Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Cross-over Evaluation of Evoked Responses as Pharmacodynamic Biomarkers in Healthy Adults and Schizophrenic Patients
NCT number:	NCT05136690
Document Date:	21-Sep-2022

Title Page

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Cross-over Evaluation of Evoked Responses as Pharmacodynamic Biomarkers in Healthy Adults and Schizophrenic Patients

Protocol Number: 007-04

Compound Number: MK-4334

Sponsor Name:

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	157,663

Approval Date: 21 September 2022

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 04	21-SEP-2022	Correct error to Hypotheses, Objectives, and Endpoints
Amendment 03	01-SEP-2022	To update the Sponsor entity name and address change
Amendment 02	15-MAR-2022	To add baseline EEGs to the study design
Amendment 01	01-DEC-2021	Corrections and clarifications
Original Protocol	03-SEP-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 007-04

Overall Rationale for the Amendments:

The text in the Endpoints were inadvertently changed

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	One of the secondary endpoints was changed to "Plasma nicotine levels at time of ERP recording" from "ITC magnitude derived from the 40 Hz-ASSR".	This was inadvertently changed in Amendment 007-03 and this restores the original text.
1.1 Synopsis	One of the endpoints in the first tertiary/exploratory endpoint was changed to "P3A, MMN magnitude derived from the DD-MMN" from "ITC magnitude derived from the 40 Hz-ASSR".	This was inadvertently changed in Amendment 007-03 and this restores the original text.
3 Hypotheses, Objectives, and Endpoints	One of the endpoints in the first tertiary/exploratory endpoint was changed to "P3A, MMN magnitude derived from the DD-MMN" from "ITC magnitude derived from the 40 Hz-ASSR".	This was inadvertently changed in Amendment 007-03 and this restores the original text.
3 Hypotheses, Objectives, and Endpoints	One of the endpoints in the second tertiary/exploratory endpoint was changed to "MMN, P3A magnitudes derived from the DD-MMN" from "MMN and P3A magnitudes derived from the DD-MMN".	This makes the endpoint consistent between Section 1 and Section 3 of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Cross-over Evaluation of Evoked Responses as Pharmacodynamic Biomarkers in Healthy Adults and Schizophrenic Patients

Short Title: Evoked Responses as Pharmacodynamic Biomarkers

Acronym: ASSR

Hypotheses, Objectives, and Endpoints:

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

This study population consists of healthy adult males and females (WONCBP) and male and female (WONCBP) patients with mild-to-moderate SZ, 18-55 years of age.

Objectives	Endpoints
Primary	
Objective: Record and measure the 40 Hz-ASSR in HC and SZ patients at baseline and determine whether the mean ITC magnitude derived from the 40 Hz-ASSR at baseline is lower in SZ patient than in HC. **Hypothesis**: The mean magnitude of the ITC recorded from SZ patients at baseline will be lower than those recorded from HC at baseline.	ITC magnitude derived from the 40 Hz-ASSR

Objectives	Endpoints
Secondary	
Objective: Record and measure the DD-MMN in HC and SZ patients at baseline and determine whether the mean MMN magnitude derived from the DD-MMN at baseline is lower in SZ patient than in HC. **Hypothesis**: The mean magnitude of the MMN derived from the DD-MMN recorded from SZ patients at baseline will be lower than that recorded from HC at baseline. **Objective**: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the 40 Hz-ASSR ITC recorded from HC or SZ patients relative to placebo treatment. **Hypothesis**: Pharmacologically relevant plasma levels of nicotine change the mean magnitude of the ITC recorded from HC or SZ patients relative to placebo treatment, with each subject group tested separately.	MMN magnitude derived from the DD-MMN ITC magnitude derived from the 40 Hz-ASSR Plasma nicotine levels at time of ERP recording
Tertiary/Exploratory	
Exploratory Objective: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the P3A, MMN or GBO recorded from HC or SZ patients relative to placebo treatment. **Estimation:** Estimate difference between the treatment groups (nicotine vs. placebo) in the mean change from baseline in the magnitude of the P3A, MMN or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately.	P3A, MMN magnitude derived from the DD-MMN Plasma nicotine levels at time of ERP recording Resting GBO magnitude

Objectives	Endpoints
Exploratory Objective: Determine if pharmacologically relevant plasma concentrations of MK-4334 change the mean magnitude of the 40 Hz-ASSR ITC, the MMN, P3A, or GBO recorded from HC or SZ patients relative to placebo treatment. **Estimation:** Estimate difference between the treatment groups (MK-4334 vs. placebo) in the mean change from baseline in the magnitude of the 40 Hz-ASSR ITC, MMN, P3A or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately. **Exploratory Objective:** To determine intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13). **Estimation:** Estimate intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13). More specifically, mean ITC over time (Days -1, 7, 13) will be summarized and graphically displayed. Pairwise (Day -1 vs. Day 7 or Day -1 vs. Day 13) ICC will be estimated. Scatter plot with diagonal line and Bland-Altman plot will also be presented.	ITC magnitude derived from the 40 Hz-ASSR MMN, P3A magnitudes derived from the DD-MMN Plasma MK-4334 levels at time of ERP recording Resting GBO magnitude
Exploratory Objective: To explore the relationship between the genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation in CYP2C19 and across the human genome may be analyzed for association with the clinical data in this study.	Germline genetic variation and association with clinical data collected from this study

Overall Design:

Study Phase	Early Phase 1
Primary Purpose	Basic Science
Indication	Cognitive Impairment Associated with Schizophrenia
Population	Healthy adults and schizophrenic patients
Study Type	Interventional
Intervention Model	Cross-over This is a multi-site study.
Type of Control	Double dummy placebo with active control
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 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 45 participants will be screened such that 36 will be randomized as evaluable participants to complete the study as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period/	Use
Healthy Controls (HC, Panel A)	Nicotine	21 mg	Single dose	Topical (patch)	Single application	Exp
	Nicotine placebo patch	N/A	Single dose	Topical (patch)	2 single applications, 7 or 14 days apart	Exp
	MK-4334	250 mg	Single dose	PO	Single dose, 250 mg	Exp
	MK-4334 placebo	N/A	Single dose	PO	2 single doses, 7 days apart	Exp
Schizophrenic Patients (SZ, Panel B)	Nicotine	21 mg	Single dose	Topical (patch)	Single application	Exp
	Nicotine placebo patch	N/A	Single dose	Topical (patch)	2 single applications, 7 or 14 days apart	Exp
	MK-4334	250 mg	Single dose	PO	Single dose, 250 mg	Exp
	MK-4334 placebo	N/A	Single dose	PO	2 single doses, 7 days apart	Exp

Abbreviations: Exp, experimental; N/A, not applicable; PO, per os (oral)

Current or former name(s) or alias(es) for study intervention(s) is NicoDerm CQ

Placebo: Tegaderm (Nexcare) patch

Total Number of Intervention Groups/ Arms

2 Panels, 2 parts, 3 periods

Duration of Participation

Each individual will participate in the study for approximately 80 days from the time they provide documented informed consent through the final contact. After a screening phase of up to 35 days, each participant will undergo study related procedures over a period of approximately 17 days. After all treatments are completed, each participant will be followed for an additional 28 days.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
There are no study governance committees for this investigation.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 12.

1.2 Schema

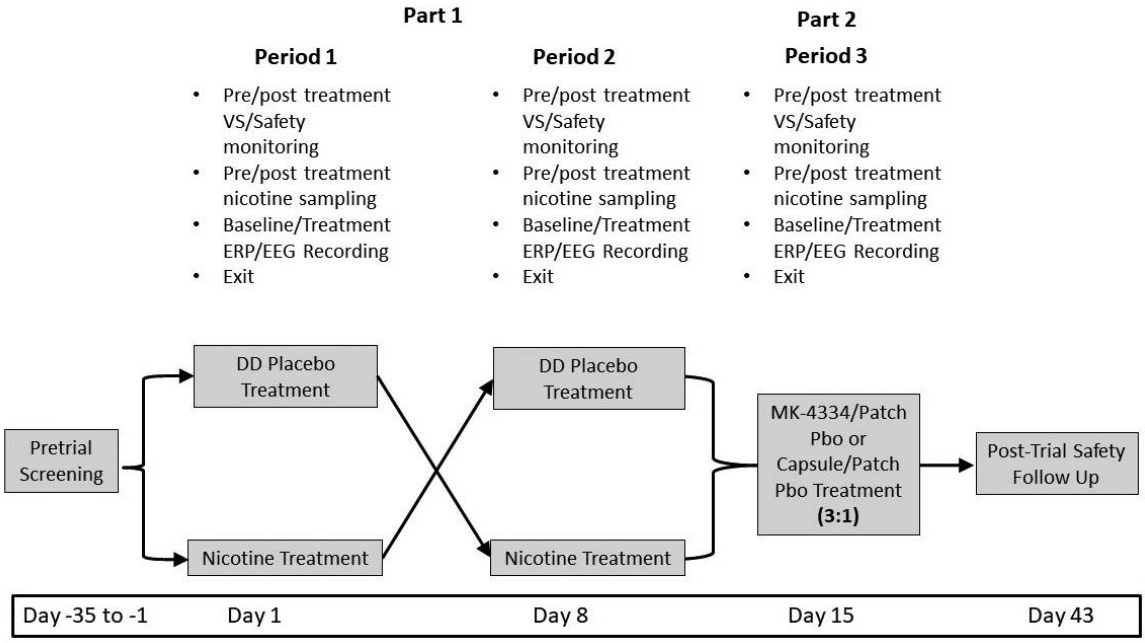
The study design is depicted in Table 1, Figure 1, and Figure 2.

Table 1 Study Treatments

	Part 1		**Part 2**
Panel	**Period 1**	**Period 2**	**Period 3**
A	• 21 mg Nicotine patch + Capsule placebo; or • Capsule placebo+ Patch placebo	• 21 mg Nicotine patch + Capsule placebo; or • Capsule placebo + Patch placebo	• 250 mg MK-4334 + Patch placebo; or • Capsule placebo + Patch placebo
B	• 21 mg Nicotine patch + Capsule placebo; or • Capsule placebo+ Patch placebo	• 21 mg Nicotine patch + Capsule placebo; or • Capsule placebo + Patch placebo	• 250 mg MK-4334 + Patch placebo; or • Capsule placebo + Patch placebo

In Part 1, twelve (12) healthy controls (HC, Panel A) and 24 schizophrenic patients (SZ, Panel B) will receive either a nicotine patch (21 mg) and capsule placebo, or matching patch and capsule placebos in in a 1:1 active:placebo ratio within each panel in 2 periods (Periods 1 and 2) in the cross-over design.

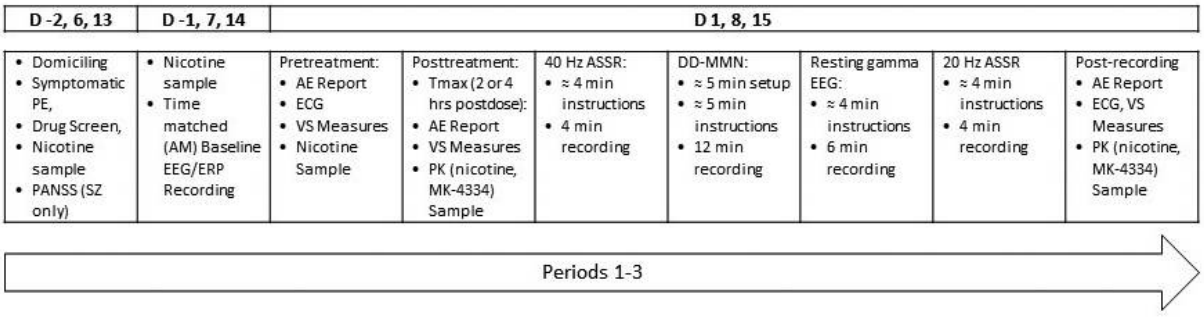
In Part 2, Period 3, participants will be randomly assigned to receive either 250 mg MK-4334 and patch placebo or patch and capsule placebos in a 3:1 active:placebo ratio within each panel. Assignment of participants to their treatments will be determined according to a computer-generated allocation schedule. MK-4334/matching capsule placebo will be administered as a DFC formulation.



Participants in both Panel A (HC, n = 12) and Panel B (SZ, n =24) will undergo the treatments outlined above. In Part 2, participants will be randomized to receive either MK-4334 (HC, n = 9; SZ, n = 18) or DD pbo (HC, n = 3; SZ, n = 6) treatment.

DD: Double dummy

Figure 1 Schedule of Monitoring and Interventions



Representative example of the relative sequence of procedures to be conducted during each of the 3 treatment periods. The timing of the procedure, sequence, number and nature of the procedures may change as necessary. ERP reflects recording of 20, 40 Hz ASSR and DD-MMN; EEG reflects recording of resting gamma EEG (GBO).

AE: adverse event, ASSR: auditory steady state response, DD-MMN: duration deviant mismatch negativity, ECG: electrocardiogram, EEG: electroencephalogram, GBO: gamma-band oscillation, PK: pharmacokinetics, VS: vital signs

Figure 2 Relative Timing of Procedures During Each Treatment Session (Period).

1.3 Schedule of Activities

All Panels/Parts												
Study Period:	**Screening**	**Intervention (Days)**									**Post-Study**	**Notes**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**43**	
Administrative Procedures												
Informed Consent	X											
Informed Consent for FBR	X											
Participant ID Card	X											
Screening Procedures/Reviews												
Medical History	X											Include substance usage: Drugs, alcohol, tobacco and caffeine; family history of systemic disease, mental illness
Prior/Concomitant Medication Review	X	X----------X										
Height	X											
Weight (BMI)	X											
Full physical examination	X										X	PE on Day 43 should be conducted within ≈ 4 hrs of the time of administration of the last dose of study intervention on Day 15.
Symptom driven physical examination		X			X			X				
Neurological examination	X										X	NE on Day 43 should be conducted within ≈ 4 hrs of the time of administration of the last dose of study intervention on Day 15.
Audiometry Test	X											To be administered to participants in both panels
Tone Matching Test	X											To be administered to participants in both panels
MINI 7.0.2 Screen	X											To be administered to participants in both panels

All Panels/Parts												
Study Period:	**Screening**	**Intervention (Days)**									**Post-Study**	**Notes**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**43**	
PANSS (Complete Assessment)	X	X			X			X			X	SZ patients (Panel B). Inclusion criteria to be applied at screening and Day -2: a. Delusions (item P1) score ≤ 4 b. Hallucinatory behavior (item P3) score ≤ 4 c. Unusual thought content (item G9) score ≤ 4 d. Conceptual disorganization (item P2) score ≤ 4 e. Hostility (item P7) score ≤ 4. f. Total score ≤ 80
WRAT-5	X											HC (Panel A) candidates and SZ patients (Panel B). Only the Letter Reading and Word Reading portions are to be administered.
BACS	X											HC (Panel A) candidates and SZ patients (Panel B).
CDSS	X											SZ patients (Panel B).
C-SSRS Screening/Baseline version	X											
C-SSRS SLA		X			X			X			X	
HIV, hepatitis B and C screen	X											
FSH screen (females only)	X											
Drug Screen	X	X			X			X			X	Drug screen may be done upon arrival at the CRU for domiciling. Matrix taken for screening (blood, urine, saliva) to be determined by site and used through study
CYP2C19 Genotyping	X											
Inclusion/Exclusion Criteria	X----------X											Review I/E criteria prior to assigning randomization number

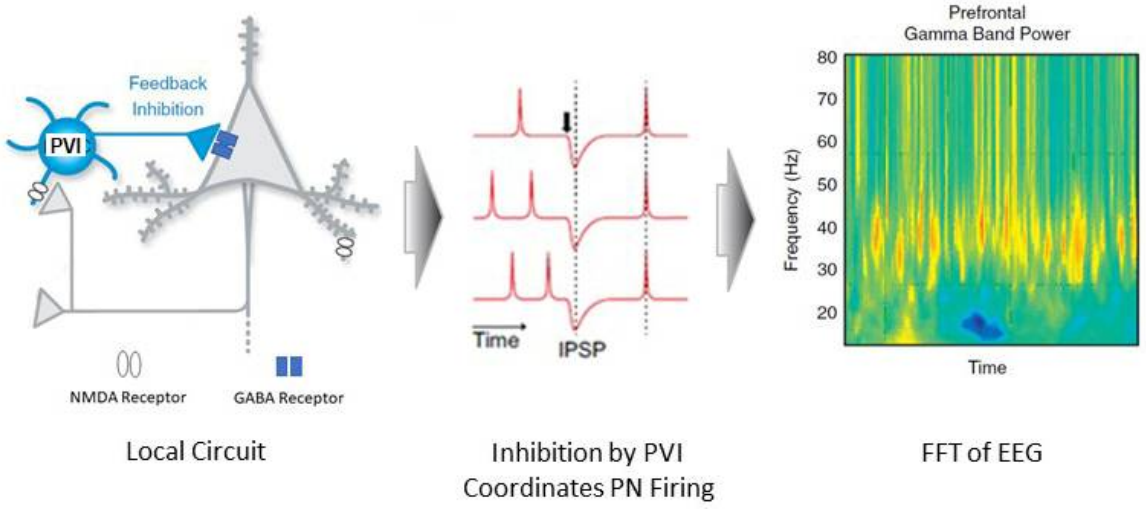
All Panels/Parts												
Study Period:	**Screening**	**Intervention (Days)**									**Post-Study**	**Notes**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**43**	
Domiciling		X	X		X	X		X	X			Participants should be instructed to arrive in the afternoon 2 days before their intervention administration date to provide sufficient time for pre-intervention processing and are expected to spend two nights domiciled.
Assignment of Treatment/Randomization Number			X							X		Participants will each receive a randomization number for Part 1 and will then be re-randomized (with a new randomization number) for continuation in Part 2. Randomization can occur on Day 1 predose if results are still pending on Day -1.
Meals		X----------X										In addition to providing meals during domiciling, a meal may be offered after completion of all safety measures post-recording and prior to site exit for periods 1-3.
Intervention Administration												
Nicotine or patch placebo Administration				X			X			X		
MK-4334 or capsule placebo Administration				X			X			X		
Safety Procedures												
Vital Signs (HR, BP, RR, BT)	X	X----------X										Triplicate measures of supine HR and BP will be taken on Day -2 as baseline reference before taking single measures of BT, RR and any recordings. Single VS (HR, BP, BT, RR) measures will be taken on days 6 and 13 after admission to the study site and on days 1, 8, and 15 at predose, ≈ 2 (nicotine/pbo) or 4 (MK/pbo) hrs postdose (before recording session) and again at ≈ 3 (nicotine/pbo), or 5 (MK/pbo) hrs (after recording session). VS measures out of normal range will be repeated up to 3 times in 15 minutes, or until measures return to normal.

All Panels/Parts												
Study Period:	**Screening**	**Intervention (Days)**									**Post-Study**	**Notes**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**43**	
Orthostatic VS (HR, BP)	X	X		X	X		X	X		X	X	Orthostatic HR and BP to be taken on Days -2, 6 and 13 after completion of the VS measures. Additional orthostatic VS measures will be taken after completing the VS measures on days 1, 8, and 15 at predose and again at ≈ 3 (nicotine/pbo), or 5 (MK/pbo) hrs postdose, or ≈ 1 hr after completing the recording session. Participants should be supine for at least 10 minutes and then stand upright. Measures of orthostatic VS will be taken after 1 min and 3 min of standing.
12-lead ECG	X	X		X	X		X	X		X	X	Single ECGs will be recorded on Days -2, 6, and 13 after VS measures. Additional ECGs will be recorded on Days 1, 8, and 15 predose at ≈ 3 (nicotine/pbo), or 5 (MK/pbo) hrs postdose (≈ 1 hr after completing the recording session) and on Day 43 at approximately the same time as during the intervention period.
Hematology	X		X			X			X		X	Blood samples will be taken at screening and on Days -1, 7, 14, and 43.
Chemistry	X		X			X			X		X	Blood samples will be taken at screening and on Days -1, 7, 14 and 43.
Urinalysis	X		X								X	Sample will be taken at screening and on Days -1 and 43.
AE/SAE Review	X----------X											
EEG/ERP Recording Session												
Passive, duration-deviant mismatch negativity			X	X		X	X		X	X		DD-MMN will be recorded at baseline, predose and ≈ 2 hrs post-nicotine or 4 hrs post MK-4334 administration
20, 40 Hz-ASSR			X	X		X	X		X	X		40 Hz-ASSR will be recorded at baseline, pre-dose and ≈ 2 or 4 hrs post-nicotine or MK-4334 dosing, respectively. Similarly, 20 Hz-ASSR will be recorded at ≈ C2 or C4.
Resting EEG			X	X		X	X		X	X		Resting EEG/GBO will be recorded at baseline, predose and ≈ 2 hrs post-nicotine or 4 hrs post MK-4334 administration

All Panels/Parts												
Study Period:	**Screening**	**Intervention (Days)**									**Post-Study**	**Notes**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**43**	
Blood Sampling												
Blood for MK-4334 assay										X		Blood samples will be taken on Day 15 at predose and at ≈ 4 hrs postdose, after VS, ECG measures and before recording.
Blood for nicotine assays	X	X	X	X	X	X	X	X	X	X		Blood samples for nicotine assessments will be taken at Screening and during all intervention days. A single sample will be taken on the first day of domiciling (Days -2 6, 13). On days when baseline recordings are being taken (Days -1, 7, 14), a sample will be taken just before recording. On days when study treatment is being administered (Days 1, 8, 15), samples will be taken predose and at ≈ 2 hrs post administration of study intervention. In all cases, blood sampling will occur after taking VS, ECG measures.
Blood for cotinine assays	X											Blood samples will be taken at screening for measures of cotinine levels to validate chronic nicotine use. Sampling will occur after taking VS, ECG measures.
Biomarkers												
Blood for Genetic Analysis			X									Collect predose only from enrolled participants during period 1. (See section 8.8.1) Sample can also be collected on Day 1 Predose.

2 INTRODUCTION

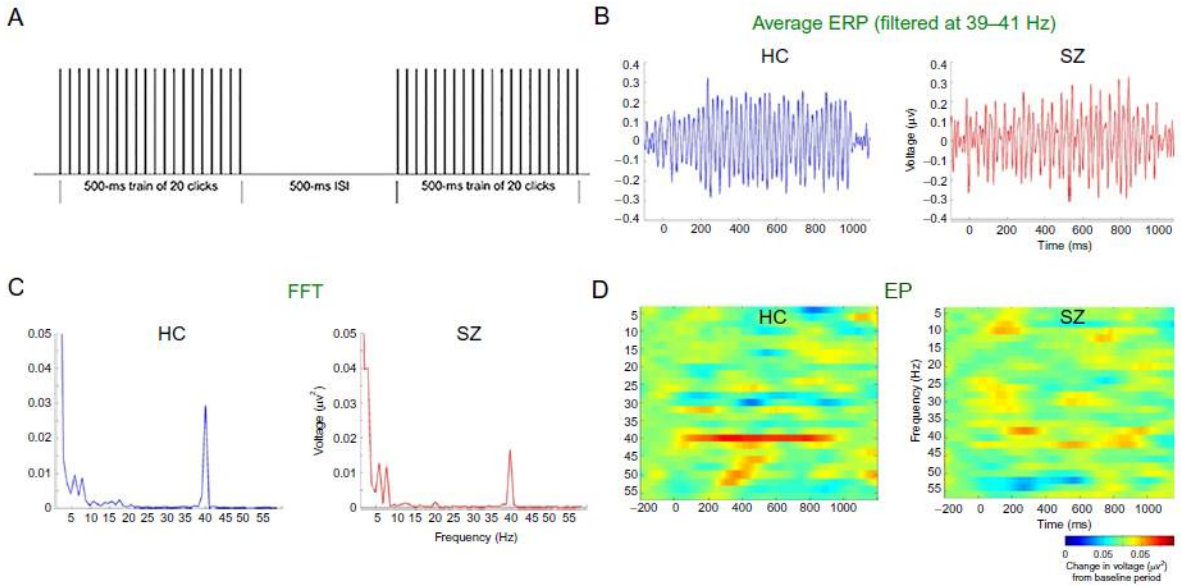
SZ is a disabling neuropsychiatric disorder characterized by clinical symptom clusters (positive and negative) and cognitive deficits [Parciauskaite, V., et al 2019]. The range of cognitive deficits observed in SZ suggests the presence of substantial abnormalities in adapting thoughts or behaviors to achieve goals [Lesh, T. A., et al 2011], consistent with a loss of coordination in the neuronal activity of multiple brain regions [Light, G. A., et al 2006]. Of several oscillation bands of neuronal activity implicated in brain function, the GBO (ranging from 30–80 Hz, centering around 40 Hz) arising from neural networks in the cortex and brainstem act as a key neural substrate for cognitive processes and the coordination of network activity across brain regions [Miller, E. K. 2001], [Howard, M. W., et al 2003]. GBO are generated by fast-spiking, parvalbumin-positive, GABAergic interneurons (PVI) residing in neural networks in the prefrontal cortex and superior temporal gyrus [Lewis, D. A., et al 2012] (Figure 3). Alterations in the synchronization of GBO may result from abnormalities in both pre- and post-synaptic function of these networks due to imbalances in glutamatergic and/or GABAergic neurotransmission.



Phasic, excitatory inputs to the PVI from cortical pyramidal neurons result in feedback inhibition of the pyramidal neurons, synchronizing their activity. Alterations in the synchronization of this oscillation may result from abnormalities in glutamatergic signaling due to decreased glutamate release from the pyramidal neurons, decreased density of glutamatergic receptors on PVI, or loss of PVI. Modified from [Lewis, D. A., et al 2012]

Figure 3 GBO are Generated by Networks of Pyramidal Neurons and Interneurons in the Cerebral Cortex.

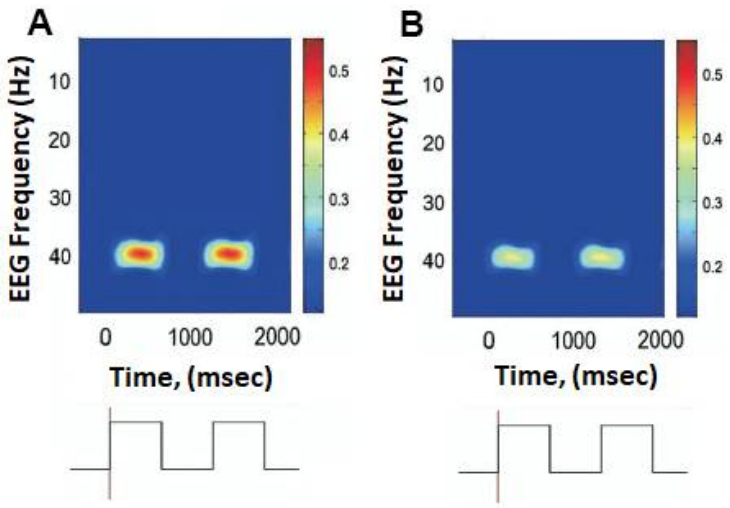
The ability of the brain to generate GBO in response to stimuli can be monitored using the ASSR [Kwon, J. S., et al 1999]. ASSRs are elicited by temporally modulated auditory stimuli, such as a train of 40 Hz clicks (Figure 4A). This stimulus train evokes synchronous neuronal oscillations in the γ frequency band that remain constant in amplitude and phase over time (Figure 3B) [O'Donnell, B. F., et al 2013], [Uhlhaas, P. J. 2010]. The evoked EEG signal is filtered (Figure 4B) and processed by FFT (Figure 4C), allowing the derivation and quantitation of event-related changes in GBO to be determined (eg, EP, ITC), (Figure 4D), (Figure 5).



(A) The 40 Hz-ASSR is elicited using an auditory stimulus of 40 Hz click trains with a 500 msec inter-train interval. (B) These evoke a GBO waveform that is averaged and filtered (39-41 Hz). Note that the regularity (phase) and amplitude of the GBO recorded from the SZ patient is disorganized relative to that from HC. (C) A power spectrum is obtained by processing the GBO using a FFT. Note that the amplitude of the 40 Hz response from the HC group is reduced in the SZ group. (D) Heat map of the EP across the stimulus epoch. The average change from baseline in EP is centered at 40 Hz (Y axis), with the area of highest amplitude lasting ≈ 0.5 seconds (X axis). The colors represent the power amplitude, with red signifying the highest voltage. Modified from [O'Donnell, B. F., et al 2013].

Figure 4 ASSR are Derived from the GBO and are Altered in SZ Patients.

Abnormalities in the EP and ITC (Figure 4, Figure 5) are observed in SZ patients and are believed to reflect NMDA receptor/glutamatergic hypofunction [Kim, J. S., et al 1980], [Tamminga, C. A. 1998] [Coyle, J. T. 2006]. This is supported by the observation that inhibition of glutamatergic signaling using NMDA receptor antagonists such as ketamine induces a psychotomimetic state analogous to SZ [Lahti, A. C., et al 1995]. Together, these observations support the hypothesis that glutamatergic hypofunction is involved in GBO abnormalities which contribute to the pathophysiological manifestations of SZ, including cognitive impairment [Dauvermann, M. R., et al 2017].



Heat maps show the correlation with on vs off stimuli between trials conducted in healthy controls (A) and SZ patients (B). Color indicates the magnitude of phase coherence (0 = no consistent phase locking across trials; 1 = absolute phase consistency across trials). ITC increases in response to faster stimulation rates, with maximal EEG coherence at 40 Hz stimulation. SZ patients show significant deficits in ITC relative to healthy controls. Modified from [Light, G. A., et al 2006].

Figure 5 ITC Time/Frequency Analyses of the 40 Hz-ASSR.

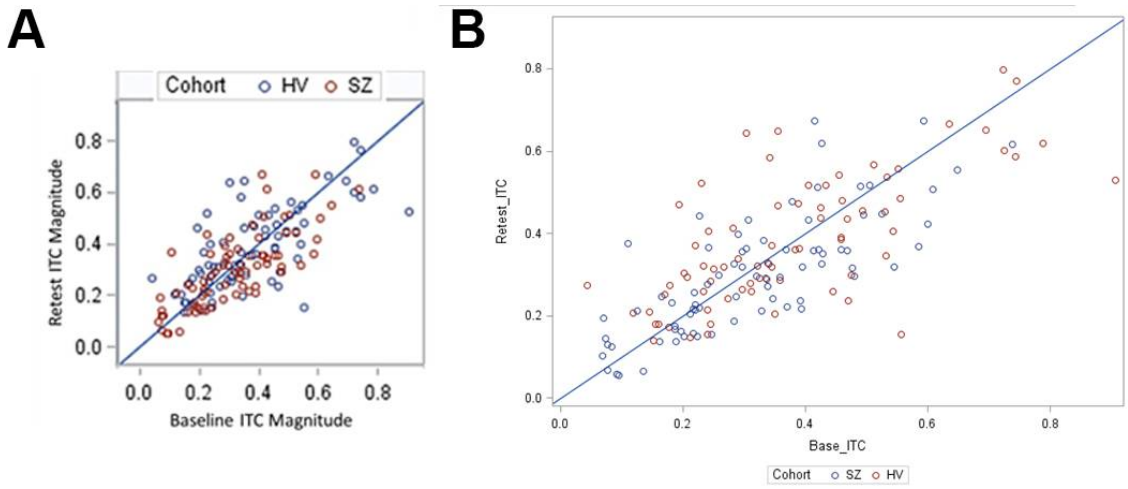
The glutamatergic hypofunction underlying these electrophysiological and cognitive impairments in SZ may be ameliorated by the administration of agents that activate glutamatergic pathways. While orthosteric agonists of glutamate receptors have not been successful in improving SZ symptomatology, it is commonly observed that SZ patients are frequent users of tobacco and nicotine containing products [Hughes, J. R., et al 1986], [Leonard, S., et al 1996]. This may reflect the ability of nicotinic cholinergic receptor agonists to increase synaptic release of glutamate [Fedele, E., et al 1998], reversing the glutamatergic hypofunction and acutely alleviating some of the symptoms of SZ [Glynn, S. M. 1990]. Such an observation would support the use of selective nicotinic receptor activators such as the [redacted] MK-4334 as treatments for CIAS [Olincy, A. 2012].

2.1 Study Rationale

This study is designed to evaluate the suitability of the 40 Hz-ASSR as a PD biomarker that can be used to identify the range of potentially efficacious doses of treatments for CIAS. Of the 2 ASSR endpoints (EP, ITC), the timing of the ITC reflects the abnormality in spike timing in pyramidal neuron networks observed in SZ, is very stable and can be recorded with high reliability both between tests at a given site and between investigational sites (Figure 6). Therefore, the study will evaluate the difference in ITC magnitude between HC and SZ patients, measure the change in ITC magnitude in these populations in response to a positive control (nicotine) and explore ITC responses to administration of [redacted], MK-4334. Successful achievement of these goals will support the use of the ASSR in future investigations as a PD biomarker.

Rationale for Amendment 007-02

Baseline ERP measurements are being taken before each treatment session to help compensate for any changes in electrophysiology over the course of the investigation. However, the baseline measure of the resting gamma band EEG (GBO) was inadvertently left out from previous versions of the protocol. For consistency with the overall experimental design, the baseline recording session for the GBO is now included in the SoA on days -1, 7 and 14.



A) The ITC parameters recorded from healthy volunteers (HV, blue circles) and schizophrenic patients (SZ, red circles) do not significantly differ between recording sessions conducted 1 week apart. Mean difference between baseline vs retest: HC, -0.00544 ± 0.133; SZ, 0.0149 ± 0.101. B) Between site variability. Each point represents the average ITC from HV (red circles) and SZ patients (blue circles) recorded from 4 different study sites. Overall intraclass correlation coefficient (ICC) = 0.7426 (Merck internal analysis of data obtained from ERP Biomarker Qualification Consortium protocol EBS-A V2).

Figure 6 Correlation Between the ITC Values Averaged over 200-500 msec Latency Blocks: SZ vs HV Responses.

2.2 Background

Refer to the IB for detailed background information on MK-4334.

While the magnitude of 40 Hz-ASSR parameters (EP, ITC) is reportedly reduced in SZ patients relative to healthy controls, this difference has not been consistently observed, due in part to the lack of uniformity in recording techniques. Moreover, the ability of either the ITC or EP to be pharmacologically modulated has not been established. Given the hypothesis that GBO synchronization depends on glutamatergic transmission within the cortical neuron network, this pathophysiology may be ameliorated by activating glutamatergic pathways in SZ patients indirectly by the administration of nicotinic cholinergic receptor activators. Therefore, the agents used in this study include the non-selective, nicotinic cholinergic receptor orthosteric agonist nicotine, which reverses the deficits in evoked responses recorded from SZ patients [Domino, E. F. 2003], [Dulude, L., et al 2010] and in the ASSR recorded from preclinical models [Sivarao, D. V., et al 2016]. In addition, the CCI [redacted]

CCI MK-4334 will be administered to evaluate the involvement of the α7 nicotinic cholinergic receptor subtype in modulating the 40 Hz-ASSR [Preskorn, S. H., et al 2014], [Antonio-Tolentino, K. 2020]. The ability of either of these agents to reverse or normalize the deficits in the 40 Hz-ASSR ITC would support the use of the 40 Hz-ASSR as PD biomarker for assessing the mechanism of action and effective dose range of novel antipsychotics/cognitive enhancers that act to increase glutamatergic activity.

2.2.1 Pharmaceutical and Therapeutic Background

MK-4334 is CCI [redacted] under development for treating cognitive impairment CCI Evidence from preclinical investigations indicates that it may increase glutamatergic neurotransmission as part of its downstream mechanisms of action. Detailed information on the pharmacology, PK, safety, and toxicity of MK-4334 is provided in the IB.

The nicotine patch administered during this study is approved for OTC use to aid in smoking cessation.

2.2.2 Preclinical and Clinical Studies

Extensive preclinical work characterizing the pharmacology of MK-4334 has been performed and is described in the IB. To date, 4 clinical studies of MK-4334 have been completed and their outcomes are described in the IB.

2.2.3 Ongoing Clinical Studies

MK-4334-006 is a 2-part study evaluating the use of selPOCE-MRS for measuring in vivo the FE of glu and gln with ^{13}C in vivo in the brain and the changes in glutamatergic signaling and neuroenergetics in response to administration of dl-ketamine or MK-4334. Part 1 of the study will assess the intra-subject T/RT variability in baseline measures of the FE of ^{13}C-glu and ^{13}C-gln in the prefrontal cortex of healthy adult males between 2 scans separated by a minimum of 7 days. No pharmacologic interventions or placebo are administered during this part of the study. Part 2 will evaluate the effects of ketamine or the CCI [redacted] MK-4334 on the turnover of glu and gln (FE of ^{13}C-glu, gln), an additional measure of glu turnover (eg, the ratio of [3-^{13}C] to [4-^{13}C] glutamate), the rate of glu to gln cycling (Vcyc) and the rate of oxidative metabolism linked to glutamatergic neurotransmission (VTCA) will be compared to placebo treatment as exploratory objectives. Successful completion of this study will validate selPOCE-MRS as a technique suitable for monitoring changes in glutamatergic activity in response to pharmacologic interventions, serving as a biomarker of the PD modulation of glutamatergic neurotransmission.

As of 12 Aug 2021, 3 participants have been infused with ^{13}C-glucose in Part 1. Two participants have received a single infusion, one has received 2 infusions spaced 1 week apart. No other investigational treatments have been administered. There have been no SAEs, deaths, or ECIs. The only AEs reported were an abnormal ECG considered NCS and not related to treatment, and an inability to tolerate confinement in the MRI chamber for the duration of the scan (2 hours).

2.2.4 A Randomized, Double-Blind, Placebo-Controlled, Cross-over Evaluation of Evoked Responses as Pharmacodynamic Biomarkers in Healthy Adults and Schizophrenic Patients

Nicotine is a non-selective orthosteric agonist of nicotinic cholinergic receptors. It will be administered by transdermal patch. Additional information about the nicotine patch is outlined in the product label (Operations Manual).

2.3 Benefit/Risk Assessment

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

It is not expected that the nicotine patch will cause any untoward responses from the participants due to their previous exposure to nicotine in tobacco products. Nonetheless, some participants may experience transient dizziness, headache, nausea and stomach upset following patch application (see Operations Manual for nicotine patch label). To reduce the risk of experiencing these effects, all study participants will be fasted at least 2 hours before administration of study treatment. Treatment of nicotine induced nausea / vomiting is at the discretion of the investigator.

MK-4334 has undergone extensive acute safety testing, both in the clinic and preclinical models. A summary of potential risks can be found in the IB. These risks are expected to be minimal due to the acute (single dose) nature of administration.

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.

This study population consists of healthy adult males and females (WONCBP) and male and female (WONCBP) patients with mild-to-moderate SZ, 18-55 years of age.

Objectives	Endpoints
Primary	
Objective: Record and measure the 40 Hz-ASSR in HC and SZ patients at baseline and determine whether the mean ITC magnitude derived from the 40 Hz-ASSR at baseline is lower in SZ patient than in HC. **Hypothesis**: The mean magnitude of the ITC recorded from SZ patients at baseline will be lower than those recorded from HC at baseline.	ITC magnitude derived from the 40 Hz-ASSR
Secondary	
Objective: Record and measure the DD-MMN in HC and SZ patients at baseline and determine whether the mean MMN magnitude derived from the DD-MMN at baseline is lower in SZ patient than in HC. **Hypothesis**: The mean magnitude of the MMN derived from the DD-MMN recorded from SZ patients at baseline will be lower than that recorded from HC at baseline. **Objective**: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the 40 Hz-ASSR ITC recorded from HC or SZ patients relative to placebo treatment. **Hypothesis**: Pharmacologically relevant plasma levels of nicotine change the mean magnitude of the ITC recorded from HC or SZ patients relative to placebo treatment, with each subject group tested separately.	MMN magnitude derived from the DD-MMN ITC magnitude derived from the 40 Hz-ASSR Plasma nicotine levels at time of ERP recording

Objectives	Endpoints
Tertiary/Exploratory	
Exploratory Objective: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the P3A, MMN or GBO recorded from HC or SZ patients relative to placebo treatment. **Estimation:** Estimate difference between the treatment groups (nicotine vs. placebo) in the mean change from baseline in the magnitude of the P3A, MMN or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately.	P3A, MMN magnitude derived from the DD-MMN Plasma nicotine levels at time of ERP recording Resting GBO magnitude
Exploratory Objective: Determine if pharmacologically relevant plasma concentrations of MK-4334 change the mean magnitude of the 40 Hz-ASSR ITC, the MMN, P3A, or GBO recorded from HC or SZ patients relative to placebo treatment. **Estimation:** Estimate difference between the treatment groups (MK-4334 vs. placebo) in the mean change from baseline in the magnitude of the 40 Hz-ASSR ITC, MMN, P3A or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately. **Exploratory Objective:** To determine intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13). **Estimation:** Estimate intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13). More specifically, mean ITC over time (Days -1, 7, 13) will be summarized and graphically displayed. Pairwise (Day -1 vs. Day 7 or Day -1 vs. Day 13) ICC will be estimated. Scatter plot with diagonal line and Bland-Altman plot will also be presented.	ITC magnitude derived from the 40 Hz-ASSR MMN, P3A magnitudes derived from the DD-MMN Plasma MK-4334 levels at time of ERP recording Resting GBO magnitude

Objectives	Endpoints
Exploratory Objective: To explore the relationship between the genetic variation and response to the treatment(s) administered and mechanisms of disease. Variation in CYP2C19 and across the human genome may be analyzed for association with the clinical data in this study.	Germline genetic variation and association with clinical data collected from this study

4 STUDY DESIGN

4.1 Overall Design

This study is a randomized, double-blind, placebo controlled, cross-over investigation with 2 panels of participants, to be conducted in 2 parts. The 2 panels consist of male and female (WONCBP) HC (Panel A, n = 12) or SZ patients (Panel B, n = 24) who range in age from 18 to 55 years of age, are moderate users of tobacco (≈ 10-15 cigarettes/day) for at least 1 year but are otherwise healthy. ERP/EEG will be recorded from participants in each panel to obtain time-matched baseline data as well as after administering study intervention during each of the 3 treatment periods. In addition, 20 Hz-ASSR will be recorded during all treatment periods to serve as a control for the specificity (eg, psychiatric status and drug effect) of the 40 Hz-ASSR.

In Part 1, participants will be treated with either a nicotine patch + a capsule placebo, or a patch placebo + a capsule placebo in cross-over fashion (Figure 1, Table 1), with a 1 week washout between treatment periods. During Part 2, participants will be randomized for treatment with either MK-4334 + patch placebo, or capsule placebo + patch placebo in a 3:1 active:placebo ratio. Both the participants and PI will be blinded to treatment. The controls will consist of matched, double-dummy placebos for both the transdermal nicotine patch and the MK-4334 DFC. Nicotine is being included as an active control for the effect of nicotinic cholinergic activation on ERPs. Participants will be randomized to the order of treatment in the first part of the study, then randomized again for the receipt of either MK-4334 or placebo in the second part of the study. Each participant will be involved in the study for a total of ≈ 80 days, including screening, intervention, and follow-up phases. In addition to recording the evoked potentials, all participants will undergo safety and PK monitoring during each intervention period and at the post-treatment follow-up. Participant safety will be monitored by recording AEs, measuring VS, recording 12-lead ECGs, conducting lab safety tests, PE and NE.

This study will use the COGNISION® Systems EEG/ERP recording device to measure the EP and ITC components of the 20, 40 Hz-ASSR and the other EEG and ERPs being monitored. Baseline recording sessions (recording 20, 40 Hz-ASSR, DD-MMN, GBO/EEG) will be conducted the day before administration of study interventions and time matched to the recording sessions conducted on treatment days to avoid diurnal variation. During the

Screening Visit, SZ patients and HC will undergo informed consent procedures, a urine drug screen, alcohol breath test, family and medical history, concomitant medications review, physical and neurological exams, and blood sampling for nicotine/cotinine levels. The SZ patient medical history review must confirm a duration of illness of at least 1 year, that they are clinically stable and in the non-acute phase of illness for at least 12 weeks. A review of concomitant medications must show that the SZ patients have been on stable medications for at least 8 weeks. There will be no washout of antipsychotic medications.

The precise timing of ERP recording, ECGs, blood sampling for PK, clinical and hematology labs and/or other procedures may be altered at any time during the study based on newly available data. Similarly, the conditions (eg, electrode placement, auditory stimulus parameters, post dose-recording time) for conducting and recording the ERPs may be altered at any time during the study based on newly available data. Finally, the doses (not to exceed 21 mg nicotine and 250 mg MK-4334) and administration times of either nicotine or MK-4334 may be altered in response to newly available information.

Because this is a Phase 1 assessment of MK-4334 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

A PD biomarker of the action of antipsychotic therapeutics is currently not available. Such a biomarker would greatly aid in determining target engagement, and a safe and potentially effective dose range for an agent under development. Moreover, a PD biomarker may provide insight into the potential efficacy of an agent in a shorter period of time than a proof-of-concept study. Because alterations in glutamatergic neurotransmission are believed to contribute to the pathogenesis of SZ [Coyle, J. T. 2006] and SZ patients commonly self-medicate with nicotine [Glynn, S. M. 1990], [Hughes, J. R., et al 1986], possibly due to its ability to modulate glutamatergic pathways [Fedele, E., et al 1998], this study will evaluate the effects of 2 nicotinic receptor activators on ERP parameters in an exploratory fashion.

4.2.1 Rationale for Endpoints

The purpose of this study is to characterize the utility of the 40 Hz-ASSR as a pharmacodynamic biomarker. To this end, the primary objective of the study is to validate the ability of the COGNISION® ERP recording system to differentiate between HC and SZ patients on the basis of the difference in magnitudes of the ITC of the 40 Hz-ASSR. Additional endpoints to be explored include monitoring the ability of two pharmacologic treatments known to enhance glutamatergic neurotransmission by activating specific

nicotinic cholinergic receptors in the brain to modulate ERP magnitude (P3A, MMN and ITC) and EEG parameters (resting γ-EEG).

4.2.1.1 Efficacy Endpoints

Not Applicable

4.2.1.2 Safety Endpoints

The safety and tolerability of MK-4334 and nicotine when administered as single doses will be monitored throughout the study by collecting the following safety endpoints: direct assessment/reporting of AEs; physical exams; C-SSRS endpoints; supine and orthostatic VS measures (SBP, DBP, HR, RR, BT); 12-lead ECG parameters; and laboratory safety tests (serum chemistry, hematology, and urinalysis).

ECG and VS monitoring (Section 8.0) will be scheduled prior to starting treatment on each intervention day, in proximity to the times when steady state plasma levels of nicotine (2 hours post application, C2) and MK-4334 (4 hours post administration, C4) have been achieved, but before ERP recording, and after completing all recording procedures (Figure 2).

The C-SSRS prospective assessment of suicidal ideation and behavior will be included in this study in compliance with the 2012 FDA guidance requiring prospective assessment in clinical trials conducted under IND applications and trials that are intended for submission in a NDA to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in trials 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). The Baseline/ Screening version of the C-SSRS will be administered at screening, while the Since Last Assessment version of the C-SSRS/SLA will be given at several points during and after intervention administration to all subjects enrolled, including at the Post-trial visit (see Section 8.0).

4.2.1.3 Pharmacokinetic Endpoints

Blood samples will be taken at approximately C2 for nicotine and prior to ERP recording for the determination of plasma concentrations of nicotine following the administration of nicotine/placebo. This reflects the approximately 2 hours it takes for nicotine levels to achieve steady state when using a topical patch [Rasmussen, S., et al 2018]. Plasma MK-4334 levels will be determined in samples taken at approximately C4 after administration of MK-4334/placebo and prior to ERP recording. While the Tmax for MK-4334 ranges from 2 to 24 hours, the 4 hour post-dose sampling time approximates the achievement of steady state plasma levels and is of reasonable time post-dose to accommodate study procedures within the treatment day (refer to MK-4334 IB for more information). Plasma concentrations of nicotine and MK-4334 will be correlated with the magnitude of the effect on ERP parameters to validate that any changes observed in the ERP are associated with pharmacologically significant plasma levels of the agents. Any plasma remaining from the MK-4334 samples will be retained for future use.

Samples taken at screening and prior to intervention administration for measures of plasma nicotine and cotinine levels will be used for monitoring nicotine consumption outside of the study parameters over the previous 2 and 30 hours [Hill, P., et al 1983].

4.2.1.4 Pharmacodynamic Endpoints/Biomarkers

All EEG/ERP assessments will be performed using the COGNISION® System. The COGNISION® System has been approved by the FDA for clinical use, 510(k): K141316. The system is a general-purpose EEG/ERP system composed of an electrode cap, which records from 7 active electrode channels, a battery powered headset control unit (HCU) with integrated response capture buttons, and medical grade insert earphones. The active electrodes are electrically coupled to the scalp using pre-gelled HydroDot® Biosensors. All study-related information is stored on the system's online database hosted in the Microsoft Azure environment.

During the EEG/ERP testing session, the participant will be seated comfortably in a chair facing a table on which a computer monitor is placed. The COGNISION® Headset is applied and a disposable chinstrap is secured to hold the Headset in place. The Biosensors are then inserted in each of 10 electrode pod locations. The Biosensors will not be used during the audiometry and tone-matching tests conducted at the Screening Visit (See Section 8.3.6 for a description of these screening tests). The participant is then asked to hold the handset and place the thumb on their dominant hand on one of the action buttons on the handset. Upon completion of the instructions, insert earphones with disposable tips are placed in their ears. The participant is now ready to begin the testing session. The COGNISION® system will be used to conduct and record the ERPs described below. Additional information on the stimulus/recording parameters can be found in the Operations Manual.

4.2.1.4.1 Passive, Duration-Deviant, Mismatch Negativity ERP

In this paradigm, 2 tones of the same frequency and sound intensity, one of short duration (Standard) and one of either shorter or longer duration than the standard (Deviant) are sequentially presented to the participant through insert earphones. The Standard stimuli are presented more often than Deviant stimuli. While the auditory stimuli are being presented to the participant, they are instructed to watch a short cartoon video on a computer monitor positioned in front of them. The sound on the video is turned off. The participant is asked to abstain from performing any tasks while watching the video. The testing session lasts approximately 12 minutes (Figure 2). Characteristics of the stimulus are provided in the Operations Manual.

4.2.1.4.2 20, 40 Hz-Auditory Steady State Responses

In this paradigm, a short stream of clicks is repeatedly presented to the participant through insert earphones (see Operations Manual). While the clickstreams are being presented, the participant is instructed to fix their gaze on a white cross displayed on a computer monitor positioned in front of them. The participant is asked not to perform any task while watching the video.

As a control for the specificity of the ASSR responses to the disease state, two sets of tone stimuli will be administered, the standard, 40 Hz tone and an additional 20 Hz tone [Light, G. A., et al 2006]. The magnitude of the ITC in response to the 40 Hz tone should be reduced in SZ patients relative to HC, while the magnitude of the ITC in response to the 20 Hz tone should be the same in both HC and SZ participants.

Each testing session will last approximately 4 minutes.

4.2.1.4.3 Resting EEG

In this paradigm, the subject is asked to close their eyes and relax while γ-band EEGs are recorded. This testing session lasts approximately 6 minutes.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

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

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

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

In addition to studying variation across the human genome, polymorphisms of CYP2C19 will be specifically investigated. MK-4334 is oxidized by CYP2C19. Participants with certain allelic variants of the CYP2C19 gene have been shown to have alterations in MK-4334 metabolism, resulting in changes in systemic exposures. Therefore, the relationship between CYP2C19 polymorphisms identified in participants tested at screening and the plasma levels of MK-4334 and other clinical endpoints will be explored.

4.2.1.6 Future Biomedical Research

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

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 that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Placebos for both nicotine and MK-4334 will be used to maintain study blinding and reduce bias. A crossover design will be used for nicotine/pbo interventions in Periods 1 and 2, allowing each participant to serve as their own control. A randomized allocation of participants to either MK-4334 or pbo (3:1) will be used in Period 3, allowing within-period comparison of the mean active intervention group response to that of pbo. Because of the different routes of administration of nicotine (topical) and MK-4334 (oral), this study is designed to use placebos for both the active comparator (nicotine patch) and the active intervention (MK-4334 capsule). To maintain participant blinding, both placebos will be administered throughout all periods of the study

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

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

4.3 Justification for Dose

All participants in this study will be treated with a nicotine patch of 21 mg dose strength (NicoDerm CQ, GSK) [U.S. User's Guide 2006]. This formulation releases the nicotine equivalent of approximately 15 cigarettes per day and is known to be safe and well-tolerated. Moreover, this dose strength has been shown to alter evoked potentials, including the mismatch negativity, while lower dose strengths do not have as consistent an effect on evoked potentials [Knott, V., et al 1999], [Inami, R., et al 2005].

MK-4334 will be administered to a subset of participants as a single dose of 250-mg. A preclinical model of cognitive impairment (rhesus object retrieval) indicates that a plasma level of MK-4334 = CCI was minimally efficacious in improving cognitive function. Because efficacious dose levels of MK-4334 have not been determined in humans, and the plasma PK is highly variable, a 100-fold multiple beyond this plasma level CCI has been targeted as a potentially efficacious exposure level (C24). This plasma concentration

has been obtained in several clinical studies at the 250 mg dose level. This dose is associated with exposures CCI approximately ≈ CCI below the rat NOAEL exposure cap (37.5 µM·hr) established in preclinical toxicology studies (See the IB for additional information on preclinical safety and PK).

The MK-4334 dose chosen for this trial is supported by favorable tolerability. Previous studies of single oral doses of MK-4334 up to 300 mg administered to healthy adults (MK-4334-002) indicated that the 250 mg dose is well-tolerated. There were no dose-limiting tolerability issues and no pattern of drug-related AEs other than headache, diarrhea and/or abdominal pain of mild-to-moderate intensity observed with doses up to 300 mg. There were no SAEs and no participants discontinued from study MK-4334-002 due to an AE. MK-4334 will be administered as an adjunct to the antipsychotic therapy that the SZ participants are already receiving. Based on clinical and non-clinical experiences, its mechanism of action CCI its metabolism (primarily via CYP2C19), and the duration of treatment (single dose), no impact of MK-4334 on the PK, PD, safety or tolerability of any antipsychotics approved for administration in this investigation are expected. Please refer to the MK-4334 IB for additional information on clinical studies of MK-4334.

As this is a Phase 1 assessment of MK-4334 in humans, and the PK, PD and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.4 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 (ie, the participant is unable to be contacted by the investigator).

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

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements,

procedure-related problems or the number of discontinuations for administrative reasons is too high. Otherwise, there are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy control male and female (WONCBP) participants between the ages of 18 to 55 years (inclusive) will be enrolled in this study.

Male and female (WONCBP) patients with SZ of mild to moderate severity who are otherwise healthy, between the ages of 18 to 55 years (inclusive) will also be enrolled in this study.

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

Healthy Control (HC) Participants

1. Be judged to be in good health based on medical history, physical examination, VS measures and ECG performed prior to randomization. Section 10.8, Appendix 8 provides a table of 12-Lead ECG Abnormality Criteria.

2. Be judged to be in good health based on laboratory safety tests (Section 8.3.5) obtained at the screening visit.

    - Participants with chronic medical conditions, including but not limited to hypertension, hyperlipidemia, diabetes (Type 1 or 2) or hypothyroidism, which have been well-controlled on a stable dose of medication for the past two months and who are not receiving any proscribed medications for intervention may be enrolled if clinically acceptable to the investigator and Sponsor.

    - Appendix 9 provides an algorithm for the assessment of out-of-range laboratory values

3. Has no history or evidence of clinically relevant neuropsychiatric illness.

4. Is fluent in English, even if English is not their primary language.

5. Has a BMI $\geq$ 18 and $\leq$38 kg/m^2, inclusive for HC and SZ participants. See Section 8.3.3 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

6. Is a mild-to-moderate tobacco user of at least 1-year duration, smoking the equivalent of approximately 10-15 cigarettes/day, as reflected in plasma cotinine levels > 100 ng/mL [Patterson, F., et al 2003], [Hill, P., et al 1983].

SZ Patients

7. Have a current diagnosis of schizophrenia. Enrolled patients should have the following PANSS scores: Delusions (item P1) score ≤ 4; Hallucinations (item P3) score ≤4; Unusual thought content (item G9) score ≤4; Conceptual disorganization (item P2) score ≤4. Total PANSS scores should be ≤ 80, consistent with a diagnosis of "mild to moderate" illness [Leucht, S., et al 2005]. Patients should be judged competent to complete all study procedures in the estimation of the investigator.

8. Duration of schizophrenia illness ≥ 1 years.

9. Clinically stable and in the residual (non-acute) phase of their illness for at least 12 weeks prior to the study.

10. Stably maintained on a regimen of up to 2 first or second-generation antipsychotics with no dose changes over 50% in combination with concomitant medications commonly prescribed to this patient population for at least 8 weeks prior to screening and during the study may be included (see Allowed Medications List and Table 4).

11. Fluent in English, even if English is not the primary language.

12. Is currently a mild-to-moderate tobacco user of at least 1 year duration, smoking the equivalent of approximately 10-15 cigarettes/day, as reflected in plasma cotinine levels > 100 ng/mL [Patterson, F., et al 2003], [Hill, P., et al 1983].

Demographics

13. Is male or female (WONCBP) from 18 years to 55 years of age inclusive, at the time of signing the informed consent.

Male Participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days/weeks after the last dose of study intervention:

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

Female Participants

A female participant is eligible to participate if:

- She is a WONCBP, as defined in Appendix 5.

Informed Consent

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

Additional Categories

15. Is a smoker and is willing to comply with restrictions on the use of nicotine or nicotine-containing products (eg, nicotine patch, gum, e-cigarettes or any form of tobacco) during the study.

16. Understands study procedures and is willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.2 Exclusion Criteria

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

Medical Conditions

Healthy Control Candidates

1. Known (identifiable) biological family history of psychotic disorder in a first or second degree relative.

SZ Candidates

2. If there is a failure to confirm a diagnosis of schizophrenia by the Investigator based on the MINI Screen or pharmaceutical treatment history.

3. They have more than a moderate severity rating on delusions as evidenced by a PANSS item P1 score > 4

4. They have more than a moderate severity rating on hallucinations and delusions as evidenced by a PANSS score on item P3 > 4

5. They have more than a moderate severity rating on positive formal thought disorder as evidenced by a PANSS item G9 > 4 or item P2 > 4.

6. They have a total PANSS score > 80.

7. They have a minimal level of depressive symptoms as evidenced by a CDSS score ≥ 11.

All Candidates

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

9. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. SZ patients must be excluded if they report suicidal ideation or behavior with intent, with or without a plan or method (eg, positive response to items 4 or 5 in the assessment of suicidal ideation of the C-SSRS) in the past 1 year prior to the Screening Visit. For HC, there should be no positive responses to items 3, 4, or 5 in the past 2 years.

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

11. Evidence of cognitive impairment as determined by performing ≥ 1.5 standard deviations lower compared to the age corrected mean on either the BACS Symbol Coding and/or Verbal Memory.

12. Significant intellectual disability as evidenced by a standardized WRAT-5 Reading Test standardized score ≥ 1.5 standard deviations lower compared to the age corrected mean.

13. Unable to tolerate the electrode cap for the duration of the recording session (≈ 30 min).

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

15. Has a history of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

16. Has a history of cancer (malignancy). Exceptions: Adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix or other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥10 years prior to the pre-study [screening] visit).

17. Participant has an estimated [eGFR ≤60 mL/min/1.73 m^2] at the screening visit, with one recheck if requested by the Investigator. The eGFR may be calculated based on the CG Equation.

Cockcroft-Gault Equation:

$$CrCl = \frac{(140\text{-age[yr]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

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

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

For females, multiply the result by 0.85.

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

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

Prior/Concomitant Therapy

18. Is unable to refrain from or anticipates the use of any non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives, whichever is longer) prior to administration of the initial dose of study intervention, and throughout the study (including washout intervals between treatment periods) until the poststudy visit. Sedative medications prescribed while participants are inpatients are allowed so long as they have not been administered within 12 hours of any EEG recording periods (see Section 6.5, Table 4). All medications being taken by candidates for enrollment in the study should be reviewed by the PI and the Sponsor to determine their propensity for altering MK-4334 exposure, or for MK-4334 to interfere with the metabolism of the medication. Medications prescribed for the candidate that are stably treating a condition should not be interrupted. Candidates should not be enrolled if they are taking clopidogrel (which requires CYP2C19 for activation), fluoxetine (> 40 mg qd), , citalopram/escitalopram or proton pump inhibitors which may inhibit CYP2C19. Enrollment of candidates taking prescription drugs that can alter QTi for an underlying condition (including anti-arrhythmics [quinidine, procainamide, disopromide, dofetilide,

sotalol] and antimicrobials) should be avoided. See Table 4 and Section 8.1.5 for more examples of excluded agents.

19. Use of any first generation, sedating H1 antihistamines within 12 hours of an EEG recording period. (see Medication Approval List)

20. Use of any sedative-hypnotic medications within 1 week prior to Screening or during the study. (see Medication Approval List)

21. Use of any other psychoactive medication known to interfere with ERP assessments within 1 week prior to Screening or during the study. (see Medication Approval List)

Prior/Concurrent Clinical Study Experience

22. Has participated in another investigational study within 6 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

23. Has a CYP2C19 genotype consistent with a poor metabolizer phenotype.

24. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

25. Any candidate unable to detect a 1000 and 2000 Hz tone at 40 dB in both ears is not eligible for enrollment.

Other Exclusions

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

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

28. Is a regular user of any illicit drugs or has a history of substance (including alcohol) use disorder per the DSM-5 (confirmed with MINI) within approximately 2 years. Cannabis use is not permitted within 4 weeks of randomization. Participants must have a negative DS prior to randomization and on Days -2, 6, and 13.

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

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, including but not limited to laboratory safety evaluations, are specified below.

Participants will fast from all food and drinks, except water, for at least 2 hours after administration of study intervention. After the post-dose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each treatment day in each panel.

Study interventions will be administered approximately 1-2 hours after breakfast. Water will be provided during study drug administration, with the restrictions noted above. Additional water will be restricted up to 1 hour after study drug administration.

Each study drug administration will need to be taken with at least 240 mL (not to exceed 500 mL) of water.

Labs will be collected nonfasting.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study including the washout interval between treatment periods and until the post-study visit.

On treatment days, participants will refrain from the consumption of all fruit juices 8 hours prior to study drug administration and 2 hours following the morning dose.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 8 hours prior to the pre-study (screening) and post-study (exit) visits. Participants may have 1 caffeine/xanthine containing beverage no later than 1 hour before the recording of VS/ECG prior to the baseline recording session. No caffeine/xanthine containing beverages are allowed until completion of the recording sessions. Outside of these

restricted periods, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (>6 units: 1 unit = 120-mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the pre-study and post-study visits and while domiciled at the CRU.

At all other times during the study (screening to post-study visit), alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted within 4 hours of study treatment dosing and for the duration of recording on treatment days (Days 1, 8, and 15), and within 4 hours of baseline recording (Days -1, 7, 14).

5.3.3 Activity Restrictions

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

If a participant 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 including 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 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
A, B (HC, SZ)	Experimental Comparator	Nicotine	Drug	Patch	21 mg	21 mg	Dermal Patch	Single Dose	Test Product	NIMP/ AxMP	Provided locally by site
A, B (HC, SZ)	Experimental Comparator	MK-4334	Drug	Capsule	250 mg	250 mg	Oral	Single dose	Test Product	IMP	Provided centrally by Sponsor
A, B (HC, SZ)	Placebo Comparator	Placebo to nicotine patch	Placebo	Patch	N/A	0 mg	Dermal Patch	Single dose	Placebo	NIMP/ AxMP	Provided locally by site
A, B (HC, SZ)	Placebo Comparator	Placebo to MK-4334	Placebo	Capsule	N/A	0 mg	Oral	Single dose	Placebo	IMP	Provided centrally by sponsor

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

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.1.1 Medical Devices

Other medical device(s) (not manufactured by or for the Sponsor or licensed by the Sponsor) provided for use in this study are: COGNISION® Systems. Refer to Appendix 4 for reporting of events associated with these devices.

Instructions for medical device use are provided in the Operations Manual.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule. Treatment groups are outlined in Table 3.

Table 3 Treatment Allocation.

	Part 1		Part 2
N	**Period 1**	**Period 2**	**Period 3**
n = 6 HC n = 12 SZ	21-mg nicotine patch MK-4334 capsule placebo	Nicotine patch placebo MK-4334 capsule placebo	
n = 6 HC n = 12 SZ	Nicotine patch placebo MK-4334 capsule placebo	21-mg nicotine patch MK-4334 capsule placebo	
n = 9 HC n = 18 SZ			250-mg MK-4334 Nicotine patch placebo
n = 3 HC n = 6 SZ			MK-4334 capsule placebo Nicotine patch placebo

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-4334, nicotine comparator and patch and capsule placebos will be packaged so that the blind is maintained (see dosing instructions in Operations Manual). The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

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

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 the ongoing study (ie, after randomization or intervention allocation) 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.

Exceptions include medications prescribed while participants are inpatients are allowed so long as they have not been initiated within 12 hours of any EEG recording period.

CYP2C19 contributes to the oxidative metabolism of MK-4334, which may be impacted by the presence of inducers, inhibitors, or high levels of substrates for CYP2C19. Therefore, any agents known to induce, inhibit or be metabolized by CYP2C19 should be avoided as prior or concomitant medications for any study participants due to their potential for altering systemic exposure to MK-4334. In addition, many other drugs can elicit changes in the ERP endpoints regardless of any underlying pathology. Therefore, any prescribed medications used to stably treat a screening candidate or enrollee should be evaluated by the investigator in cooperation with the Sponsor to determine its propensity to interact with MK-4334 in any way, or to non-specifically alter the ERP before either altering the treatment or enrolling the candidate. A representative list of concomitant medications to be avoided is found in Table 4.

Table 4 List of Restricted Medications

Medication	Use by Panel	
	HC	**SZ**
	Illicit Drugs (from DS)	
Amphetamines Cocaine Opioids (including Buprenorphine) PCP Benzodiazepines Barbiturates	Not allowed	Not Allowed
Cannabis	No use within 4 weeks of screening or study visits	No use within 4 weeks of screening or study visits
	First- or second-generation antipsychotics or other medications commonly prescribed for SZ	
Risperidone Clozapine Quetiapine Olanzapine Aripiprazole Paliperidone Ziprasidone Lurasidone Haloperidol Chlorpromazine Loxapine Fluphenazine Perphenazine	Not allowed	Up to 2 with no dose changes over 50% during course of study Clozapine not allowed (CYP2C19 substrate)
	First-generation, sedating H1 antihistamines	
Diphenhydramine Carbinoxamine Clemastine Chlorpheniramine Brompheniramine	No use within 12 hours of EEG recording periods	No use within 12 hours of EEG recording periods
	Sedative-hypnotics and anxiolytics	
Secobarbital Pentobarbital Triazolam Eszoplicone Zaleplon Diazepam Chlordiazepoxide Lorazepam Alprazolam Bromazepam Clorazepate Flurazepam	No use within 1 week of screening or study visits	No use within 1 week of screening or study visits. The short duration benzodiazepine Lorazepam 1 mg prn is allowed for inpatient use if prescription is not initiated within 12 hours of EEG recording session.

Medication	Use by Panel	
	HC	**SZ**
Other Psychoactives		
Glutamatergics: Ketamine Amantadine Dextromethorphan Memantine Methadone Dextropropoxyphene Ketobemidone Glycine N-Acetylcysteine Riluzole	Not allowed	Not allowed
Anticholinergics Benzhexol Benztropine Biperiden Orphenadrine Procyclidine Scopolamine Trihexylphenidyl	Not allowed	Not allowed
Antidepressants Sertraline Fluoxetine Citalopram Escitalopram Paroxetine Fluvoxamine Doxepin Clomipramine Bupropion Amoxapine Nortriptyline Duloxetine	Not allowed	Not allowed
Anticonvulsants Acetazolamide Clobazam Clonazepam Ethosuximide	Not allowed	Not allowed
Mood stabilizers Lithium Valproate Topiramate Oxcarbazepine Lamotrigine Carbamazepine Gabapentin	Not allowed	Not allowed

Medication	Use by Panel	
	HC	**SZ**
Neuropathic Pain Analgesics Pregabalin	Not allowed	Not allowed
Psychostimulants Methylphenidate Dexmethylphenidate Lisdexamfetamine Dextroamphetamine	Not allowed	Not allowed
Agents Interacting with CYP2C19		
Inhibitors Clopidogrel Felbamate Proton pump inhibitors Probenecid Phenylbutazone Ticlopidine Efavirenz Isoniazid Ketoconazole Voriconazole Eslicarbazepine Oxcarbazepine Topiramate Methimazole Modafanil	Not allowed	Not allowed
Inducers Carbamazepine Norethisterone Prednisone Rifampin	Not allowed	Not allowed

Medication	Use by Panel	
	HC	**SZ**
Substrates Labetalol Verapamil Nelfinavir Quinine Terbinafine Voriconazole Amitriptyline Citalopram, escitalopram Clomipramine Diazepam Imipramine Milnacipram Trimipramine Carisoprodol Tofacitinib Clobazam Trazodone Propranolol Progesterone Tolbutamide	Not allowed	Not allowed
Homeopathics, OTC compounds		
St John's wort Artemisinin Ginseng Cassia Licorice (glycyrrhizin) Ginkgo Epimedium DHA/EPA (Omega-3 dietary supplements)	No use within 1 week of screening or study visits	No use within 1 week of screening or study visits
Alcohol	Use limited per protocol	Use limited per protocol
Nicotine	No use 4 hrs before baseline recording	No use 4 hrs before baseline recording

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

Reason for use

Dates of administration including start and end dates

Dosage information including dose and frequency

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

Rescue medications/supportive care may be administered by the investigator as necessary, in consultation with the Sponsor.

6.6 Dose Modification (Escalation/Titration/Other)

Not applicable. Only single, fixed doses of either study treatment are being administered in the study.

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 safety data available. The study may continue with joint agreement of the Sponsor and investigator.

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.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study. If a participant feels abnormal after conclusion of their participation in the study/completion of the study follow up exam, the PI should advise the participant to see their primary physician.

6.8 Clinical Supplies Disclosure

This study is blinded, but supplies are provided open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention

identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are [not]provided.

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

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 regimen 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 positive UDS at any time during the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor. For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

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.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes

provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

The maximum amount of blood collected from each participant over the duration of the study will not exceed 500 mL (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

Inclusion and exclusion criteria are listed in sections 5.1 and 5.2. The following are screening measures that are being used for this study.

All HC and SZ candidates will undergo audiometric testing to establish their ability to hear the 20 Hz and 40 Hz auditory stimuli

Audiometry: In this test, a series of short-duration tones will be played in each ear through insert earphones at increasing sound intensity and then decreasing sound intensity. The participant is instructed to press a button on the handset whenever they hear a tone in either ear.

Tone-Matching: In this test, pairs of short-duration tones will be presented to the participant through insert earphones. The participant is instructed to press a button on the handset whenever they think the tones are the same frequency.

Psychometric assessments to be used at screening include the following:

WRAT-5: Parts 1 and 2 (Word Reading and Letter Reading) of the WRAT-5 Reading Test are quick measures of fundamental academic skills, helpful in evaluating learning disabilities. This test is performed to ensure that all study subjects are not intellectually impaired which could inadvertently bias the EEG/ERP test results. Evidence of intellectual impairment in HC, as indicated by scoring ≥ 1.5 standard deviations lower compared to the age corrected mean standard score is exclusionary.

MINI Screen 7.0.2: The MINI is a short, structured clinical interview that enables researchers to confirm a diagnosis of schizophrenia in SZ subjects. This test meets the criteria of the 5th edition of the DSM-5

BACS: The BACS is an instrument that assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia: verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency. The BACS will be administered to HC participants and SZ patients. Potential cognitive impairments in HC participants will be assessed with the Symbol Coding and Verbal Memory domains of the BACS. The BACS requires less than 35 min to complete in patients with schizophrenia, yields a high completion rate in these patients, and has high reliability.

In addition to the above to be administered to both SZ and HC candidates, SZ patients will undergo the following confirmatory tests:

CDSS: The CDSS is a rating scale used to assess the level of depression in schizophrenia. It is the only depression scale designed for the assessment of depression in schizophrenia and it differentiates between depression and the negative and positive symptoms of schizophrenia.

The PANSS will be administered to SZ candidates at screening, and to SZ patients enrolled in the study during the intervention period to monitor the status of their condition:

PANSS: The PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia and is widely used in the study of antipsychotic therapy. Positive symptoms refer to an excess or distortion of normal functions (eg, hallucinations and delusions), and negative symptoms represent a diminution or loss of normal functions. The PANSS is a relatively brief interview, requiring 45 to 50 minutes to administer and will be performed to correlate with the EEG/ERP test results.

CYP2C19 Genotyping: Evidence from human hepatocytes in vitro indicates that CYP2C19 is responsible for approximately 50% of the metabolism of MK-4334 (see MK-4334 IB). Therefore, systemic exposures to MK-4334 may increase by as much as 2- fold in participants with a CYP2C19 poor metabolizer phenotype. To avoid excessive exposure to MK-4334 and any attendant safety issues, participants will be screened for CYP2C19 genotypes consistent with the poor metabolizer phenotype. Any participant expressing a CYP2C19 poor metabolizer genotype will be excluded from 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.

Participants will be administered 2 cards during the study. The initial card will be provided at the time of informed consent and will be updated with the Part 1 randomization number.

Participants will return the original card and be issued a new card at the start of Part 2 which will include the new randomization number for Part 2.

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 prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 4 weeks or 5 half-lives before the screening visit. Any medications necessary for keeping a candidate stably treated for an underlying condition should be reviewed by the PI for potential interference with/by the study medication (eg, CYP2C19 inhibitors) and brought to the attention of the Sponsor for mutual agreement on whether to enroll the candidate in the study (Section 6.5).

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 allocation/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 initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.7 Assignment of Randomization Number

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

Participants will each receive a randomization number for Part 1 and will be re-randomized with a new randomization number for continuation in Part 2.

8.1.8 Study Intervention Administration

Study intervention should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

The nicotine patch/matching placebo patch should be applied at approximately the same time for Periods 1 and 2, after completion of all pre-dosing procedures (eg, AE report, ECG, VS, blood sampling, (Figure 1). Approximately 2 hours after patch application, post dosing procedures may commence, followed by ERP/EEG recordings. After all recordings are obtained, post-recording safety monitoring will be conducted. Upon completion of all the safety monitoring procedures are completed, the patches will be removed, and the participant allowed to exit the facility (approximately 3-4 hours after patch application). Patch disposal procedures are outlined in the Operations Manual.

Study treatment will be provided with matching placebos: Nicotine patch/matching placebo patch; MK-4334/matching capsule placebo. MK-4334/placebo capsules will be administered orally with at least 240 mL (not to exceed 500 mL) of water upon completion of all pre-dose procedures for that day, with administration of study medication witnessed by the investigator and/or study staff. Participants will not be allowed access to food for 2 hours after dosing. The nicotine patch/matching placebo patch should be applied prior to oral administration of MK-4334/matching placebo capsules.

8.1.8.1 Timing of Dose Administration

In Periods 1 and 2, the nicotine or placebo patch will be applied in the morning at approximately the same time every day after completion of all pre-dose procedures. Similarly, MK-4334 or placebo will be administered in the morning at approximately the same time and upon completion of all pre-dose procedures (Section 8.1.8). The time of administration of study treatment will constitute Time “0” for initiation of subsequent study events. All capsules will be distributed and consumed with water within 10 minutes of the recorded administration time. Participants will remain resting in bed in a semi-recumbent position for approximately 1 hour after dosing. Ancillary procedures (AE reports) may occur during this period. Blood samples for PK measures should be taken close to steady state (C2 or C4 hrs post-nicotine or MK-4334 dosing, respectively). ERP recording and related activities will commence after the last ancillary procedure is completed, either 2 (nicotine/pbo) or 4 (MK-4334/pbo) hours after dosing. During the intervening period, the participant is free to ambulate. Refer to Figure 2 for relative timing of events during treatment periods and the Operations manual for further guidance.

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 or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days

described in Section 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

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

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

8.1.11 Domiciling

Participants will report to the CRU on Days -2, 6, and 13 for domiciling (2 overnights per study part, for a total of 6 overnight stays). Participants will remain in the unit until all recordings and post-dose procedures have been completed on the day of treatment. At the discretion of the investigator, participants may be requested to remain in the CRU longer. Decisions on how to monitor the participant during any post-treatment stays will be at the discretion of the investigator after discussion with the Sponsor.

8.1.12 Calibration of Equipment

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

8.2 Efficacy Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.7.

8.3 Safety Assessments

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

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

8.3.1 Complete Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at screening and at poststudy. 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 Symptom Driven Physical Examinations

A symptom driven physical examination will be conducted upon domiciling only if participant symptoms warrant an exam or at the investigator's discretion. The symptom driven physical should be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard, specifically targeting any areas for which there are symptoms of concern.

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

8.3.4 Vital Signs

Oral or temporal artery temperature will be assessed. Whatever method for measuring BT is settled on by the site should be used throughout the study.

PR, RR, and BP will be assessed.

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

BP and HR measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

VS to be taken before blood collection for laboratory tests will be measured in a supine position after 10 minutes rest and will include temperature, systolic and diastolic BP, HR, and RR.

8.3.4.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The HR and BP measurements will be taken in triplicate before recording on Day -2 only. These measures will be obtained at least 1-2 minutes apart. The mean of these measurements will be used as the baseline to calculate the change from baseline for safety evaluations and rechecks, if needed. On all other days indicated in the SoA (See Section 1.3), pre-dose HR and BP will be single measurements. Post-dose VS measurements will be single measurements unless there is an out-of-range reading. In this case, at least three measures of VS (either resting or orthostatic HR, BP) will be taken within a 15-minute period, or until readings fall into normal range.

Participants will continue to rest in a semi-recumbent position from dosing until 1 hour post-dose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedures.

Body Temperature

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

8.3.4.2 Orthostatic Vital Signs

Orthostatic VS (HR, SBP, DBP) will be obtained. Participants should be supine for at least 10 minutes and then stand upright. Measures of orthostatic VS will be taken after 1 min and 3 min of standing.

8.3.4.3 Electrocardiograms

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

When triplicate ECGs are requested, 3 individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

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

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

The correction formula to be used for QTc is Fridericia.

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

During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a post-dose ECG, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval is ≥500 msec, the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the QRS duration from any post-dose ECG is 20% greater than the mean baseline QRS duration and is >120 msec (and change is not considered rate related or pacing induced) or there appears to be new onset intermittent bundle branch block, then the ECG will be immediately repeated twice within 5 minutes. The mean value of the QRS interval from the 3 ECGs will represent the value at that time point. If the mean QRS interval increase from baseline for any post-dose time point is >20%, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

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

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

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

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

8.3.5 Clinical Safety Laboratory Assessments

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

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

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

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

For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Pregnancy Testing

Pregnancy testing is not required as only WONCBP will be enrolled in this study.

8.3.7 Suicidal Ideation and Behavior Monitoring

8.3.7.1 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 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.

8.3.8 Photograph of Rash

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

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/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 allocation/randomization through 28 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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

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

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

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

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

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are WONCBP or males and partner pregnancy/lactation information is not required.

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. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X 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 and/or suicidal behavior. A supplemental document will be provided that contains guidance for additional information to be collected and reported for these events (Appendix 11).

8.4.8 Medical Device and Drug-device Combination Products - PQCs/Malfunctions

The method of documenting and reporting of such events [Complaints associated with medical devices including PQCs/malfunctions] will occur as below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

PQCs/malfunctions including those that involve a participant or any user/associated person must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the medical device or device constituent of combination product.

8.5 Treatment of Overdose

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for MK-4334 Determinations

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

8.6.2 Blood Collection for Plasma Nicotine Determinations

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

8.7 Pharmacodynamics

N/A. See Section 8.8.

8.8 Biomarkers

The PD parameters to be collected in this study are surrogate biomarkers of pharmacological activity. They are electrophysiological in nature and are derived from the ERP tests conducted at a specified time after treatment (see Section 4.2.1). No active responses are required by the participant to these auditory stimuli. Collection of samples for other

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

Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C19 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C19. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

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

8.9 Future Biomedical Research Sample Collection

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

Leftover main study plasma from MK-4334 assay will be stored for future research

Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Screening

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

Participants may be rescreened after consultation with the Sponsor. Rescreening should be conducted if more than 35 days have elapsed between the participant's initial screening and planned randomization. Rescreening should include all screening procedures listed in the SoA, including consent review. However, repeating the CYP2C19 genotyping is not required if the previous results remain in the participant's record. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol. All results of screening 2 should be entered in Inform.

8.10.2 Treatment Period Visit

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

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.10.4 Poststudy

Participants will be required to return to clinic approximately 28 days after the last dose of study intervention for the poststudy visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

The relative timing of procedures can be found in Figure 2 and the Operations Manual. For this study, the time of administration of study treatment is the critical procedure. The time of administration will be T0 on the day of treatment. All other procedures will be conducted in relation to T0.

Pre-dose blood samples for either nicotine or MK-4334 can be taken within 1 hour of dosing. The post-dose blood sample for MK-4334 needs to be collected as close to the C4 (4 hours post-dose) as possible, but before recording. Similarly, the post-dose blood sample for nicotine needs to be collected as close to the C2 as possible, but before recording. Post-recording blood samples should be collected within 30 minutes of finishing all recording procedures, ECGs, and VS measures. 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, within the windows outlined below.

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.

Screening 2 procedures: up to additional 4 hours of scheduled time

PK Collection as outlined in Table 6.

Table 6 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
1 to 6 h (postdose)	30 min

The baseline ERP recording will commence after breakfast and all pre-recording procedures are completed. Study-treatment related ERP recordings will commence approximately 2 or 4 hours after administration of nicotine/pbo or MK-4334/pbo, respectively, with a window of ±

30 min. The timing of recordings should follow the sequence laid out in Figure 2, Relative Timing of Procedures During Each Treatment Session (Period).

Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam

- Prior to 24-hours postdose may be obtained within 30 minutes of the theoretical sampling time
- From 48-hours to 168-hours postdose may be obtained within 2 hours of the theoretical sampling time

Note: Visit windows defined by +/- X day(s) refers to calendar days.

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

This is a Phase 1 assessment of MK-4334 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel
- Modify the ratio of active:placebo treated subjects in part 2.
- Entire period(s) or panel(s) may be omitted
- Changes in the relative timing/duration of psychometric testing, blood sampling, VS, ECG, and ERP recordings.
- Changes in the timing of the tobacco and caffeine washouts.
- Lengthening of the washout period
- Instructions to take study intervention with or without food or drink may be modified based on newly available data
- Modification of the PK sample processing and shipping details based on newly available data
- Changes to the time intervals between dosing and ERP recording.

If it is determined that incomplete or aberrant data has been captured during the ERP recordings at any post-randomization study visit, the participant may be asked to repeat the treatment period. The evaluation to determine whether the treatment period is to be repeated will be performed on an individual basis per participant, and the decision will be reached by mutual agreement of the Sponsor and investigator. Up to 2 treatment periods per participant may be repeated. Repeating treatment periods may result in an increase in the total blood volume sampled, with 50 mL per repeated period. The resulting exposure and blood volume increases will be deemed acceptable by the Sponsor and investigator for that participant. The total blood volume should remain <500 mL. If there are >2 failed treatment periods for a certain participant, the participant may be discontinued from the study intervention and replaced.

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

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

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

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a summary of the statistical analyses for this trial. Full details can be found in the subsequent sections.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department.

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

9.3 Hypotheses/Estimation

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

Primary Objective: Record and measure the 40 Hz-ASSR in HC and SC patients at baseline.

> **Hypothesis:** The mean magnitude of the ITC recorded from SZ patients at baseline is lower than those recorded from HC at baseline and determine whether the mean ITC magnitude derived from the 40 Hz-ASSR at baseline is lower in SZ patient than in HC.

Secondary Objectives:

Objective: Record and measure the DD-MMN in HC and SZ patients at baseline and determine whether the mean MMN magnitude derived from the DD-MMN at baseline is lower in SZ patient than in HC.

Hypothesis: The mean magnitude of the MMN derived from the DD-MMN recorded from SZ patients at baseline will be lower than that recorded from HC at baseline.

Objective: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the 40 Hz-ASSR ITC recorded from HC or SZ patients relative to placebo treatment.

Hypothesis: Pharmacologically relevant plasma levels of nicotine change the mean magnitude of the ITC recorded from HC or SZ patients relative to placebo treatment, with each subject group tested separately.

Exploratory/Tertiary Objectives:

1. **Exploratory Objective**: Determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the P3A, MMN or GBO recorded from HC or SZ patients relative to placebo treatment

   > **Estimation**: Estimate difference between the treatment groups (nicotine vs. placebo) in the mean change from baseline in the magnitude of the P3A, MMN or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately

2. **Exploratory Objective**: Determine if pharmacologically relevant plasma concentrations of MK-4334 change the mean magnitude of the 40 Hz-ASSR ITC, MMN, P3A or GBO recorded from HC or SZ patients relative to placebo treatment

   > **Estimation**: Estimate difference between the treatment groups (MK-4334 vs. placebo) in the mean change from baseline in the magnitude of the 40 Hz-ASSR ITC, MMN, P3A or GBO recorded from HC or SZ patients, with the difference for the two groups (HC and SZ) estimated separately

3. **Exploratory Objective**: To determine intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13)

   Estimation: Estimate intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13). More specifically, mean ITC over time (Days -1, 7, 13) will be summarized and graphically displayed. Pairwise (Day -1 vs. Day 7 or Day -1 vs. Day 13) ICC will be estimated. Scatter plot with diagonal line and Bland-Altman plot will also be presented

9.4 Analysis Endpoints

Primary Endpoint

The primary endpoint is the ITC derived from the 40 Hz-ASSR recorded from HC and SZ patients at baseline.

Secondary Endpoints

The secondary endpoints are the ITC derived from the 40 Hz-ASSR in the presence of nicotine and the MMN derived from the DD-MMN in the presence of nicotine recorded from HC and SZ patients.

Exploratory Endpoints

The exploratory endpoints are the ITC, P3A, MMN and resting GBO recorded from HC and SZ patients in the presence of MK-4334/placebo, and the MMN and resting GBO recorded from HC and SZ patients in the presence of nicotine/placebo.

9.5 Analysis Populations

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

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

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment CCI [redacted], MK-4334), 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 subjects 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 subjects 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 all primary and exploratory/tertiary analyses.

9.6 Statistical Methods

Safety

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

To conduct initial data exploration, summary statistics and plots will be generated as deemed clinically appropriate. For the primary endpoint, ITC, and secondary endpoint, MMN, descriptive summaries (mean, standard deviation, median, min, max) will be provided.

Pharmacokinetics/Pharmacodynamics

Descriptive summary will be provided for plasma concentrations (C2 [nicotine], 4 [MK-4334]) following the administration of study treatment. To assess the association between plasma concentration and the magnitude of ERP, appropriate display such as scatter plot will be provided, and correlation coefficient will be reported.

Primary Hypothesis: Comparison of SZ Patients to HC Participants

To determine whether, at baseline, the mean ITC recorded from SZ patients is lower than HC participants, a Bayesian approach will be used. Utilizing a non-informative flat prior, the posterior probability that the difference in observed means of ITC measurements of SZ and HC participants is greater than zero will be calculated, and the criteria for success will be met if the following condition is satisfied.

Posterior-probability (PP) $(\mu_{HC} - \mu_{SZ} > 0) \geq 0.60$

Where

μ_{HC} = mean of the ITC measurements for HC participants

μ_{SZ} = mean of the ITC measurements for SZ patients

Secondary Hypothesis:

Comparison of SZ patients to HC Participants

To determine whether, at baseline, the mean MMN amplitude recorded from SZ patients is lower than in HC participants, a Bayesian approach will be used. Utilizing a non-informative flat prior, the posterior probability that the difference in observed means of MMN

measurements of SZ patients and HC participants is greater than zero will be calculated, and the criteria for success will be met if the following condition is satisfied.

Posterior-probability (PP) ($\mu_{HC} - \mu_{SZ} > 0) \geq 0.60$

Where

μ_{HC} = mean of the MMN amplitudes for HC participants

μ_{SZ} = mean of the MMN amplitudes for SZ patients

Comparison of SZ patients and HC Participants for the effect of nicotine relative to the placebo group

To determine if pharmacologically relevant plasma concentrations of nicotine change the mean magnitude of the 40 Hz-ASSR ITC recorded from HC or SZ patients relative to placebo treatment, we undertake a similar Bayesian approach as described above. In this case, the criterial for success will be met if the following condition is satisfied

Posterior-probability (PP) ($abs(\mu_{nicotine} - \mu_{placebo}) > 0) \geq 0.60$

Where

$\mu_{nicotine}$ = mean of the ITC measurements from HC and SZ subjects treated with nicotine

$\mu_{placebo}$ = mean of the ITC measurements from HC and SZ subjects treated with placebo

abs() = absolute value of the difference

Exploratory/Tertiary Hypothesis/Estimation:

For the tertiary hypotheses outlined above, we estimate the magnitude of MMN or GBO recorded from HC and SZ subjects with nicotine and placebo, respectively, to characterize the effect of nicotine. The sample sizes are too small for testing hypotheses given the variability.

Similarly, the magnitude of the ITC, MMN and P3A or GBO measurements in the SZ with MK-4334 versus the placebo will be estimated as the sample sizes are too small for testing hypothesis given the variability.

With respect to the objective of estimating intra-subject variability of ITC measurements collected using the 40 Hz-ASSR in HC and SZ patients at baseline conditions (Days -1, 7, 13), descriptive statistics such as arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, and maximum will be provided. Graphical results using (including but not limited to) Box plots will also be displayed. Other measures of reproducibility including the PCC, ICC, and CCC will be calculated to assess the agreement of ITC at various baseline measurement (Day -1 vs. Day 7 or Day -1 vs. Day 13). The PCC measures the linear correlation between two sets of

measurements; the ICC measures the replication reliability; and the CCC measures the degree to which pairs of measurements coincide with a 45-degree line.

9.7 Interim Analyses

Not applicable

9.8 Multiplicity

Because there is only one primary hypothesis, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

Approximately 45 subjects (30 SZ patients and 15 HC participants) are planned to be screened for this study in order to enroll 36 subjects in total (24 SZ patients and 12 HC participants). The success criterion is that the posterior probability (PP) of the delta, the detectable difference in mean ITC of the placebo treated SZ and HC subjects, greater than zero, is at least 60%. Assuming the mean difference from 0.06 to 0.08, PP is calculated based on 10,000 simulations and results are presented in the table below for sample size of n=36 (24 in SZ vs 12 in HC). These assumptions are based on available data on test-retest ITC measurements from Event-Related Potential (ERP) Biomarkers Qualification Consortium (CT.Gov ID: NCT04025502).

Table 7 Sample Size Calculations

Param	Type	Mean HC	Mean SZ	Delta	Std HC	Std SZ	Num HC	Num SZ	Prob. Of Success (%)
ITC‡	BaseLn	0.3794	0.3185	0.0609	0.1787	0.1577	12	24	77.38
ITC‡	Retest	0.3851	0.3015	0.0837	0.1561	0.1443	12	24	90.04
ITC‡	Avg.	0.3799	0.3089	0.0709	0.1541	0.1409	12	24	**86.00**

‡ITC here refers to ITC 200/500

As displayed in the table above, the probability of success that PP(delta>0)>60% is 86% assuming mean ITC of 0.3799 in HC and 0.3089 in SZ subjects based on average of ITC measurements at baseline and retest from available data from ERP Biomarkers Qualification Consortium (CT.Gov ID: NCT04025502).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

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

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 8.1.2. 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, non-fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	FSH (as needed in WONCBP only) Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, PCP, cannabinoids, and benzodiazepines) if applicable. Breath test for alcohol acceptable Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)			
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; [HBsAg=hepatitis B surface antigen]; hCG=human chorionic gonadotropin; [HIV=human immunodeficiency virus]; 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; WONCBP=women of nonchildbearing potential				

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

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

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

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

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

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

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

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

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity /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.

Assessment of causality

Follow-up of AE and SAE

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

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

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

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

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

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

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol, that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product - A product comprised of two or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint - Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part - A drug, device, or biological product that is part of a combination product.

Customer Feedback - A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark which may suggest an improvement in the functionality or quality of a medical device or device-like features of a drug delivery system).

Malfunction - The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device - Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

PQC - Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury - An injury or illness that:

1. Is life-threatening,

2. Results in permanent impairment of a body function or permanent damage to a body structure, or

3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

- When a Complaint including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

Assessing Causality

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

- The investigator will use clinical judgement to determine the relationship.

- Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

- The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

Women of Childbearing Potential (WOCBP) Nonparticipant Only

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

- Women in the following categories are not considered WOCBP:
  - Premenarchal
  - Premenopausal female with 1 of the following:
  - Hysterectomy

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

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

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 are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage[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 utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Blood Volume Table

Panels A and B	Prestudy	Intervention Days (All Periods)	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	4	1	7	12.5	87.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for Nicotine/cotinine screen	1				5	5
Blood for Nicotine PK		12		12	4	48
Blood for MK-4334 PK		2		2	4	8
Total Blood Volume per Participant[a]						**162 mL**

[a] If additional pharmacokinetic or safety analyses are necessary, additional blood (no more than 50 mL in total) may be obtained. Note: never to exceed 500 mL total volume withdrawn.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

	Screen Failure Criteria	Potentially Significant Post-Randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With 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 Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms

	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

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

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

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

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

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

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

   a. The participant may be excluded from the study;

   b. 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).

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

   OR

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

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

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

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

10.11 Appendix 11: Mapping Between Suicidal Ideation and Behavior Categories and the C-SSRS

Mapping Between the 11 Categories
of Suicidal Ideation and Behavior and the C-SSRS

Category	C-SSRS Question (from eCRF)[†]
Suicidal ideation	
1. Passive	1. Wish to be dead
2. Active: Nonspecific (no method, intent, or plan)	2. Non-specific active suicidal thoughts
3. Active: Method, but no intent or plan	3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active: Method and intent, but no plan	4. Active suicidal ideation with some intent to act, without specific plan
5. Active: Method, intent and plan	5. Active suicidal ideation with specific plan and intent
Suicidal behavior	
6. Preparatory actions toward imminent suicidal behaviors	Preparatory acts or behavior
7. Aborted attempt	Aborted attempt
8. Interrupted attempt	Interrupted attempt
9. Suicide attempt	Actual attempt
10. Completed suicide	Completed suicide
Self-injurious behavior, no suicidal intent	Has participant engaged in nonsuicidal self-injurious behavior?

C-SSRS=Columbia-Suicide Severity Rating Scale; eCRF=Electronic Case Report Form
[†]Data are "yes" or "no"

10.12 Appendix 11: Abbreviations

Abbreviation	Expanded Term
CCI [redacted]	[redacted]
AD	Alzheimer disease
AE	adverse event
AP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
ASSR	auditory steady-state response
AST	aspartate aminotransferase
AUC	area under the curve
BDS	blood drug screen
bid	twice daily
BLA	biologics license application
BMI	body mass index
BP	blood pressure
BT	body temperature
C2, C4	plasma concentration at 2 hours post-dose (nicotine) or 4 hours post-dose (MK-4334)
CCU	coronary care unit
CDSS	Calgary Depression Scale for Schizophrenia
CG	Cockcroft-Gault
CI	confidence interval
CIAS	cognitive impairment associated with schizophrenia
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CrCl	creatinine clearance
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CZ	center, midline electrode
CYP	cytochrome P450
DBP	diastolic blood pressure
DD	double-dummy
DFC	dry-filled capsule
DILI	drug-induced liver injury

Abbreviation	Expanded Term
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
eCTA	exploratory clinical trial application
EDC	electronic data collection
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EP	evoked power
ERP	event related potential
FBR	Future biological research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FE	fractional enrichment
FFT	fast Fourier transform
FZ	frontal, midline electrode
GABAergic	gamma-amino butyric acid-ergic
GBO	gamma-band oscillation (EEG)
GCP	Good Clinical Practice
GI	gastrointestinal
gln	Glutamine
glu	Glutamate
H1	histamine receptor type 1
HBsAg	hepatitis B surface antigen
HC	healthy control
HCU	headset control unit
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
Hz	Hertz (cycles per second)
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICC	intraclass correlation coefficient
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Expanded Term
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITC	inter-trial coherence
IV	intravenous
mg	milligram
min	minute
MINI	Mini-Mental Status Exam
mL	Milliliter
MRS	magnetic resonance spectroscopy
msec	milliseconds
MTD	maximum tolerated dose
NCS	not clinically significant
NDA	new drug application
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OTC	over-the-counter
PANSS	Positive and Negative Symptom Scale for Schizophrenia
pbo	placebo
PCL	protocol clarification letter
PD	Pharmacodynamic
PE	physical exam
PK	pharmacokinetic
po	per os, orally
PP	per-protocol
PVI	parvalbumin-positive interneuron
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
selPOCE	selective, proton observed, carbon-edited
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities

Abbreviation	Expanded Term
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
SZ	schizophrenia
t1/2	half life
Tmax	time to maximum plasma concentration
T/RT	test/retest
UDS	urine drug screen
ULN	upper limit of normal
Vcycle	rate of glutamate to glutamine conversion
VS	vital signs
VTCA	turnover rate of tricarboxylic acid cycle
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
WRAT-5	Wide-Range Achievement Test 5

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