informed consent for FBR, FBR-specific sample collections, including leftover samples, will be obtained. The following specimens will be included for FBR:

- Leftover samples listed in Section 8.8

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

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

8.11.1 Screening

Within approximately 4 weeks ± 1 week (or 7 days); before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

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

8.11.2 Treatment Period Visit

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

In Part 1, each treatment period will be separated by ≥ 4 days to allow for a full washout of the study intervention and data entry in the EDC.

In Part 2, each treatment period will be separated by ≥ 2 days to allow for a full washout of the study intervention.

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

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

8.11.4 Poststudy

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

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

Part 1

The blood sample for MK-6552 is the critical procedure.

At any postdose time point, the blood sample for MK-6552 needs to be collected as close to the exact time point as possible.

CCI [redacted]

[redacted]

[redacted]

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

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 7.

Table 7 Pharmacokinetic Blood Collection Windows

PK Collection	PK Collection Window
Predose	Up to -1h
0 to <1 h	±5 min
1 to <18 h	±15 min
18 to ≤24 h	±1 h

Study Intervention Administration

Study intervention administration: within 30 minutes of the theoretical administration time

Predose and Postdose Procedures

CCI [redacted]

Postdose VS evaluations:

- Prior to 1 hour postdose may be obtained within 5 minutes of the scheduled sampling time
- Prior to 24 hours postdose may be obtained within 15 minutes of the scheduled sampling time

- 24 hours postdose may be obtained within 1 hour of the scheduled sampling time.

CCI

Laboratory safety tests collected for Panel B participants in each period of Part 2 on Day 4 can be obtained ± 1 day (from Day 3 to Day 5) from the scheduled sampling time.

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

This is a Phase 1 assessment of MK-6552 in participants with NT1, 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 study part and/or period
- Entire period(s) may be omitted (applicable only for the highest dose level for a given participant)
- For Part 2, decrease in the duration of study intervention administration (eg, number of days)
- Adjustment of the dosing interval (eg, bid to qd or vice versa)
- Lengthening of the washout period between doses
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK sample processing and shipping details based on newly available data
- CCI

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 and/or PK analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during their participation in the entire study (refer to the Central Laboratory Services Manual for approximate total blood volume to be drawn for each participant).

CCI [redacted]. 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 their participation in the entire study.

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

9 KEY STATISTICAL CONSIDERATIONS

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

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.

CCI [redacted]

[redacted]

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Safety: Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, ECGs, C-SSRS and vital signs.

CCI [redacted]

9.3.2 Secondary Endpoints

CCI [redacted]

9.3.3 Exploratory Endpoints

CCI [redacted]

[redacted]

CCI [redacted]

9.4 Analysis Populations

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

9.4.1 All Participants As Treated Population

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

9.4.2 Per-Protocol (PP) Population

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

9.5 Statistical Methods

9.5.1 Statistical Methods for Safety Analyses

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

QTC: 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 by time point (Part 1).

9.5.2 Statistical Methods for Pharmacodynamic Analyses

CCI

[redacted]

9.5.3 Statistical Methods for Pharmacokinetic Analyses

CCI

[redacted]

CCI [redacted]

9.6 Interim Analyses

During the in-life portion of the trial, data will be reviewed CCI [redacted] in an on-going basis to support decision-making. The aggregate summaries will be presented in an unblinded manner. No individual participant level results will be provided unless needed to assess patient safety. The sponsor study statistician and pharmacokineticist will be unblinded in order to perform the in-life analysis. There are no planned interim analyses to test any formal hypotheses.

9.7 Multiplicity

CCI [redacted]

9.8 Sample Size and Power Calculations

CCI [redacted]

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), Regulation (EU) 536/2014, the 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 Committees Structure

In this Phase 1 study, the number of events is anticipated to be low, which will diminish the statistical power and interpretation of the results. Therefore, a DMC will not be utilized.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical 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.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

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

Table 8 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 (fasted)[a]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum (Screening Visit) OR urine (predose in each treatment period) hCG pregnancy test (as needed for POCBP)			

Laboratory Assessments	**Parameters**
Other Screening Tests	• FSH (as needed in PONCBP only) • Breath alcohol test • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • Genotyping for HLA-DQB1*06:02 allele • All study-required laboratory assessments will be performed by a central laboratory

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

[a] For Panel B, no fasting requirement for safety laboratory blood collection on Day 4 of each period in Part 2.

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.

Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

Is a cancer.

Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

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

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

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

Assessment of causality

Did the study intervention cause the AE?

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

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

- **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant reexposed to the study intervention in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

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

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

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

The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).

- Yes, there is a reasonable possibility of study intervention relationship:
  - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
- No, there is not a reasonable possibility of study intervention relationship:
  - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

Follow-up of AE and SAE

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

New or updated information will be recorded in the CRF.

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

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

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

The primary mechanism for reporting to the Sponsor will be the EDC tool.

- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
- Reference Section 8.4.1 for reporting time requirements.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

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

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

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

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

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

Premenarchal

Premenopausal with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

Postmenopausal

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

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.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[a,b] • IUS[a,c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception [a,b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception [a,b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Penile/external condoms must be used in addition to the POCBP's hormonal contraception. . [b] IUS is a progestin-releasing IUD. Note: • Tubal occlusion includes tubal ligation

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: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	**Potentially Significant Postrandomization Findings**
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	All	All
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male/Female	QTc ≥450ms	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,; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1.

10.9 Appendix 9: Algorithm for Assessing Out of Range Laboratory Values

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

A. If all protocol-specified laboratory values are normal, the participant may enter the study.
B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including repeats if performed), the participant will be excluded from the study.
C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
    - The participant may be excluded from the study.
    - The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
    - The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.
    - The abnormal test may be repeated (refer to items below for continuation of algorithm for repeated values).
        ◦ If the repeat test value is within the normal range, the participant may enter the study.
        ◦ If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.
D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: 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.

10.10.1 The General Neurological Examination

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

10.10.1.1 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.

10.10.1.2 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

10.10.1.3 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

10.10.1.4 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

10.10.1.5 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

10.10.1.6 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)

10.10.2 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:

10.10.2.1 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)

10.10.2.2 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

10.10.2.3 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

10.10.2.4 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

10.10.2.5 Module 6 – Sensory

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

10.11 Appendix 11: List of Caffeine Products and Caffeine Content

This list is not inclusive; many products contain caffeine, including over-the-counter medications, weight loss products, mineral and herbal supplements, etc. Please check the labels of any concomitant therapies and/or supplements for caffeine content.

Product	**Serving Size (in fluid ounces [oz] and milliliters [mL])**	**Caffeine (mg)**
Coffee		
Brewed	8 oz. (237 mL)	95-200 mg
Brewed, decaffeinated	8 oz. (237 mL)	2-12 mg
Brewed, single-serve varieties	8 oz. (237 mL)	75-150 mg
Brewed, single-serve varieties, decaffeinated	8 oz. (237 mL)	2-4 mg
Espresso, restaurant-style	1 oz. (30 mL)	47-75 mg
Espresso, restaurant-style, decaffeinated	1 oz. (30 mL)	0-15 mg
Instant	8 oz. (237 mL)	27-173 mg
Instant, decaffeinated	8 oz. (237 mL)	2-12 mg
Specialty drink (latte or mocha)	8 oz. (237 mL)	63-175 mg
Tea		
Brewed tea		
Black tea	8 oz. (237 mL)	14-70 mg
Black tea, decaffeinated	8 oz. (237 mL)	0-12 mg
Green tea	8 oz. (237 mL)	24-45 mg
Iced tea		
Instant, prepared with water	8 oz. (237 mL)	11-47 mg
Ready-to-drink, bottled	8 oz. (237 mL)	5-40 mg

Product	Serving Size (in fluid ounces [oz] and milliliters [mL])	Caffeine (mg)
Soft Drinks		
A&W Root Beer	12 oz. (355 mL)	0 mg
Barq's Root Beer	12 oz. (355 mL)	16-18 mg
Coca-Cola	12 oz. (355 mL)	23-35 mg
Diet Coke	12 oz. (355 mL)	23-47 mg
Diet Pepsi	12 oz. (355 mL)	27-37 mg
Dr. Pepper, regular and diet	12 oz. (355 mL)	36-42 mg
Mountain Dew, regular and diet	12 oz. (355 mL)	42-55 mg
Mug Root Beer, regular and diet	12 oz. (355 mL)	0 mg
7UP	12 oz. (355 mL)	0 mg
Pepsi	12 oz. (355 mL)	32-39 mg
Sierra Mist, regular and diet	12 oz. (355 mL)	0 mg
Sprite, regular and diet	12 oz. (355 mL)	0 mg
Energy Drinks		
Amp, regular or sugar-free	8 oz. (237 mL)	71-74 mg
5-Hour Energy shot	2 oz. (60 mL)	200-207 mg
Full Throttle, regular or sugar-free	8 oz. (237 mL)	70-100 mg
Red Bull, regular or sugar-free	8.4 oz. (248mL)	75-80 mg
Rockstar, regular or sugar-free	8 oz. (237 mL)	79-80 mg
Other Products		
Chocolate chips, semisweet	1 cup (168 grams)	104 mg
Dark chocolate-coated coffee beans	28 pieces	336 mg
Energy mints	2 mints	95-200 mg

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-24h	area under the curve from time 0 to 24 hours
AUC0-inf	area under the curve from time 0 to infinity
BDS	blood drug screen
BICR	blinded independent central review
bid	twice daily
BLA	Biologics License Application
BLOQ	below limits of quantification
BMI	body mass index
BP	blood pressure
BT	body temperature
C2h	concentration at 2 hours
C6h	concentration at 6 hours
C8h	concentration at 8 hours
C18h	concentration at 18 hours
C21h	Concentration at 21 hours
C24h	concentration at 24 hours
CAC	Clinical Adjudication Committee
CCU	Cardiac care unit
CG	Cockcroft-Gault
CI	confidence interval
CL/F	oral clearance
Cmax	maximum plasma concentration

Abbreviation	Expanded Term
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CRF	Case Report Form
CRU	clinical research unit
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTA	Clinical Trial Application
CTFG	Clinical Trial Facilitation Group
CTMS	Clinical Trial Management System
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EMA	European Medicines Agency

Abbreviation	Expanded Term
EMG	electromyogram
EOC	Executive Oversight Committee
EOG	Electro-oculogram
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPCR	G protein-coupled receptor
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA-DQB1	human leukocyte antigen DQ Beta 1
HR	heart rate
HRT	hormone replacement therapy
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
IC20	20% inhibitory concentration
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

Abbreviation	Expanded Term
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
KSS	Karolinska Sleepiness Scale
LAM	lactational amenorrhea method
LFT	liver function test
LSEQ	Leeds Sleep Evaluation Questionnaire
MAD	maximum administered dose
MWT	Maintenance of wakefulness test
N1	sleep stage 1
N2	sleep stage 2
N3	sleep stage 3
NCS	not clinically significant
NDA	New Drug Application
NE	neurological examination
NOAEL	no observed adverse effect level
NR	normal range
NT1	narcolepsy type 1
OR	objective response
OX1R	orexin 1 receptor
OX2R	orexin 2 receptor
PBO	placebo
PCL	Protocol Clarification Letter
PD	pharmacodynamic(s)
PE	physical examination
pEFD	preliminary embryo-fetal developmental

Abbreviation	Expanded Term
PK	pharmacokinetic
PN	protocol number
po	orally
POCBP	participant of childbearing potential
PONCBP	participant of nonchildbearing potential
PP	per-protocol
PR	pulse rate
PSG	polysomnography
q3h	every 3 hours
q6h	every 6 hours
q8h	every 8 hours
REM	rapid eye movement
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SR	semirecumbent
SUSAR	suspected unexpected serious adverse reaction
Tmax	time to maximum plasma concentration
t1/2	half life

Abbreviation	Expanded Term
UDS	urine drug screen
ULN	upper limit of normal
US	United States (of America)
UTN	Universal Trial Number
Vd	volume of distribution
VS	vital signs
Vz/F	apparent volume of distribution
WBC	white blood cell

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