

Official Title of Study:

A Phase 4, Open-label, Multicenter, Two-cohort, Two-Period, Slow-titration and Food Effect Study to Assess the Safety and Efficacy of KarXT in Participants with DSM-5 Schizophrenia

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CLINICAL PROTOCOL CN0120048

A Phase 4, Open-label, Multicenter, Two-cohort, Two-Period, Slow-titration and Food Effect Study to Assess the Safety and Efficacy of KarXT in Participants with DSM-5 Schizophrenia

Compound: BMS-986510

Brief Title:

A Phase 4 Open-label Slow-titration and Food Effect Study to Assess Safety and Efficacy of KarXT in Participants with Schizophrenia

Protocol Amendment 01

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 01	18-Nov-2024	This protocol has been amended to collect safety and efficacy data for the KarXT 100 mg/20 mg twice daily dose, in addition to the 125/30mg twice daily dose, which is reflected as an updated two-cohort study design. Additionally, this amendment also clarifies certain eligibility criteria, mitigation strategies, and provides guidance for laboratory assessments and orthostatic vital signs measurements.
Original Protocol	17-Jul-2024	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

This protocol has been amended to collect safety and efficacy data for the KarXT 100 mg/20 mg twice daily (BID) dose, in addition to the KarXT 125/30 mg BID dose, which is reflected as an updated two-cohort study design. Additionally, this amendment also clarifies certain eligibility criteria, mitigation strategies, and provides guidance for laboratory assessments and orthostatic vital signs measurements.

The protocol summary is updated to reflect the changes made in the protocol amendment.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated the Medical Monitor name and contact information.	Change in study Medical Monitor.
Title Page Section 5.1 : Overall Design Figure 5.1-1 : Study Design Schema Section 5.4 : Scientific Rationale for Study Design	Updated the study from Phase 3b to Phase 4.	Updated due to KarXT approval by United States (US) Food and Drug Administration.
	Updated to capture the two-cohort study design.	Updated study design.
Table 2-1 : Screening Procedural Outline - All Participants (CN0120048) Table 2-2 : Inpatient On-treatment Procedural Outline (CN0120048) Table 2-3 : Outpatient Safety Follow-up Procedural Outline (CN0120048) Section 9.2.10 : AEs of Special Interest	Clarified that orthostatic vital signs (blood pressure and heart rate) should be measured supine and standing.	To ensure consistency throughout the protocol.
Section 3.3.1 : Risk Assessment	Updated risks and mitigation strategies related to KarXT.	To align with the US Prescribing Information (USPI).
Section 4 : Objectives and Endpoints	Secondary - Other Safety Endpoints: - Removed timepoints Day 7 and Day 14 from the endpoint “Change from baseline in orthostatic vital signs” and clarified the vital signs as blood pressure (systolic and diastolic) and heart rate - Removed the description of laboratory assessments from the endpoint “Change from baseline in clinical laboratory assessments.”	Orthostasis will be assessed throughout the study at multiple timepoints (each visit). Descriptive summaries will be provided for clinical laboratory data.

Section 5.1: Overall Design Section 5.2: Number of Participants Section 10.2: Sample Size Determination	Updated the number of participants to be enrolled from approximately 100 to 175.	To align with dosing described in the USPI, which allows dosing of 100/20 mg BID or 125/30 mg BID based on safety and efficacy.
Section 5.5 : Justification for Dose	Added the following text: “This observation led to an approval with dose instructions in the USPI of patients escalating to 100/20 BID, with an option to further escalate to 125/30 BID based on patient response. Therefore, both dosages are expected to be used by patients who receive KarXT in clinical practice.”	To provide an additional rationale to support the 2 doses.
Section 6.1 : Inclusion Criteria	Updated Inclusion Criterion 2.d. to clarify that the participant must be taking an oral antipsychotic medication either at a dose and frequency consistent with the drug label or at a stable dose based on investigator judgement for at least 30 days prior to screening.	To provide further clarity.
	Removed requirements for male contraception from Inclusion Criterion 4.	Requirement for male contraception is no longer needed, as there is no genotoxicity effect of KarXT on sperm.
Section 6.2 : Exclusion Criteria	Updated Exclusion Criterion 1.d. to clarify that it includes participants with untreated or unstable hypertension and clinically significant tachycardia, and participants with GI obstructive disorders, conditions that may decrease GI motility, such as ulcerative colitis, intestinal atony, and myasthenia gravis, and active biliary disease, including symptomatic gallstones.	To align with [REDACTED] and the USPI.
	Updated Exclusion Criterion 1.e. to include Child-Pugh classes related to hepatic impairment.	To align with the USPI.
	Updated Exclusion Criterion 4.b. to clarify the positive blood screen for hepatitis C virus (HCV) is the HCV antibody at screening or within 3 months unless HCV-RNA negative test is documented.	To provide clarity and align with the Schedule of Activities.
	Updated Exclusion Criterion 5.a. from a history of allergy/hypersensitivity to any component (including excipients) of the study intervention or related compounds to a history of hypersensitivity to KarXT or trospium chloride.	To align with the USPI.
Section 7.1 : Study Interventions Administered	Included description of the two study cohorts and dosing guidelines for each cohort.	To collect safety and efficacy data of the approved KarXT doses.

Table 7.1-1 : Study Intervention(s) Administered	Added the following footnote: “KarXT 50 mg/20 mg and 125 mg/30 mg capsules are packaged in blister card wallets, KarXT 100 mg/20 mg capsules are supplied in 2 packaging presentations; blister card wallets and bottles. KarXT 100 mg/20 mg capsules packaged in bottles will be dispensed for participants in Cohort 2 only. For all other participants, 100 mg/20 mg capsules will be dispensed in the blister card wallet presentation (if applicable).”	To provide additional information regarding drug supply packaging for Cohorts 1 and 2.
Section 7.4 : Dosage Modification	Added the following: “Participants will not be permitted to de-escalate to the 50/20 mg BID dose.”	To meet study objectives.
Section 7.7.2 : Drug Interactions	Included a new section to describe drug interactions with KarXT.	To align with [REDACTED] and the USPI.
Section 9.4.5 : Electrocardiograms Section 9.4.6 : Clinical Safety Laboratory Assessments	Added language to allow “qualified designee” to perform study procedures.	To add clarity on who can perform the assessments other than the investigator.
Section 9.4.6: Clinical Safety Laboratory Assessments	Included recommendation for fasted glucose and HbA1c laboratory assessments.	[REDACTED]
	Added HbA1c to chemistry laboratory assessments.	[REDACTED]
	Clarified parameters to be assessed for creatinine, creatine kinase, and urinalysis.	To clarify laboratory parameters to be performed during the study.
Section 10.5 : Interim Analyses	Updated timing of interim analyses to after all participants in Cohort 1 have completed the 9-week treatment and safety follow-up periods.	To specify timing of interim analysis
All	Minor formatting and typographical corrections.	Minor, therefore, have not been summarized.

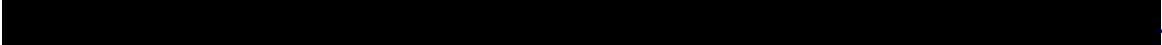
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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 4, Open-label, Multicenter, Two-cohort, Two-Period, Slow-titration and Food Effect Study to Assess the Safety and Efficacy of KarXT in Participants with DSM-5 Schizophrenia

Brief Title:

A Phase 4 Open-label Slow-titration and Food Effect Study to Assess Safety and Efficacy of KarXT in Participants with Schizophrenia

Rationale:

KarXT is a novel combination of the muscarinic agonist xanomeline and the antagonist trospium chloride, designed to preferentially stimulate muscarinic acetylcholine receptors in the CNS and unlock the therapeutic potential of xanomeline, while trospium blocks the activation of peripheral muscarinic receptors. This results in reduction of peripheral adverse events (AEs) when compared with using xanomeline alone. KarXT is being developed for multiple potential CNS indications, including the treatment of schizophrenia and psychosis associated with Alzheimer's disease (AD) dementia.

The primary evidence of the efficacy and safety of treatment with KarXT in the treatment of schizophrenia is based on 3 completed, 5-week, randomized, double-blind, placebo-controlled studies (KAR-004, KAR-007, and KAR-009) that evaluated the proposed dosing regimen of KarXT in adults with schizophrenia. In these studies, KarXT was taken twice daily (BID) on an empty stomach. Dosing with food has been shown to substantially reduce the bioavailability and plasma concentrations of trospium, which could increase the likelihood of a pro-cholinergic AE. By ensuring dosing on an empty stomach, variability in trospium concentrations can be minimized across patients. If data were generated that dosing with food would not adversely affect tolerability or safety, or if it leads to a reduction of anticholinergic AEs associated with trospium, this could potentially improve treatment compliance and outcomes.

AE data in the 3 pivotal clinical studies suggests that in adults with schizophrenia, common xanomeline related AEs of KarXT resolve over time with continued KarXT treatment.¹ Therefore, the need to maintain higher trospium concentrations may diminish as this acclimation to xanomeline occurs, and if an individual takes KarXT with food, the decrease in trospium exposure might be mitigated by this acclimation. The purpose of this current study is to assess the safety and efficacy of KarXT in adult participants with schizophrenia administered BID on an empty stomach over a slow up-titration at the start of treatment (Period 1) and administered BID with food after being on a stable dose (Period 2).

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of KarXT in adults with a DSM-5 diagnosis of schizophrenia after an initial slow titration of KarXT	Incidence of TEAEs from first dose of treatment to end of safety follow-up.

Objectives	Endpoints
administered BID on an empty stomach, followed by administration of KarXT BID with food.	
Secondary	
- To assess other measures of safety and tolerability - To assess efficacy following administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: - To evaluate the reduction in PANSS total score - To evaluate the reduction in PANSS positive score - To evaluate the improvement in CGI-S score - To evaluate the reduction in PANSS negative score - To evaluate the reduction in PANSS Marder Factor negative symptoms score	<u>Safety:</u> - Incidence of TEAEs by study period (from first dose of study intervention to Day 28 and from Day 29 to EoT [Day 56]). - Incidence of serious TEAEs overall and by study period (from first dose of study intervention to Day 28, from Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). - Incidence of TEAEs leading to study intervention discontinuation overall and by study period (from first dose of study intervention to Day 28, from Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). - Incidence of pro- and anticholinergic TEAEs overall and by study period (from first dose of study intervention to Day 28, from Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). <u>Efficacy:</u> - Change from baseline in PANSS total score - Change from baseline in PANSS positive score - Change from baseline in PANSS negative score - Change from baseline in PANSS negative Marder Factor score - Change from baseline in CGI-S score <u>Other Safety:</u> - Spontaneously reported AESIs - Change from baseline in body weight, BMI, and waist circumference - Change from baseline in orthostatic vital signs (blood pressure [systolic and diastolic] and heart rate supine and standing after 2 minutes) - Change from baseline in clinical laboratory assessments - Change from baseline in 12-lead ECG - Change from baseline in physical examination - Suicidal ideation scale with the use of C-SSRS

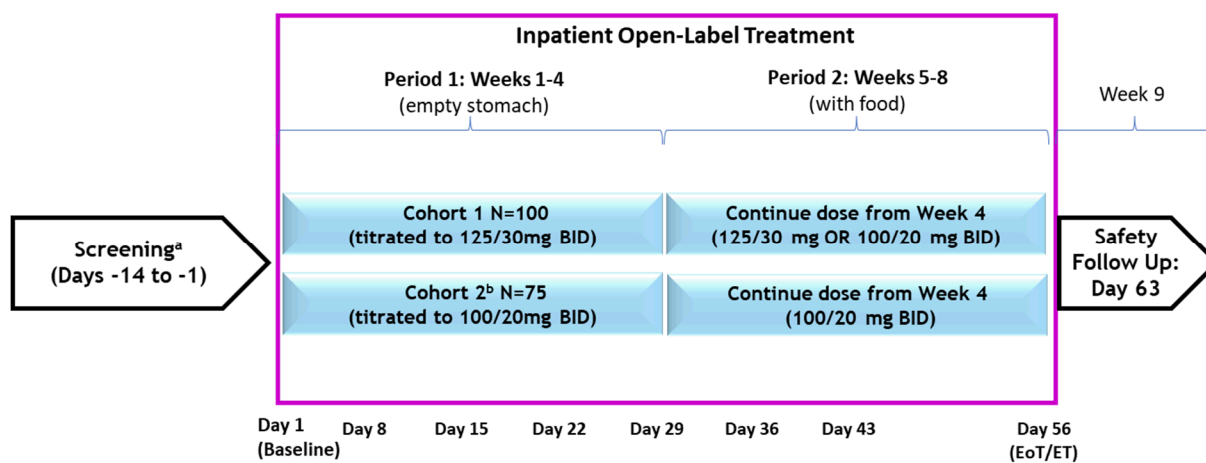
Abbreviations: AESI, adverse event of special interest; BID, twice daily; BMI, body mass index; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; EoT, end of treatment; PANSS, Positive and Negative Syndrome Scale; TEAE, treatment-emergent adverse event.

Note: Baseline is defined as Day 1.

Overall Design:

This is a two-cohort, multicenter, Phase 4 study that includes two periods of open-label treatment with KarXT. Approximately 175 participants with DSM-5 schizophrenia will be enrolled in the study; approximately 100 participants will up-titrate to the 125/30 mg BID dose (Cohort 1), followed by the initiation of Cohort 2, which will consist of a maximum of 75 participants who will up-titrate to the 100/20 mg BID dose. Participants enrolled in the study will remain in an inpatient setting for approximately 8 weeks of treatment and 1 week of follow up. The duration of the study will be approximately 11 weeks, including the screening and safety follow-up periods.

Study Design Schema:



Abbreviations: EoT, end of treatment; ET, early termination.

^a May include down-taper as necessary.

^b Cohort 2 will be initiated after enrollment completion of Cohort 1.

Number of Participants:

Approximately 175 participants will be enrolled in this study.

Study Population:

Adults aged 18 to 65, inclusive, with a DSM-5 diagnosis of schizophrenia deemed psychiatrically stable in the opinion of the investigator may be eligible for participation in the study.

Key Inclusion Criteria

Participants are eligible to be included in the study if all of the following criteria apply:

- Participants, age 18 to 65, inclusive, at the time of signing the ICF
- Participant has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview (MINI) for Schizophrenia and Psychotic Disorder Studies version 7.0.2.
- PANSS total score of ≤ 80 at screening and Baseline

- CGI-S score of ≤ 4 at screening and Baseline
- Participant must be taking an oral antipsychotic medication at a dose and frequency consistent with the drug label or at a stable dose based on the judgement of the Investigator for at least 30 days prior to screening.
- In the opinion of the investigator, it is clinically appropriate for the participant to discontinue current antipsychotic therapy and initiate KarXT.
- Participant is willing and able, in the opinion of the investigator, to discontinue all antipsychotic medications at least 3 days prior to the Baseline visit.

Note: Antipsychotic down-taper, if clinically appropriate in the opinion of the investigator, may occur during the screening period.

- Participant is willing and able to be confined to an inpatient setting for the study duration, follow instructions, and comply with the protocol requirements.
- BMI must be ≥ 18 and ≤ 40 kg/m².
- Individuals of childbearing potential (IOCBP) must be willing and able to adhere to the contraception guidelines

Key Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

- Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening). Exclusionary disorders include but are not limited to major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment.
- The participant has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline.
- History or presence of clinically significant cardiovascular (eg, untreated or unstable hypertension, clinically significant tachycardia), pulmonary, renal, hematologic, gastrointestinal ([GI,] eg, obstructive disorders [including conditions that may decrease GI motility, such as ulcerative colitis, intestinal atony, and myasthenia gravis], active biliary disease [including symptomatic gallstones]), endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the participant or the validity of the study results.
- An estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m² at the screening visit. One repeat measurement is allowed.
- All grades of hepatic impairment (mild [Child-Pugh Class A], moderate [Child-Pugh Class B], and severe [Child-Pugh Class C]).
- Participants with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test (LFT) results.
- History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.

- A positive COVID test at the time of admittance to the inpatient unit if testing is required by the site
- For males ≥ 45 years of age only, any one of the following:
 - History of bladder stones.
 - History of recurrent urinary tract infections.
 - Serum prostate-specific antigen (PSA) >10 ng/mL at the screening visit.
 - An International Prostate Symptom Score (IPSS) of 5 (almost always) on items 1, 3, 5, or 6 at the screening visit.
 - A sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 at the screening visit.
- History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
- Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
 - "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or
 - "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Nonsuicidal self-injurious behavior is not exclusionary.
- Participant has a history of treatment resistance to schizophrenia medications defined as:
 - Failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) within the past 12 months.
- Individuals who are pregnant, lactating, or less than 3 months postpartum.
- If, in the opinion of the investigator (and/or Sponsor), participant is unsuitable for enrollment in the study or participant has any finding that, in the opinion of the investigator (and/or Sponsor), may compromise the safety of the participant or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
- Participant has had psychiatric hospitalization(s) for more than 30 days (cumulative) within the 6 months before screening.
- Participant has required psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 8 weeks of screening and is not psychiatrically stable in the opinion of the investigator.
- Participants with prior exposure to KarXT within 3 months of screening.
- Current participation in another clinical trial, or participation in another clinical study in which the participant received an experimental or investigational drug agent within 30 days prior to screening.
- Participants taking a long-acting injectable antipsychotic who have received a dose of medication within 2 cycles before Baseline.
- Participants who have taken lithium therapy within 2 weeks of Baseline.

Intervention Groups and Duration:

The total study duration is up to 11 weeks, including a screening period of up to 2 weeks, an 8-week open-label (OL) treatment period, and a 1-week follow-up period. Initially, a cohort of approximately 100 participants will be enrolled to up-titrate to the 125/30 mg BID dose (Cohort 1). Subsequently, a maximum of 75 participants will be enrolled to up-titrate to the 100/20 mg BID dose (Cohort 2).

Cohort 1:

Dosing during Period 1 is as follows:

- Days 1-7 (Week 1) - KarXT 50/20 BID on empty stomach; ie, at least one hour before meals or at least two hours after meals
- Days 8-14 (Week 2) - KarXT 100/20 BID on empty stomach (at least one hour before meals or at least two hours after meals).
- Days 15-28 (Week 3 - Week 4) - KarXT 125/30 BID on empty stomach (at least one hour before meals or at least two hours after meals) unless the participant is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All participants who are increased to KarXT 125/30 mg BID in Period 1, depending on tolerability as assessed by the investigator, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period.

Dosing during Period 2 is as follows:

- On Day 29 (start of Week 5), participants will receive the same KarXT dose as Day 28 (last day of Week 4) BID taken with food; ie, taken within 30 minutes of morning/evening meal or snack.
- During Period 2, participants will have the option to dose de-escalate one time from 125/30 mg BID to 100/20 mg BID depending on tolerability as assessed by the investigator. Dose escalation will not be permitted during Period 2.

Cohort 2:

Dosing during Period 1 is as follows:

- Days 1-7 (Week 1) - KarXT 50/20 BID on empty stomach; ie, at least one hour before meals or at least two hours after meals
- Days 8-28 (Week 2 - Week 4) - KarXT 100/20 BID on empty stomach (at least one hour before meals or at least two hours after meals).

Dosing during Period 2 is as follows:

- On Day 29 (start of Week 5), participants will receive the same KarXT dose (100/20 mg BID) as Day 28 (last day of Week 4) BID taken with food; ie, taken within 30 minutes of morning/evening meal or snack.
- Dose escalation will not be permitted during Period 2.

Cohorts 1 and 2:

There will be one safety follow-up visit (Week 9) following the last KarXT dose for all participants in Cohorts 1 and 2 who complete the 8-week treatment period, and those who discontinue early from the study.

Dose de-escalation from 100/20 mg BID to 50/20 mg BID will not be permitted during the study duration.

Study Intervention:

Study Intervention for CN0120048		
Intervention Name	Unit Dose Strength(s)	IP/IMP
KarXT	• 50/20 BID (50 mg xanomeline/20 mg trospium chloride) • 100/20 BID (100 mg xanomeline/20 mg trospium chloride) • 125/30 BID (125 mg xanomeline/30 mg trospium chloride)	IP

Abbreviations: BID, twice daily; IMP, Investigational Medicinal Product; IP, Investigational Product.

Statistical Methods:

This study is a two-cohort open-label study collecting data for publication. No inferential testing will be performed and no p-values will be provided. Descriptive statistical summaries for the observed data will be provided by study period and overall.

Interim analyses may be performed after all participants in Cohort 1 have completed the 9-week treatment and safety follow-up periods. The final study analysis will be performed when all participants have completed the 9-week treatment and safety follow-up periods or discontinued early from the study.

Data Monitoring Committee: No

A Data Monitoring Committee will not be used in the study.

Other Committees: No

Other review committees will not be used in the study.

Brief Summary:

The purpose of this study is to assess the safety and efficacy of KarXT in adult participants with schizophrenia when using slower up-titration compared to the up-titration schedule in the pivotal trials, as well as when taken with food after being on a stable dose.

Study Duration: Approximately 11 weeks, including a screening period of up to 2 weeks, an 8-week open-label treatment period, and a 1-week safety follow-up period.

Study Intervention Duration: Approximately 8 weeks

Study Visit Frequency: Weekly.

REFERENCES

¹ KarXT for Schizophrenia NDA 216158, Module 2.7.4 Summary of Clinical Safety. Karuna Therapeutics, Inc.; 2023.

2 SCHEDULE OF ACTIVITIES

All procedures in the Schedule of Activities apply to both Cohorts 1 and 2. If multiple procedures are required at a single time point, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring that the [REDACTED] samples can be collected on time.

Table 2-1: Screening Procedural Outline- All Participants (CN0120048)

Procedure	Screening Visit Day -14 to Day -1	Baseline Visit 1 Day 1 ^a	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol-specific informed consent is signed; informed consent must be obtained prior to performing any screening procedures.
Inclusion/Exclusion Criteria	X	X	See Sections 6.1 and 6.2 .
Demography	X	X	See Section 9.4.1 .
Medical and Psychiatric History	X	X	See Section 9.4.1 .
MINI version 7.0.2	X		MINI should be performed before PANSS assessment. See Section 9.9.1 .
Admission to Inpatient Unit ^b		X	
Safety Assessments			
Complete Physical Exam	X	X	See Section 9.4.3 .
Physical Measurements	X	X	Includes height, weight, waist circumference, and BMI. See Section 9.4.2 .
Vital Signs ^c	X	X	Includes body temperature, respiratory rate, blood pressure, and heart rate. See Section 9.4.4 for details.
International Prostate Symptom Score ^d	X		See Section 9.4.7 .
C-SSRS ^e	X	X	See Section 9.4.8 for details.
Prior/Concomitant Medication Use	X	X	See Section 7.7 . for details.

Table 2-1: Screening Procedural Outline- All Participants (CN0120048)

Procedure	Screening Visit Day -14 to Day -1	Baseline Visit 1 Day 1 ^a	Notes
ECG ^f	X	X	See Section 9.4.5 . for details.
Simpson-Angus Scale ^g		X	See Section 9.4.9 .
Barnes Akathisia Rating Scale ^g		X	See Section 9.4.10 .
Abnormal Involuntary Movement Scale ^g		X	See Section 9.4.11 .
Laboratory Tests			See Section 9.4.6 for specific assessments.
Clinical Laboratory Assessments	X	X	Includes blood and urine samples. See Table 9.4.6-1 .
Pregnancy Test (IOCBP Only) ^h	X	X	See Table 9.4.6-1 .
Serology ⁱ	X		See Table 9.4.6-1 for list of serology assessments.
Drug Test (Urine)	X	X	
COVID-19 Screen ^j		X	
PSA ^d	X		See Table 9.4.6-1 .
Efficacy Assessments			
PANSS ^k	X	X	See Section 9.1.1.1 for details.
CGI-S	X	X	See Section 9.1.1.2 for details.
AE Reporting			
Monitor for Serious and Non-serious AEs	X	X	See Section 9.2.1 .

Table 2-1: Screening Procedural Outline- All Participants (CN0120048)

Procedure	Screening Visit Day -14 to Day -1	Baseline Visit 1 Day 1 ^a	Notes
Study Intervention			
Administer IP		X	See Section 7.1 .
Contact IRT	X	X	

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; CGI-S, Clinical Global Impression-Severity; COVID-19, coronavirus disease 2019; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; HCV, hepatitis C virus; IOCBP, individual of childbearing potential; IP, investigational product; IRT, Interactive Response Technology; MINI, Mini International Neuropsychiatric Interview; PANSS, Positive and Negative Syndrome Scale; [REDACTED]; PSA, prostate-specific antigen; RNA, ribonucleic acid.

- ^a All clinical and safety assessments to be performed prior to dosing at Baseline visit.
- ^b Participants may be admitted to inpatient unit within 5 days of Baseline Visit if required for washout in the judgement of the investigator.
- ^c BP and heart rate will be taken supine and standing after 2 minutes. BP includes systolic and diastolic measurements; BP should be taken in the same arm throughout the study. Heart rate is measured in beats/minute.
- ^d To be performed in male participants ≥ 45 years of age.
- ^e C-SSRS at screening will be the assessment of Lifetime; all other visits “Since Last Visit” will be performed.
- ^f ECG on Day 1 will be done at 2 hours (± 15 minutes) post morning dose. ECGs at all other scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or [REDACTED] analysis.
- ^g Assessment to be performed prior to dosing.
- ^h A serum pregnancy test for individuals of childbearing potential will be performed at screening. Urine pregnancy tests will be performed at other visits. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.
- ⁱ If the participant tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.
- ^j COVID-19 Screen to be performed at the time of admission to inpatient unit if required by the site.
- ^k It is recommended that the PANSS assessment be performed before all other safety and efficacy assessments during the screening and Baseline visits, and prior to dosing at the Baseline visit.

Table 2-2: Inpatient On-treatment Procedural Outline (CN0120048)

Procedure	Period 1			Period 2				Notes
	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 EoT/ET	
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 56	
	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	
Safety Assessments								
Targeted PE	X	X	X	X	X	X	X	See Section 9.4.3.
Vital Signs ^a	X	X	X	X	X	X	X	See Section 9.4.4.
Weight and Waist Circumference							X	See Section 9.4.2.
Concomitant Medication Use	X	X	X	X	X	X	X	See Section 7.7.
ECG ^b				X			X	See Section 9.4.5.
C-SSRS ^c	X	X	X	X	X	X	X	See Section 9.4.8.
Simpson-Angus Scale				X			X	See Section 9.4.9.
Barnes Akathisia Rating Scale				X			X	See Section 9.4.10.
Abnormal Involuntary Movement Scale				X			X	See Section 9.4.11.
AE Reporting								
Monitor for Non-serious and Serious AEs	X	X	X	X	X	X	X	See Section 9.2.1.

Table 2-2: Inpatient On-treatment Procedural Outline (CN0120048)

Procedure	Period 1			Period 2				Notes
	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 EoT/ET	
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 56	
	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	
Laboratory Tests								
Clinical Laboratory Assessments	X	X		X	X		X	Includes blood and urine samples. See Table 9.4.6-1 .
Pregnancy Test (IOCBP Only) ^d							X	See Table 9.4.6-1 .
Alcohol and Drug Testing ^e	X							See Section 6.3.2 .

Efficacy Assessments								
Positive and Negative Syndrome Scale (PANSS) ^g				X ^h			X	See Section 9.1.1.1 for details.
Clinical Global Impression–Severity scale (CGI-S)				X ^h			X	See Section 9.1.1.2 for details.

Table 2-2: Inpatient On-treatment Procedural Outline (CN0120048)

Procedure	Period 1			Period 2				Notes
	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 EoT/ET	
	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 56	
	Visit Window	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	
Study Intervention								
Administer Study Intervention	X	X	X	X	X	X		See Section 7.1 for details.

Abbreviations: AE, adverse event; BP, blood pressure; CGI-S, Clinical Global Impression–Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; EoT, end of treatment; ET, early termination; IOCBP, individual of childbearing potential; PANSS, Positive and Negative Syndrome Scale; PE, physical examination; [REDACTED].

- ^a BP and heart rate will be taken supine and standing after 2 minutes. BP includes systolic and diastolic measurements; BP should be taken in the same arm throughout the study. Heart rate is measured in beats/minute.
- ^b ECGs at all visits should be performed 2 hours (± 15 minutes) post morning dose, and before blood withdrawal for any safety laboratory tests and/or [REDACTED] analysis.
- ^c At all visits after screening, C-SSRS “Since Last Visit” will be performed.
- ^d If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.
- ^e Breathalyzer or urine tests will only be used if participant leaves and returns to the site at any time during the study.
- ^f [REDACTED].
- ^g It is recommended that the PANSS assessment be performed before all other safety and efficacy assessments during the visit.
- ^h Assessment to be performed prior to dosing.

Table 2-3: Outpatient Safety Follow-up Procedural Outline (CN0120048)

Procedure	Visit 9	Notes
Timepoint	Day 63	
Visit Window	± 5 days	
Safety Assessments		
Concomitant Medication Use	X	See Section 7.7 .
AE and SAE Assessment	X	See Section 9.2.1 .
Clinical Laboratory Assessments	X	Includes blood and urine samples.
Pregnancy Test (IOCBP Only) ^a	X	See Table 9.4.6-1 .
C-SSRS ^b	X	See Section 9.4.8 .
Vital Signs ^c	X	See Section 9.4.4 .
Simpson-Angus Scale	X	See Section 9.4.9 .
Barnes Akathisia Rating Scale	X	See Section 9.4.10 .
Abnormal Involuntary Movement Scale	X	See Section 9.4.11 .

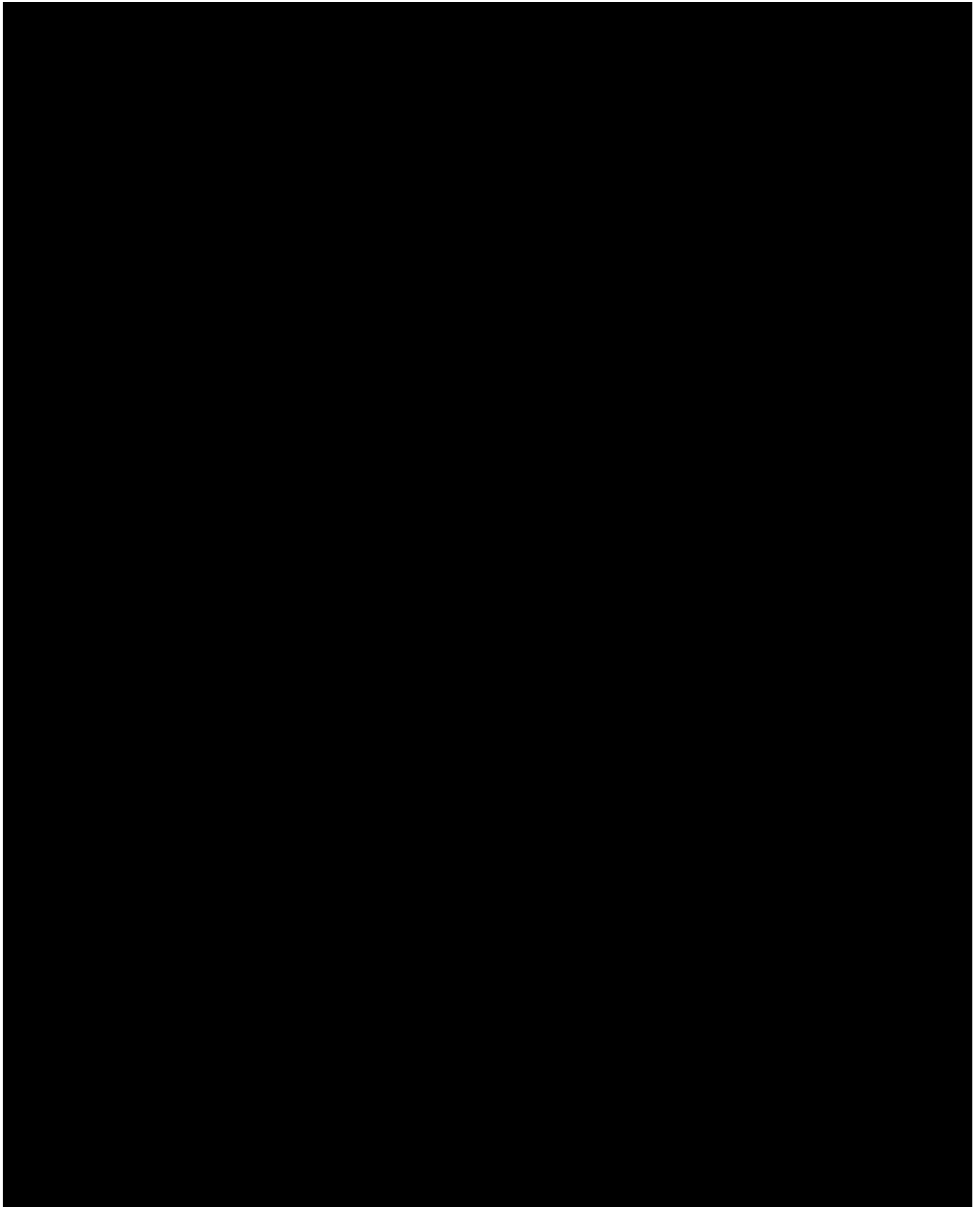
Abbreviations: AE, adverse event; BP, blood pressure; C-SSRS, Columbia-Suicide Severity Rating Scale; IOCBP, individual of childbearing potential; IP, Investigational Product; SAE, serious adverse event.

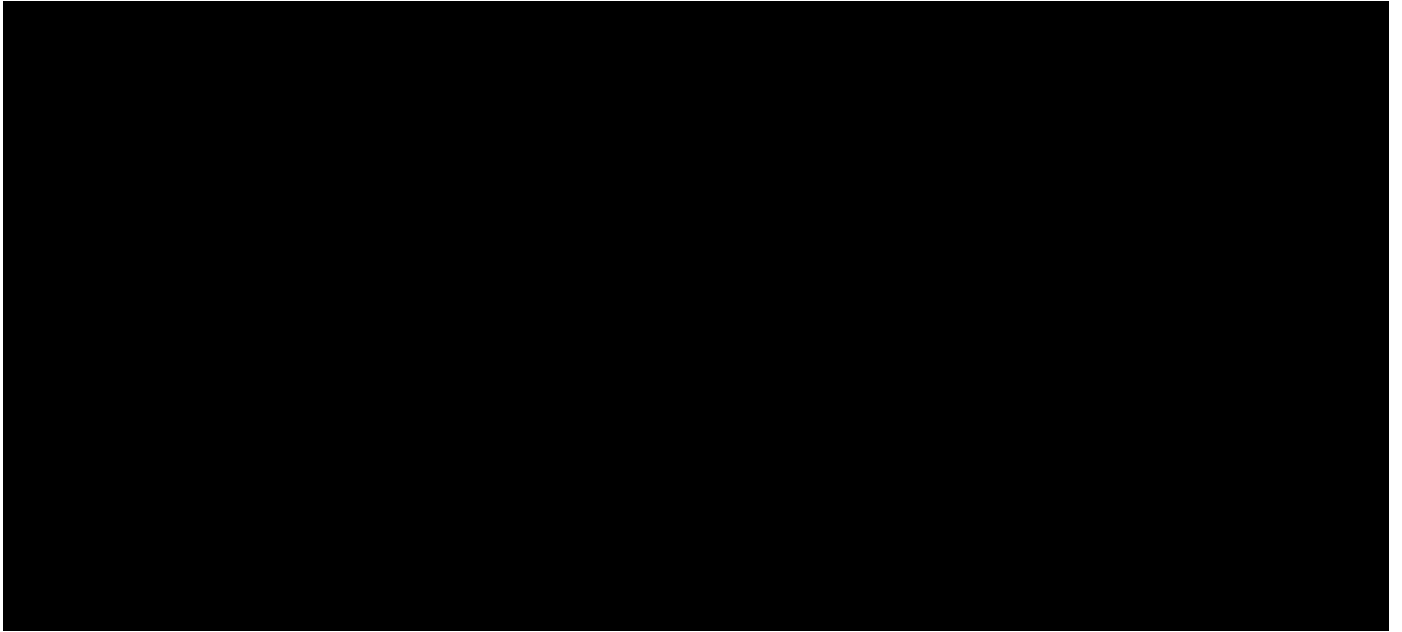
Note: Participants may stay in the inpatient setting for up to 5 days for stabilization after discontinuing IP. Any additional time required for stabilization during the safety follow-up period should be discussed with the Medical Monitor.

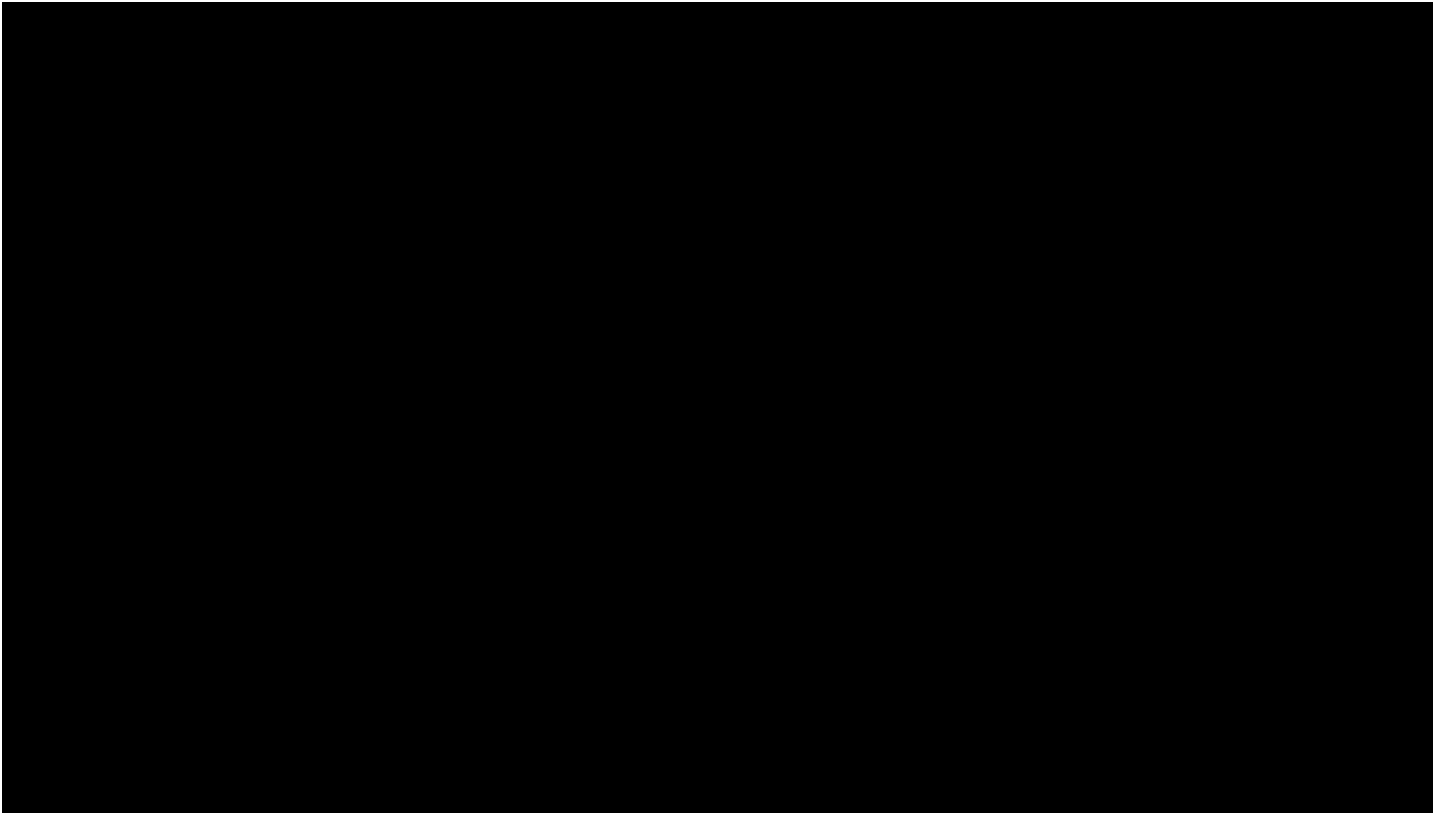
^a If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.

^b At all visits after screening, C-SSRS “Since Last Visit” will be performed.

^c BP and heart rate will be taken supine and standing after 2 minutes. BP includes systolic and diastolic measurements; BP should be taken in the same arm throughout the study. Heart rate is measured in beats/minute.







3 INTRODUCTION

3.1 Study Rationale

KarXT (xanomeline-trospium) is being developed for multiple potential central nervous system (CNS) indications, including the treatment of schizophrenia and psychosis associated with Alzheimer's disease (AD) dementia. For the treatment of schizophrenia in adults, KarXT is taken twice daily (BID) on an empty stomach, as dosing with food has been shown to reduce trospium bioavailability and plasma concentrations. By dosing on an empty stomach, variability in trospium concentrations in plasma can be minimized. Previous studies have indicated that the body may adapt to xanomeline over time, which could decrease the need for higher trospium concentrations after the adaptation and thus allow dosing of KarXT without a food restriction. If an individual takes KarXT with food, any loss of trospium might be mitigated by this acclimation.¹ The purpose of this current study is to assess the safety and efficacy of KarXT in adult participants with schizophrenia administered BID with slower up-titration compared to up-titration in the pivotal trials, as well as taken with food when being on a stable dose. The current study is designed to demonstrate that taking KarXT with food, after an initial slow up-titration, is safe and tolerable.

3.2 Background

3.2.1 Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.² The prevalence of schizophrenia is between 0.6% and 1.9% in the United States (US) population.³ Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the US is 5.1 per 1000 lives.⁴ It is found equally in males and females, with males usually having an earlier onset of symptoms.⁵ The mainstay for treating schizophrenia is antipsychotic drugs (APDs).⁶ All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia, and, consequently, have limited use today. The second-generation agents that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.^{7,8,9} These side effects contribute to poor medication adherence, resulting in frequent relapses and hospitalizations.^{10,11} Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence, including both animal and human

studies.^{12,13} There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the CNS.¹⁴ However, compounds that agonize M1 and M4 receptors are often not specific enough and also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share. This leads to adverse events (AEs) related to activation of these peripheral receptors, so any potential benefit of muscarinic agonists in schizophrenia (or other indications, such as AD) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

3.2.2 **KarXT (Xanomeline Tartrate and Trospium Chloride)**

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors but preferentially stimulates M1 and M4 receptors in the CNS, which is thought to be responsible for the drug's therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M4 muscarinic agonist in vivo, measured by various second messenger assays.¹⁵ Xanomeline enters the brain rapidly achieving a brain-to-plasma ratio of greater than 10, making it an attractive CNS drug candidate.¹⁶ Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement. Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 dosages of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.^{17,18} Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in participants who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.^{17,18} In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant participants with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.¹⁹ Xanomeline is currently not approved or marketed in any country.

In both the Alzheimer's Dementia and schizophrenia trials, as well as in previous healthy volunteer studies, dose-dependent "cholinergic" AEs were also reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. These side effects were frequent and, at the higher doses of xanomeline, led to significant rates of discontinuation in the AD studies. This "procholinergic" AE profile curtailed further development of xanomeline as a single agent.

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of peripheral rather than central muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist that binds to and antagonizes all five muscarinic receptor subtypes.²⁰ It is a commonly used generic drug approved for 20 years or

more by the Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.²⁰ Several human participant studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure.²¹

KarXT represents a novel approach to the treatment of people with schizophrenia that will provide an important and meaningful alternative to current therapies. KarXT is a novel combination of xanomeline and trospium chloride, designed to allow xanomeline to be administered and stimulate CNS muscarinic receptors while reducing the dose-limiting peripheral side effects associated with muscarinic agonism.

The primary evidence of the efficacy and safety of KarXT in the treatment of schizophrenia is based on 3 completed, 5-week, randomized, double-blind, placebo-controlled studies (KAR-004, KAR-007, and KAR-009) that evaluated KarXT in adult participants with a diagnosis of schizophrenia according to the DSM-5 criteria. The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 5. The PANSS is a 30-item scale that measures the positive, negative, and general psychopathology symptoms of schizophrenia. In all three studies, participants randomized to KarXT showed a statistically significant reduction from baseline to Week 5 in the PANSS Total Score compared to the placebo group and was superior to placebo on the PANSS Positive Subscale.

The evaluation of KarXT in the treatment of schizophrenia is supported by long-term data from 2 Phase 3 open label extension (OLE) studies. The first study, KAR-008, was a 52-week OLE study that included participants who completed KAR-007 and KAR-009, and the second study, KAR-011, was a 52-week, open-label, outpatient study in de novo participants with schizophrenia.

Participants in all 3 pivotal studies adhered to the same titration regimen: a lead-in dose of xanomeline 50 mg/trospium chloride 20 mg (50/20) BID for at least the first 2 days, followed by xanomeline 100 mg/trospium chloride 20 mg (100/20) BID for at least 5 days (Days 3 to 7). On Day 8, dosing was titrated upwards to xanomeline 125 mg/trospium chloride 30 mg (125/30) BID, unless the participant was continuing to experience AEs from the previous dose increase to 100/20 BID. All participants who were increased to 125/30 BID, depending on clinical response and tolerability, had the option to return to 100/20 BID for the remainder of the treatment period.

3.3 Benefit/Risk Assessment

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by participants who were either institutionalized or studied in an inpatient hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side-effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration-quality pivotal trial in 182 participants met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs -5.9 placebo) at Week 5.

KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all postrandomization time points (Weeks 2, 4, and 5) with a calculated effects size (Cohen's d) of 0.81. Compared to placebo, KarXT demonstrated significant improvement at all postrandomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and Clinical Global Impression-Severity (CGI-S) scores.

Over 1632 participants have been exposed to xanomeline tartrate (oral formulation; either alone in combination with trospium, or as the combination drug KarXT) in clinical studies. Clinical studies and nonclinical pharmacology and toxicology studies have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic-related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, participants treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better-tolerated therapy. A titration phase also increases the tolerability of KarXT.

The most frequently reported AEs in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation.

In a Phase 2 clinical study (KAR-004), KarXT (100/20 BID and 125/30 BID) significantly reduced the symptoms of schizophrenia in participants with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common treatment-emergent adverse events (TEAEs) being constipation, nausea, dry mouth, dyspepsia, and vomiting. All reported TEAEs were mild or moderate in intensity.

In participants with schizophrenia in the Phase 3 studies (KAR-007 and KAR-009), administration of KarXT for 5 weeks resulted in consistent, significant reductions in both positive and negative symptoms of schizophrenia and CGI-S compared with placebo. In addition, the safety and tolerability were consistent with the previous placebo-controlled trial (KAR-004) and between the trials (KAR-007 and KAR-009) and notably, free of many common side effects associated with currently approved antipsychotic drugs. At Day 8, most participants on KarXT up-titrated to the highest dose, thus indicating how well this patient population tolerates KarXT. These results confirm and extend the antipsychotic benefit of xanomeline observed in past studies and well-tolerated nature of KarXT.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of KarXT may be found in the Investigator's Brochure and the Package Insert.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: KarXT		
Urinary Retention	KarXT can cause urinary retention. Geriatric patients and patients with clinically significant bladder outlet obstruction and incomplete bladder emptying (eg, patients with BPH, diabetic cystopathy) may be at increased risk of urinary retention. KarXT is contraindicated in patients with pre-existing urinary retention and is not recommended in patients with moderate or severe renal impairment.	Inform participants that KarXT may cause symptoms of urinary retention, including urinary hesitancy, weak stream, incomplete bladder emptying, and dysuria. Inform participants that urinary retention may increase the risk of urinary tract infection. Instruct participants to be aware of the risk and promptly report symptoms of urinary retention to their study physician and advise participants to seek immediate medical attention if they are unable to urinate. In participants with symptoms of urinary retention, consider reducing the dose of KarXT (if allowed per protocol), discontinuing KarXT, or referring participants for urologic evaluation as clinically indicated.
Angioedema	Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, a component of KarXT. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life threatening.	Advise participants that hypersensitivity reactions to KarXT could occur and result in life-threatening airway obstruction. Instruct participants to seek medical attention if they experience edema of the tongue, edema of the laryngopharynx, or difficulty breathing occurs, discontinue KarXT, and seek immediate medical attention If involvement of the tongue, hypopharynx, or larynx occurs, discontinue KarXT and initiate appropriate therapy and/ or measures necessary to ensure a patent airway.
Decreased Gastrointestinal Motility	KarXT contains trospium chloride. Trospium chloride, like other antimuscarinic agents, may decrease gastrointestinal motility. Administer KarXT with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Use KarXT with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis. KarXT contains trospium chloride. Trospium chloride, like other antimuscarinic agents, may decrease GI	Inform participants that KarXT can delay or slow emptying of food in their stomach. Advise participants to inform their study doctor about the presence of or symptoms of gastrointestinal obstructive disorders and conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	motility. Administer KarXT with caution in participants with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.	
Narrow-angle Glaucoma	Pupillary dilation may occur due to the anticholinergic effects of KarXT. This may trigger an acute angle closure attack in individuals with anatomically narrow angles.	In participants known to have anatomically narrow angles, KarXT should only be used if the potential benefits outweigh the risks and with careful monitoring. Inform participants pupillary dilation may occur with KarXT use and in susceptible individuals, can lead to an episode of angle closure glaucoma. Advise participants to inform their study doctor if they develop any signs or symptoms of narrow-angle glaucoma during treatment with KarXT.
Increases in Heart Rate	KarXT can increase heart rate.	Assess heart rate at baseline and at scheduled timepoints during the study and as clinically indicated during treatment with KarXT. Inform participants that KarXT can increase heart rate. Advise participants to inform their study doctor if they develop a racing or pounding feeling in their chest during treatment with KarXT.
Biliary Disease	In clinical studies with KarXT, transient increases in liver enzymes with rapid decline occurred, consistent with transient biliary obstruction due to biliary contraction and possible gallstone passage. KarXT is not recommended for participants with active biliary disease such as symptomatic gallstones.	Assess liver enzymes and bilirubin prior to initiating KarXT and as clinically indicated during treatment. The occurrence of symptoms such as dyspepsia, nausea, vomiting, or upper abdominal pain should prompt assessment for gallbladder disorders, biliary disorders, and pancreatitis, as clinically indicated. Discontinue KarXT in the presence of signs or symptoms of substantial liver injury such as jaundice, pruritus, or in cases outlined in Section 9.2.10 . Advise participants to inform study physician if they develop any signs or symptoms of biliary disorders during treatment with KarXT.
Hepatic Impairment	Participants with hepatic impairment have higher systemic exposures of xanomeline, a component of KarXT, compared to participants with normal hepatic function, which may result in	Assess liver enzymes prior to initiating KarXT, at scheduled timepoints during the study, and as clinically indicated during treatment. Instruct participants to report signs of hepatic impairment (eg, skin and eyes that

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	increased incidence of KarXT-related adverse reactions. KarXT is contraindicated in participants with moderate or severe hepatic impairment. KarXT is not recommended in participants with mild hepatic impairment.	appear yellowish, abdominal pain and swelling, itchy skin, dark urine color) and symptoms of hepatic injury (eg, biliary spasm, pancreatitis, and cholangitis) to the investigator.
Anticholinergic Adverse Reactions in Participants with Renal Impairment	Trospium chloride, a component of KarXT, is substantially excreted by the kidney. KarXT is not recommended in participants with moderate or severe renal impairment (eGFR < 60 mL/min). Systemic exposure of trospium chloride is high in participants with moderate and severe renal impairment. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in participants with moderate and severe renal impairment.	Inform participants that KarXT is associated with anticholinergic adverse reactions such as dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention and the effects are expected to be greater in participants with renal impairment.
Central Nervous System Effects	Trospium chloride, a component of KarXT, is associated with anticholinergic central nervous system effects. A variety of CNS anticholinergic effects have been reported with trospium chloride, including dizziness, confusion, hallucinations, and somnolence	Monitor participants for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise participants that KarXT is associated with central nervous system effects such as dizziness, confusion, hallucinations, and somnolence. Caution participants about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that KarXT therapy does not adversely affect their ability to engage in such activities If a participant experiences anticholinergic CNS effects, consider dose reduction (per protocol) or drug discontinuation.

Abbreviations: ALT, alanine aminotransferase; BPH, benign prostatic hyperplasia; CNS, central nervous system; eGFR, estimated glomerular filtration rate; GI, gastrointestinal.

3.3.2 Benefit Assessment

For an individual participant, there is a potential clinical benefit of receiving KarXT during the study. Studies of KarXT in adults have shown significantly reduced symptoms of schizophrenia in participants after treatment for 28 days.²² Individual participants may benefit from treatment,

which may improve schizophrenia symptoms. Participants may also benefit from receiving regular medical evaluation/assessments associated with study procedures that may be helpful for disease management.

3.3.3 Overall Benefit/Risk Conclusion

KarXT has been developed as a first-in-class muscarinic receptor antipsychotic. Treatment with KarXT led to clinically meaningful and statistically significant improvements in schizophrenia symptoms in the placebo-controlled studies, and these improvements appear to be sustained based on long-term data. KarXT has been shown to be safe, generally well-tolerated, and not associated with many troublesome side effects typically associated with existing approved therapies. The most common AEs associated with KarXT were procholinergic and anticholinergic events that were mostly mild/moderate and infrequently led to treatment discontinuation. KarXT was associated with transient increases in liver function tests (LFTs) in a small percentage of participants that resolved with continued treatment in most cases. Small increases in BP (primarily diastolic) and elevations in HR have been observed that attenuate with continued dosing. KarXT was not associated with clinically relevant metabolic abnormalities (weight gain, hyperglycemia, and dyslipidemia), seizures, hematological abnormalities (leukopenia, neutropenia, and agranulocytosis), cognitive or motor impairment, sedation-related events (somnolence, lethargy, and fatigue), prolactin elevations, NMS, orthostatic hypotension, or QTc prolongation. The rates of EPS were lower than other approved antipsychotics. There were no safety signals with respect to suicidal ideation or behavior.

KarXT represents a completely new drug class with a novel mechanism of action for the treatment of schizophrenia. The clinical development program for KarXT demonstrated significant benefits in improving schizophrenia symptoms. KarXT was well-tolerated with a safety profile fully differentiated from the current approved therapies. The overall benefit-risk profile is strongly favorable for the use of KarXT in patients with schizophrenia.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of KarXT in adults with a DSM-5 diagnosis of schizophrenia after an initial slow titration of KarXT, administered BID on an empty stomach, followed by KarXT BID with food.	Incidence of TEAEs from first dose of study intervention to end of safety follow-up.
Secondary	
- To assess other measures of safety and tolerability - To assess efficacy following administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:	Safety: - Incidence of TEAEs by study period (from first dose of study intervention to Day 28 and from Day 29 to EoT [Day 56]). - Incidence of serious TEAEs overall and by study period (from first dose of study intervention to Day 28, from

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
– To evaluate the reduction in PANSS total score – To evaluate the reduction in PANSS positive score – To evaluate the improvement in CGI-S score – To evaluate the reduction in PANSS negative score – To evaluate the reduction in PANSS Marder Factor negative symptoms score	Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). • Incidence of TEAEs leading to study intervention discontinuation overall and by study period (from first dose of study intervention to Day 28, from Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). • Incidence of pro- and anticholinergic TEAEs overall and by study period (from first dose of study intervention to Day 28, from Day 29 to EoT [Day 56], and from first dose of study intervention to end of safety follow-up). <u>Efficacy:</u> • Change from baseline in PANSS total score • Change from baseline in PANSS positive score • Change from baseline in PANSS negative score • Change from baseline in PANSS negative Marder Factor score • Change from baseline in CGI-S score <u>Other Safety:</u> • Spontaneously reported AESIs • Change from baseline in body weight, BMI, and waist circumference • Change from baseline in orthostatic vital signs (blood pressure [systolic and diastolic] and heart rate supine and standing after 2 minutes) • Change from baseline in clinical laboratory assessments • Change from baseline in 12-lead ECG • Change from baseline in physical examination • Suicidal ideation scale with the use of C-SSRS

Abbreviations: AESI, adverse event of special interest;

; BID, twice daily; BMI, body mass index; CGI-S, Clinical Global Impression-Severity;

; C-SSRS, Columbia-Suicide Severity Rating Scale;

DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; EoT, end of treatment;

PANSS, Positive and Negative Syndrome Scale;

TEAE, treatment-emergent adverse event.

Note: Baseline is defined as Day 1.

5

STUDY DESIGN

5.1

Overall Design

This is a Phase 4, open-label, multicenter, two-cohort study to assess the safety and efficacy of KarXT in participants with DSM-5 schizophrenia in an inpatient setting. Total duration of the study will be up to approximately 11 weeks. This includes a screening period of up to 2 weeks, an 8-week open-label treatment period, and a 1-week safety follow-up period.

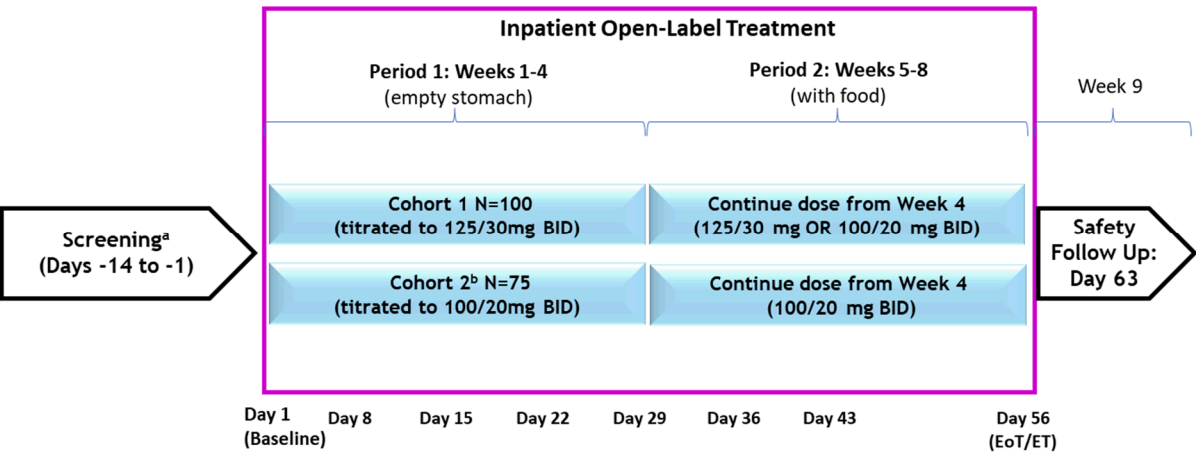
Approximately 175 participants with schizophrenia will be enrolled.

After signing the study informed consent form (ICF), participants will enter the screening period. During the screening period, participants will complete the screening procedures and assessments to determine if they meet eligibility criteria. The screening period will last no more than 14 days. Eligible participants will be enrolled at the Baseline visit, admitted to the inpatient unit, and begin OL treatment of KarXT for up to 8 weeks. The 8-week OL treatment period is divided into two periods (Period 1 and Period 2). There will be 8 study visits during the Treatment Period: Day 1 (Baseline), 8, 15, 22, 29, 36, 43, and 56/ET. For each study visit after screening the visit window is ± 3 days.

There will be a 1-week safety follow-up period, with a visit occurring at Day 63 (Week 9), following the last KarXT dose for participants who complete the 8-week treatment period and those who discontinue early from the study.

The study design schema is presented in [Figure 5.1-1](#).

Figure 5.1-1: Study Design Schema



Abbreviations: EoT, end of treatment; ET, early termination.

^a May include down-taper as necessary.

^b Cohort 2 will be initiated after enrollment completion of Cohort 1.

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will

be closely monitored for AEs throughout the study.

5.1.1 Data Monitoring Committee and Other Committees

A Data Monitoring Committee will not be used in the study.

Other review committees will not be used in the study.

5.2 Number of Participants

Approximately 175 participants (aged 18 to 65 years, inclusive) are planned to be enrolled in this study.

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

The primary completion date is defined as the date on which the last data point is collected for the study's last primary endpoint (outcome). For this study, the last primary outcome for the primary endpoints is Day 63.

End of study is defined as the last participant's last visit.

Participants are considered to have completed the study if they have completed all periods of the study, including the last visit or the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

This is a Phase 4, open-label, multicenter, two-cohort study to assess the safety and efficacy of KarXT in participants with DSM-5 schizophrenia in an inpatient setting. The primary evidence of the efficacy and safety of treatment with KarXT in the treatment of schizophrenia is based on 3 completed, 5-week, randomized, double-blind, placebo-controlled, studies (KAR-004, KAR-007, and KAR-009) that evaluated the proposed dosing regimen of KarXT in adults with schizophrenia. In these studies, KarXT was taken BID on an empty stomach. Participants were up-titrated from a starting dosage of 50/20 BID over the course of 1 week, with the goal to achieve a dosage of 125/30 BID if tolerated, otherwise participants could remain at or be reduced to 100/20 BID. This treatment paradigm resulted in most participants being able to tolerate doses of either 125/30 BID or 100/20 BID and demonstrated a favorable benefit-risk profile in treating symptoms of schizophrenia.

Adverse event data in clinical studies indicate that people adapt to the adverse reactions of xanomeline over time. Therefore, the need to maximize trospium concentrations may diminish as this acclimation to xanomeline occurs, and if an individual takes KarXT with food, any loss of trospium might be mitigated by this acclimation.¹

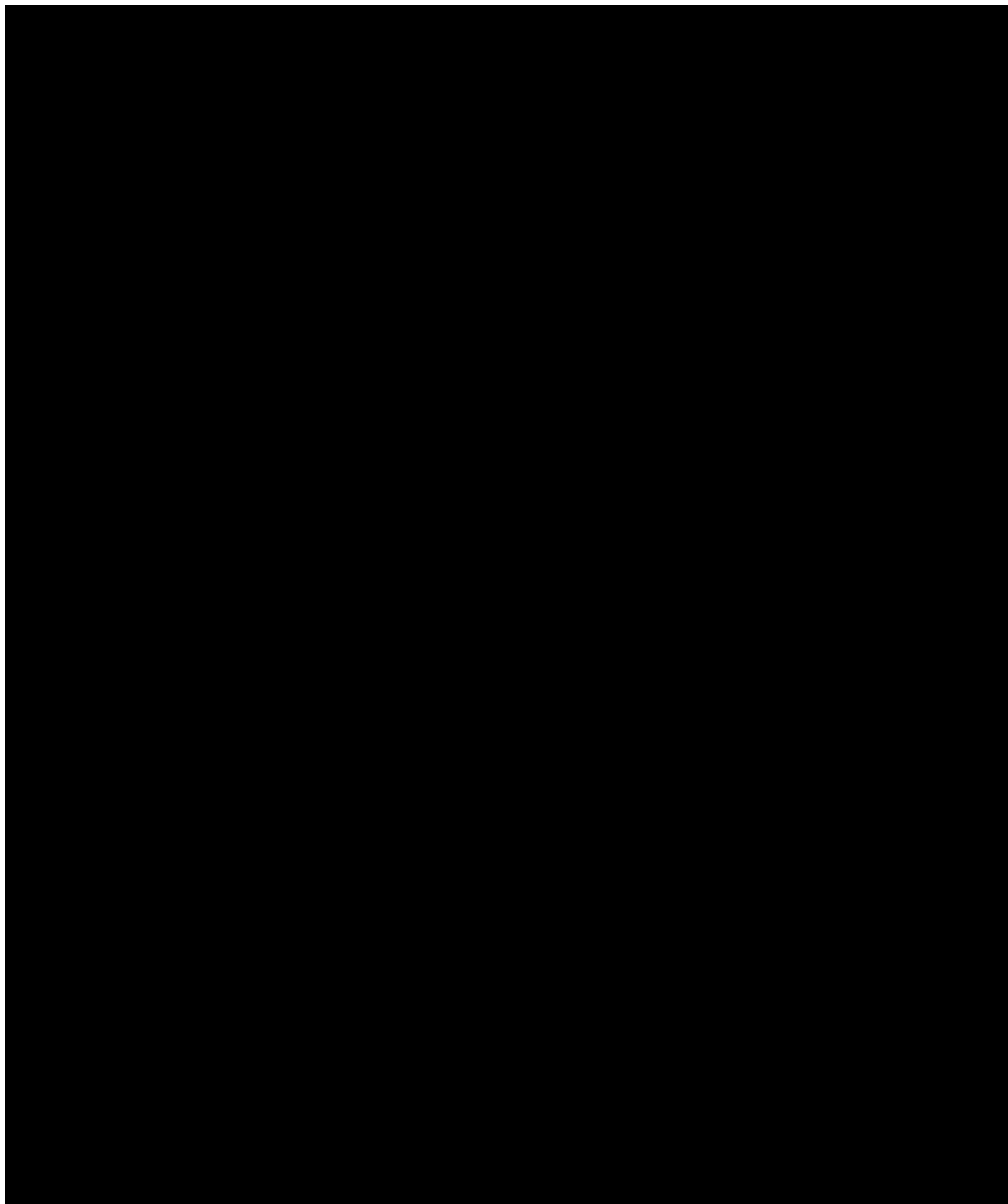
The purpose of this current study is to assess the safety and efficacy of KarXT in adult participants with schizophrenia administered at both the 100/20 mg BID and 125/30 mg BID doses on an empty stomach over a slower up-titration at the start of treatment (Period 1), followed by BID taken with food when being on a stable dose (Period 2).

5.5 Justification for Dose

KarXT has been shown in 3 clinical studies in patients with schizophrenia to produce a robust benefit-risk profile when titrated from 50/20 BID to 125/30 BID. In these clinical studies, participants were titrated over 8 days, with the goal to achieve a dosage of 125/30 BID if tolerated, otherwise participants could remain at or be reduced to 100/20 BID. This treatment paradigm resulted in most participants with schizophrenia being able to tolerate dosages of either 125/30 BID or 100/20 BID and demonstrated a favorable benefit-risk profile in treating symptoms of schizophrenia. This observation led to an approval with dose instructions in the USPI of patients escalating to 100/20 BID, with an option to further escalate to 125/30 BID based on patient response. Therefore, both dosages are expected to be used by patients who receive KarXT in clinical practice.

In clinical studies with other populations, including healthy non-elderly and healthy elderly participants, this rapid titration scheme has been less well tolerated. Using a longer titration scheme in healthy elderly participants—increasing to 12, 15, and finally 17 days to titrate to the top dose—allowed for improved tolerability, suggesting that all populations may benefit from a longer escalation scheme.²²

The [REDACTED] of KarXT has been shown to be impacted by food. In KAR-055, a high-fat high-calorie meal increased xanomeline AUC by 30% while a lower-fat lower-calorie meal had no impact on xanomeline. In contrast, both types of meals reduced trospium AUC by 70% to 75%. Due to these [REDACTED] effects, it is anticipated that administration of KarXT with food may adversely impact tolerability by increasing the risk of procholinergic events associated with xanomeline.



6 STUDY POPULATION

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Signed Written Informed Consent

- a. Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory, local, and institutional guidelines. This ICF must be obtained before performing any protocol-related procedures that are not part of normal patient care.

2. Type of Participant and Target Disease Characteristics

- a. Participant has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview (MINI) for Schizophrenia and Psychotic Disorder Studies version 7.0.2.
- b. PANSS total score of ≤ 80 at screening and Baseline
- c. CGI-S score of ≤ 4 at screening and Baseline
- d. Participant must be taking an oral antipsychotic medication at a dose and frequency consistent with the drug label or at a stable dose based on investigator judgement for at least 30 days prior to screening.
- e. In the opinion of the investigator, it is clinically appropriate for the participant to discontinue current antipsychotic therapy and initiate KarXT.
- f. Participant is willing and able, in the opinion of the investigator, to discontinue all antipsychotic medications at least 3 days prior to the Baseline visit.
Note: Antipsychotic down-taper, if clinically appropriate in the opinion of the investigator, may occur during the screening period.
- g. Participant is willing and able to be confined to an inpatient setting for an 8-week duration, follow instructions, and comply with the protocol requirements.
- h. BMI ≥ 18 and ≤ 40 kg/m².

3. Age of Participant

- a. Participant must be 18 to 65 years of age, inclusive, at the time of signing the ICF.

4. Reproductive Status

- The investigator or designee shall counsel individuals of childbearing potential (IOCBP) participants (as defined in [Appendix 4](#)) and male (as assigned at birth) participants who are sexually active with IOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator or designee shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraceptive methods.

a. Female (as assigned at birth) participants:

- i. Female (as assigned at birth) participants who are not of childbearing potential must have documented proof. Note: Documentation can be obtained from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
 - Individuals who are not of childbearing potential (as defined in [Appendix 4](#)) are exempt from contraceptive requirements.
- ii. IOCBP must have a negative highly sensitive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) at screening.
 - Additional requirements for pregnancy testing during and after study intervention are in [Section 2](#): Schedule of Activities.
 - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of an individual with an undetected pregnancy.
- iii. IOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.
 - IOCBP are permitted to use hormonal contraceptive methods (as described in [Appendix 4](#)).
- iv. A female (as assigned at birth) is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:
 - Is not an IOCBP
OR
 - Is an IOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with user dependent or user independent methods as described in [Appendix 4](#), during the intervention period and for at least 4 weeks and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same period.

b. Male (as assigned at birth) participants:

- Male (as assigned at birth) participants should maintain their usual practice regarding contraception (if any); however, no specific or additional contraceptive measures are required.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Medical Conditions

- a. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening). Exclusionary disorders include but are not limited to major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and post-traumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment.

- b. The participant has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline.
Note: A participant with mild substance abuse disorder within the 12 months before screening must be discussed and agreed upon with the Medical Monitor before he/she can be allowed into the study. Participants with a positive UDS for cannabis are permitted to enroll in the study provided that the participant's pattern of use is not indicative of a substance use disorder.
- c. Participants who are newly diagnosed or are experiencing their first treated episode of schizophrenia.
- d. History or presence of clinically significant cardiovascular (eg, untreated or unstable hypertension, clinically significant tachycardia), pulmonary, renal, hematologic, gastrointestinal ([GI] eg, obstructive disorders [including conditions that may decrease GI motility, such as ulcerative colitis, intestinal atony, and myasthenia gravis], active biliary disease [including symptomatic gallstones]), endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the participant or the validity of the study results.
- e. All grades of hepatic impairment (mild [Child-Pugh Class A], moderate [Child-Pugh Class B], and severe [Child-Pugh Class C]).
- f. Participants with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or LFT results.
- g. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
- h. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
- i. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
 - "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or
 - "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Nonsuicidal self-injurious behavior is not exclusionary.
- j. Participant has a history of treatment resistance to schizophrenia medications defined as:
 - Failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) within the past 12 months
- k. If, in the opinion of the investigator (and/or Sponsor), participant is unsuitable for enrollment in the study or participant has any finding that, in the opinion of the investigator (and/or Sponsor), may compromise the safety of the participant or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
- l. Participant has had psychiatric hospitalization(s) for more than 30 days (cumulative) within the 6 months before screening.
- m. Participant has required psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 8 weeks of screening and is not psychiatrically stable in the opinion of the investigator.

- n. A positive COVID-19 test at the time of admittance to the inpatient unit if testing is required by the site.
- o. For males ≥ 45 years of age only, any one of the following:
 - i. History of bladder stones.
 - ii. History of recurrent urinary tract infections.
 - iii. Serum prostate-specific antigen (PSA) >10 ng/mL at the screening visit.
 - iv. An International Prostate Symptom Score (IPSS) of 5 (almost always) on items 1, 3, 5, or 6 at the screening visit.
 - v. A sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 at the screening visit.

2. Reproductive Status

- a. Individuals who are breastfeeding.
- b. Individuals who are pregnant, lactating, or less than 3 months postpartum.

3. Prior/Concomitant Therapy

- a. Inability to comply with restrictions and prohibited treatments as listed in [Section 7.7: Concomitant Therapy](#).
- b. Participants with prior exposure to KarXT within 3 months of screening.
- c. Participants who experienced any significant adverse effects due to xanomeline or trospium
- d. Participants taking a long-acting injectable antipsychotic who have received a dose of medication within 2 cycles before Baseline.
- e. Participants who have taken lithium therapy within 2 weeks of Baseline.

4. Physical and Laboratory Test Findings

- a. Clinically significant abnormal findings on the physical examination, medical history, ECG, or clinical laboratory results at screening.
- b. Positive blood screen for hepatitis C virus (HCV) antibody at screening or within 3 months unless HCV-RNA negative test is documented, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV).
- c. An estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m² at the screening visit. One repeat measurement is allowed.

5. Allergies and Adverse Drug Reactions

- a. History of hypersensitivity to KarXT or trospium chloride.
- b. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

6. Other Exclusion Criteria

- a. Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)
- b. Inability to comply with restrictions as listed in [Section 6.3: Lifestyle Restrictions](#).
- c. Current participation in another clinical trial, or participation in another clinical study in which the participant received an experimental or investigational drug agent within 30 days prior to screening.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Not applicable.

6.3.2 Alcohol

Alcohol use will not be permitted during the study. Alcohol testing will be performed using a breathalyzer or urine alcohol test. If a participant leaves the study site, they should have a urine drug screen test and test for alcohol (breathalyzer or urine alcohol test) upon returning to the study site.

6.3.3 Activity

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently dosed. Rescreening will be permitted with approval of the Medical Monitor.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been treated) upon approval of the Medical Monitor on a case-by-case basis. If re-enrolled, the participant must be re-consented.

Re-testing of laboratory parameters and/or other assessments in any single screening period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Baseline is the value by which study inclusion will be assessed because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are required during screening may be repeated to identify all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of a parameter is clinically relevant. When re-testing within the same screening procedure, only the exclusionary laboratory tests will be repeated once in case the exclusionary laboratory result was not due to a pathological condition and was occasional (except for individuals who have positive serology results).

7 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study interventions are defined as all pre-specified, investigational interventions, marketed products, placebos, procedures, or medical devices intended to be administered to study participants according to the study protocol.

Study intervention includes Investigational [Medicinal] Product (IP/IMP) as indicated in [Table 7.1-1](#).

An Investigational Product (IP), also known as an Investigational Medicinal Product (IMP) in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, used for an unauthorized indication, or when used to gain further information about the authorized form.

In this study, IP will be used for treatment of adults with schizophrenia. Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered Non-IMPs/AxMPs. Not applicable for this study.

7.1 Study Interventions Administered

The investigator must ensure that the study intervention will be used in accordance with the protocol. Study interventions for all participants shown in [Table 7.1-1](#) and [Table 7.1-2](#), respectively. Every participant's first dose should be administered by a physician or appropriately trained and licensed medical practitioner.

All investigational agents are to be stored according to requirements.

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non- IMP/AxMP	Sourcing	Packaging and Labeling ^a	Current Name
Drug/KarXT/Capsule	50 mg xanomeline/ 20 mg trospium chloride	IMP	Provided centrally by the Sponsor	Each container will be labeled as required per country requirements and packaged according to the pharmacy manual.	KarXT/ BMS-986510

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/ Dose Formulation	Unit Dose Strength(s)	IMP/Non- IMP/AxMP	Sourcing	Packaging and Labeling ^a	Current Name
Drug/KarXT/Capsule	100 mg xanomeline/ 20 mg trospium chloride	IMP	Provided centrally by the Sponsor	Each container will be labeled as required per country requirements and packaged according to the pharmacy manual.	KarXT/ BMS-986510
Drug/KarXT/Capsule	125 mg xanomeline/ 30 mg trospium chloride	IMP	Provided centrally by the Sponsor	Each container will be labeled as required per country requirements and packaged according to the pharmacy manual.	KarXT/ BMS-986510

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; Non-IMP, Non-investigational Medicinal Product.

^a KarXT 50 mg/20 mg and 125 mg/30 mg capsules are packaged in blister card wallets, KarXT 100 mg/20 mg capsules are supplied in 2 packaging presentations; blister card wallets and bottles. KarXT 100 mg/20 mg capsules packaged in bottles will be dispensed for participants in Cohort 2 only. For all other participants, 100 mg/20 mg capsules will be dispensed in the blister card wallet presentation (if applicable).

Table 7.1-2: Study Arm(s)

Arm Title/ Arm Use	Intervention Description/ Dosage Levels	Route of Administration
KarXT Fixed Dose 50/20	50 mg xanomeline/20 mg trospium chloride BID	Oral
KarXT Fixed Dose 100/20	100 mg xanomeline/20 mg trospium chloride BID	Oral
KarXT Fixed Dose 125/30	125 mg xanomeline/30 mg trospium chloride BID	Oral

Abbreviations: BID, twice daily.

Cohort 1:

Dosing during Period 1 is as follows:

- Days 1-7 (Week 1) - KarXT 50/20 BID on empty stomach, ie, at least one hour before meals or at least two hours after meals
- Days 8-14 (Week 2) - KarXT 100/20 BID on empty stomach, ie, at least one hour before meals or at least two hours after meals
- Days 15-28 (Week 3 - Week 4) - KarXT 125/30 BID on empty stomach, ie, at least one hour before meals or at least two hours after meals, unless the participant is continuing to experience AEs from the previous dose increase to KarXT 100/20 BID. All participants who are increased to KarXT 125/30 mg BID in Period 1, depending on tolerability as assessed by the investigator, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period.

Dosing during Period 2 is as follows:

- On Day 29 (start of Week 5) participants will receive the same KarXT dose as Day 28 (last day of Week 4) BID taken with food, ie, taken within 30 minutes of morning/evening meal or snack.

During Period 2, participants will have the option to dose de-escalate one time from 125/30 BID to 100/20 BID depending on tolerability as assessed by the investigator. Dose escalation will not be permitted during Period 2.

Cohort 2:

Dosing during Period 1 is as follows:

- Days 1-7 (Week 1) - KarXT 50/20 BID on empty stomach; ie, at least one hour before meals or at least two hours after meals
- Days 8-28 (Week 2 - Week 4) - KarXT 100/20 BID on empty stomach (at least one hour before meals or at least two hours after meals)

Dosing during Period 2 is as follows:

- On Day 29 (start of Week 5), participants will receive the same KarXT dose as Day 28 (last day of Week 4) BID taken with food; ie, taken within 30 minutes of morning/evening meal or snack.
- Dose escalation will not be permitted during Period 2.

Cohorts 1 and 2:

There will be one safety follow-up visit (Week 9) following the last KarXT dose for all participants in Cohorts 1 and 2 who complete the 8-week treatment period, and those who discontinue early from the study.

Dose de-escalation from 100/20 to 50/20 will not be permitted during the study duration.

7.2 Assignment to Study Intervention

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by the Sponsor for assignment of a [REDACTED] participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [REDACTED]. For example, the first participant screened (ie, enrolled) at [REDACTED]. Once it is determined that the participant meets the eligibility criteria following the [REDACTED].

screening visit, the investigative site will call the IRT to enroll the participant into the open-dose panel.

7.3 Blinding

Blinding is not applicable, as this is an open-label study.

7.4 Dosage Modification

All participants in Cohort 1 who are increased to KarXT 125/30 BID in Period 1, depending on tolerability as assessed by the investigator, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period.

During Period 2, all participants will have the option to dose de-escalate one-time from 125/30 mg BID to 100/20 mg BID depending on tolerability as assessed by the investigator. Dose escalation will not be permitted during Period 2.

Participants will not be permitted to de-escalate to the 50/20 mg BID dose.

7.5 Preparation/Handling/Storage/Accountability

The IP/IMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/IMP is only dispensed to study participants. The IP/IMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP/IMP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm that 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, prepare, or administer study intervention.
- All study intervention 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, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

7.6 Study Intervention Compliance

The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to each participant, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study participants. Administration of study intervention will be supervised by study site personnel to ensure compliance. Investigators will maintain records that adequately document that the participants were provided with the correct study intervention bulk supply and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor or designee until accountability has been fully monitored through the end of the study. Study intervention accountability will be assessed periodically by the assigned study monitor or designee.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Participants will be asked to confirm all prior medications they were taking up to 6 months before the study, up to the time of consent. All prior medications will be recorded on the eCRF, and all medications and other treatments taken by the participant during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

During the study (ie, from the time consent until study completion), participants should refrain from the use of any new concomitant medications without the approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the approval of the investigator unless its use is deemed necessary in a medical emergency.

After written informed consent is obtained from the participant, those participants who are taking the following medications must have the minimum washout periods specified below and not take the medications for the duration of the study:

- The use of monoamine oxidase inhibitors, anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), centrally acting anticholinergics (eg, Cogentin, Benadryl), or any other psychoactive medications other than daily antipsychotic maintenance therapy within 5 half-lives before Baseline is prohibited.
- Selective serotonin reuptake inhibitors (SSRI's)/serotonin and norepinephrine reuptake inhibitors (SNRI's) taken at stable dose for at least 8-weeks prior to screening, and that are anticipated to be continued at the same dose throughout the 8-week treatment period, may be permitted.

7.7.2 Drug Interactions

7.7.2.1 Clinically Significant Drug Interactions with KarXT

Drugs Eliminated by Active Tubular Secretion:

Concomitant use of KarXT with drugs that are eliminated by active tubular secretion may increase plasma concentrations of trospium, a component of KarXT, and/or the concomitantly used drug due to competition for this elimination pathway, which may increase the frequency and/or severity of AEs from KarXT or the drug eliminated by active tubular secretion.

Participants should be monitored for increased frequency and/or severity of AEs related to KarXT and AEs related to drugs eliminated by active tubular secretion in participants concomitantly receiving such drugs.

Strong Inhibitors of CYP2D6:

CYP2D6 contributes significantly to the metabolism of xanomeline, a component of KarXT. Concomitant use of KarXT with strong CYP2D6 inhibitors may increase plasma concentrations of xanomeline, which may increase the frequency and/or severity of AEs from KarXT.

Participants should be monitored for increased frequency and/or severity of AEs related to KarXT in participants taking strong inhibitors of CYP2D6.

Oral Drugs that are Sensitive Substrates of CYP3A4:

Xanomeline, a component of KarXT, transiently inhibits CYP3A4 locally in the gut but not systemically. Concomitant use of KarXT with oral drugs that are sensitive substrates of CYP3A4 may result in increased plasma concentrations of the oral drugs that are sensitive substrates of CYP3A4. This may increase the frequency and/or severity of AEs from such substrates.

Participants should be monitored for increased frequency and/or severity of AEs related to oral drugs that are sensitive substrates of CYP3A4 in participants taking KarXT with such substrates.

Oral Drugs that are Substrates of P-glycoprotein:

Xanomeline, a component of KarXT, transiently inhibits P-glycoprotein locally in the gut but not systemically. Concomitant use of KarXT with oral drugs that are substrates of P-glycoprotein may result in increased plasma concentrations of the oral drugs that are substrates of P-glycoprotein, which may increase the frequency and/or severity of AEs from such substrates.

Participants should be monitored for increased frequency and/or severity of AEs related to oral drugs that are narrow therapeutic index substrates of P-glycoprotein in participants taking KarXT with such substrates.

7.7.2.2 Other Antimuscarinic Drugs

Concomitant use of KarXT with other antimuscarinic drugs that produce anticholinergic adverse reactions (eg, dry mouth, constipation) may increase the frequency and/or severity of such effects. Monitor participants for increased frequency and/or severity of anticholinergic adverse reactions when KarXT is used concomitantly with other antimuscarinic drugs.

7.7.2.3 Effects on Absorption of Drugs

KarXT may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Dosage adjustment of concomitant medications may be necessary based on clinical response and tolerability.

7.7.3 Permitted Treatments

Participants are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, or insomnia on an as needed (PRN) basis. Participants may also use non-benzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid, also on a PRN basis.

Participants are allowed to take antiemetics (eg, ondansetron) for nausea, vomiting on a PRN basis.

All medications and other treatments taken by the participant during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF. Participants should refrain from the use of any new concomitant medications without the approval of the investigator (see [Section 7.7.1](#)).

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, the Sponsor will not continue to provide Sponsor-supplied study intervention to participants unless prohibited by local law. The investigator must ensure that participants receive appropriate standard of care to treat the condition under study. The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of KarXT is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or other health program, or commercial supply. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

Discontinuation of the study at specific sites or of the entire study is detailed in [Appendix 2](#).

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information. Every effort should be made within the bounds of safety and participant's choice to have each participant complete the early termination (ET) visit and SFU visit. If a participant withdraws consent, the only additional investigational data to be collected will be the follow-up of SAEs as mandated by the protocol.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue the study. Strict conditions apply, and Sponsor approval is required.)
- Lack of efficacy
- Pregnancy, positive pregnancy test, or participant expresses an interest in becoming pregnant (see [Section 9.2.5](#)).
- Inability or failure to comply with protocol requirements in the opinion of the Investigator.
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in [Section 9.2.7](#), or if the investigator believes that it is in the best interest of the participant.
- Participant reports suicidal ideation as assessed by C-SSRS, suicidal behavior, or suicide attempts at any time after inclusion. The participant should then be immediately referred to a mental health professional for evaluation of suicide risk.
- Participant has not taken KarXT for ≥ 7 days.

See [Section 2](#): Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified procedures as outlined in [Section 2](#): Schedule of Activities for an end of treatment/early termination visit. The only exception is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Sponsor Medical Monitor/designee of this event. The study intervention will be permanently discontinued.

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.2 Discontinuation From the Study

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

- If vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- Participants may withdraw completely from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in [Section 2: Schedule of Activities](#). See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up, if applicable, and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in [Section 2](#): Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before dosing. 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, complete blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame defined in the Schedule of Activities.
- The investigator may, at his/her discretion, arrange for a participant to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Activities ([Section 2](#)). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the Medical Monitor.
- Scale assessments must be performed by certified raters. Raters must provide documentation of valid training at the start of the study only.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

9.1.1.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of participants with schizophrenia and is widely used in the study of antipsychotic therapy.²⁹ The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Participants are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other efficacy and safety assessments for all visits at which it is performed, except during screening when the MINI should be conducted first.

9.1.1.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in participants with mental disorders. It is used to rate the severity of a participant's illness at the time of assessment. The CGI-S modified asks the clinician 1 question: "Considering your total clinical experience, how mentally ill is the participant at this time?" The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill participants.³⁰

This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. As symptoms and behavior can fluctuate over a week, the score should reflect the average severity level across the 7 days.

9.2 Adverse Events

The definitions of an AE or SAE can be found in [Appendix 3](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, or informant).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the informed consent form, including those thought to be associated with protocol-specified procedures and until 28 days following discontinuation of dosing or the last scheduled visit as noted in the Schedule of Activities ([Section 2](#)).

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure.

- All SAEs will be recorded and reported to the Sponsor or designee promptly and not to exceed 24 hours of awareness of the event, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee promptly and not to exceed 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs 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 reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in [Appendix 3](#).

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in [Section 8.3: Lost to Follow-up](#)).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including up to the last study

visit and at least 4 weeks after any study intervention administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor or designee promptly and not to exceed 24 hours of awareness of the event. Pregnancy reporting must follow the same transmission timing and processes to the Sponsor as those used for SAEs, in accordance with reporting procedures described in [Appendix 3](#).

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non-serious and Serious Events CRF page. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see [Section 9.2: Adverse Events](#) and [Appendix 3](#) for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation $> 3 \times$ upper limit of normal (ULN)
AND

- Total bilirubin $> 2 \times$ ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.2.8 Anticholinergic and Procholinergic Adverse Events

Anticholinergic events may include dizziness, confusion, hallucinations, somnolence, dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention. Procholinergic events may include nausea, vomiting, diarrhea, sweating, and excess salivation. Any new onset or worsening of these events should be recorded as AEs and reported as SAEs when appropriate. Participants should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose.

9.2.9 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.2.10 AEs of Special Interest

The AEs of special interest (AESIs) will be monitored and include symptomatic orthostasis, syncope (a transient loss of consciousness or fainting), and liver function test elevations as defined below. For SAE reporting requirements for events of liver injury, see [Section 9.2.7](#).

Orthostasis will be defined as the participant being symptomatic (associated with an AE, eg, syncope or dizziness) with at least 1 of the following differences in orthostatic vitals between the supine and standing positions after 2 minutes:

- A decrease of systolic BP of 20 mmHg or more
- A decrease in diastolic BP of 10 mmHg or more
- An increase in HR of 30 bpm or more

AESIs of liver enzyme elevations will be defined as serum ALT or AST $> 3 \times$ ULN and at least $2 \times$ the baseline level. Such an occurrence should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, alkaline phosphatase, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about any symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).

Management should include the following:

- Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the IP has been discontinued, and the participant is asymptomatic.
- Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, direct bilirubin)
- Conduct abdominal ultrasound when liver enzymes rise substantially (ie, ALT or AST $> 5 \times$ ULN and/or ALP $> 2 \times$ ULN)
- Seek a specific diagnosis by the following:
 - Obtain a more detailed history of symptoms and prior or concurrent diseases.
 - Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
 - Obtain a history of exposure to environmental chemical agents
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
 - Rule out COVID-19. Either rapid antigen or PCR testing can be done at the discretion of the investigator
- Follow-up to the resolution of elevated liver enzymes
- Consider gastroenterology or hepatology consultations

Discontinuation of treatment should be considered if any one or more are met:

- ALT or AST $> 8 \times$ ULN
- ALT or AST $\geq 5 \times$ ULN for more than 2 weeks
- ALT or AST $\geq 3 \times$ ULN and (total bilirubin $> 2 \times$ ULN or international normalized ratio > 1.5)
- ALT or AST $\geq 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia ($> 5\%$)

9.3 Overdose

For this study, any dose of KarXT greater than 125/30 mg BID within a 24-hour period will be considered an overdose. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (refer to [Appendix 3](#)).

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT. Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in BP with or without bradycardia, and severe anxiety and panic may occur. Supportive treatment should be

used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Atropine sulfate should be available for intravenous or intramuscular administration. Several doses ranging from 0.5 to 2.0 mg may be required. Epinephrine 0.1 to 1.0 mg subcutaneous may also be of value in overcoming severe cardiovascular or bronchoconstrictor responses. AEs associated with overdoses should be reported in the eCRF.

9.4 Safety

Planned time points for all safety assessments are listed in [Section 2: Schedule of Activities](#).

9.4.1 Demographics, Medical History, and Psychiatric History

Demographic data will be collected for all participants at screening. The information to be captured includes date of birth (alternatively year of birth if full date of birth is not allowed to be collected for legal reasons), age, sex, race, and ethnicity, which will be obtained from the participant and recorded in the eCRF.

Medical, psychiatric, and medication history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the participant's preexisting conditions, including all baseline symptoms, ongoing illnesses, other chronic conditions, and surgical history at screening. All medical history relevant to disease under study will be collected. Findings from physical examination will be recorded in the medical history and recorded on the appropriate CRF. Medical history will also include history of drug, substance, or alcohol abuse/dependence within 1 year before Screening.

Illnesses first occurring or detected during the study and worsening of any conditions reported as medical history during the study are to be documented as AEs on the eCRF in accordance with [Section 9.2](#).

9.4.2 Weight, Height, Body Mass Index, and Waist Circumference

Height (screening only), weight, and waist circumference measurements will be obtained at visits as specified in [Table 2-1](#) and [Table 2-2](#).

9.4.3 Physical Examination

A complete physical examination (general appearance, head/eyes/ears/nose/throat, examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in [Section 2](#). Physical examinations will be performed by a physician or qualified designee.

A targeted physical examination includes, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the participant's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

Any findings during the PE will be recorded as medical history in the participant's medical records and on the appropriate CRF.

9.4.4 Vital Signs

Orthostatic vital signs (supine and standing systolic and diastolic BP and heart rate measurements) will be evaluated at the visits indicated in the Schedule of Activities (Table 2-1 and Table 2-2). BP measurements should be taken in the same arm for the duration of the study. During treatment, beginning with Day 1, orthostatic vital signs should occur 2 ($\pm$ 1) hours after morning dosing. Orthostatic vital signs are only required after the morning dose of the specified visit days, but additional orthostatic vital sign monitoring is allowed at the investigator's discretion. At all visits, temperature and heart rate will be collected.

Vital sign measurements may be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP or heart rate measurements may be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

9.4.5 Electrocardiograms

A 12-lead, resting ECG should be obtained whenever possible within 1 to 2 hours post morning dose at the visits indicated in the Schedule of Assessments (Table 2-1 and Table 2-2). ECG at all scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or analysis.

ECGs will be assessed for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), QTcF (msec) measurements, and any other results. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the eCRF. ECGs should be repeated if clinically significant abnormalities are observed or artifacts are present.

At screening, the investigator or qualified designee will examine the ECG traces for signs of cardiac disease that could exclude the participant from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

9.4.6 Clinical Safety Laboratory Assessments

- Investigators or qualified designees must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- Results of clinical laboratory tests performed at screening must be available prior to dosing.
- In order to measure fasting glucose, clinical laboratory assessments should be collected while the participant is fasted when possible.

Table 9.4.6-1: Clinical Laboratory Assessments

Hematology	
Full and differential blood count	
RBC count	
WBC count with differential	
Hemoglobin	
Hematocrit	
Mean corpuscular hemoglobin concentration	
Mean corpuscular hemoglobin	
Mean corpuscular volume	
Platelet count	
Chemistry	
Aspartate aminotransferase	Total protein
Alanine aminotransferase	Albumin
Gamma glutamyltransferase	Electrolytes (sodium, potassium, chloride, calcium, phosphorus)
Glucose (fasting, when possible)	
HbA1c ^a	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase	
Lactate dehydrogenase	
Creatinine	
Creatine kinase ^b	
Carbon dioxide	
Blood urea nitrogen or serum urea	
Uric acid	
HDL	
LDL	
Total cholesterol	
Triglycerides	
Urinalysis^c	
Appearance	
Protein	
Glucose	
Indicators of blood, leukocyte esterase	
Specific gravity	
pH	
Urobilinogen	
Occult blood	
Serology^d	
Serum for hepatitis C virus, hepatitis B surface antigen, HIV	
Other Assessments	
Drug Screen ^e	
COVID-19 Screen ^f	
PSA ^g	
Pregnancy Test (IOCBP only: screening, predose, discharge)	

Abbreviations: COVID-19, coronavirus disease 2019; HCV, hepatitis C virus; HDL, high density lipoprotein; HIV, human immunodeficiency virus; IOCBP, individuals of childbearing potential; LDL, low density lipoprotein; PSA, prostate-specific antigen; RBC, red blood cell; RNA, ribonucleic acid; WBC, white blood cell.

- ^a HbA1c to be measured at screening and end of treatment.
- ^b Creatine kinase subtypes (CKMM, CKBB, CKMB) should be performed as reflex tests in cases of elevated creatine kinase.
- ^c If urinalysis is abnormal, a microscopic examination can be conducted at the discretion of the investigator.
- ^d Completed at screening only. If the participant tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.
- ^e Completed at screening and baseline, and any time after participant leaves and returns to the site during the study.
- ^f COVID-19 Screen will only be performed if required by the site. All COVID-19 testing will be performed locally.
- ^g To be performed in male participants ≥ 45 years of age at screening.

All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed in the medical record for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

Pregnancy test: In IOCBP, a serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed in IOCBP at each scheduled visit. If a urine pregnancy test result is positive, the investigator will instruct the participant to suspend further dosing, if applicable, and schedule a follow-up appointment as soon as possible. A serum pregnancy test will be performed for confirmation, including during the safety follow-up period, if needed.

Other Laboratory Assessments:

- A urine drug screen will be performed using a dipstick at the scheduled visits.
- Alcohol testing will be performed using a breathalyzer or urine alcohol test.

9.4.7 International Prostate Symptom Score (IPSS)

The IPSS questionnaire will be clinician-administered. The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the participant to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 (not at all) to 5 (almost always). The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic). The questions refer to the following urinary symptoms: 1. Incomplete emptying 2. Frequency 3. Intermittency 4. Urgency 5. Weak Stream 6. Straining 7. Nocturia.

Question eight refers to the participant's perceived quality of life. The score on question eight is not included in the total score calculation. Assessment will only be performed in male participants ≥ 45 years of age.

9.4.8 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study.³¹ The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the screening visit, the “lifetime” version will be completed; for all subsequent visits the “Since Last Visit” version of the C-SSRS will be administered.

9.4.9 Simpson-Angus Scale

The SAS is an established instrument to measure drug-related extrapyramidal syndromes. It is a 10-item testing instrument used to assess gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The range of scores is from 0 to 40 with increased scores indicating increased severity.

9.4.10 Barnes Akathisia Rating Scale

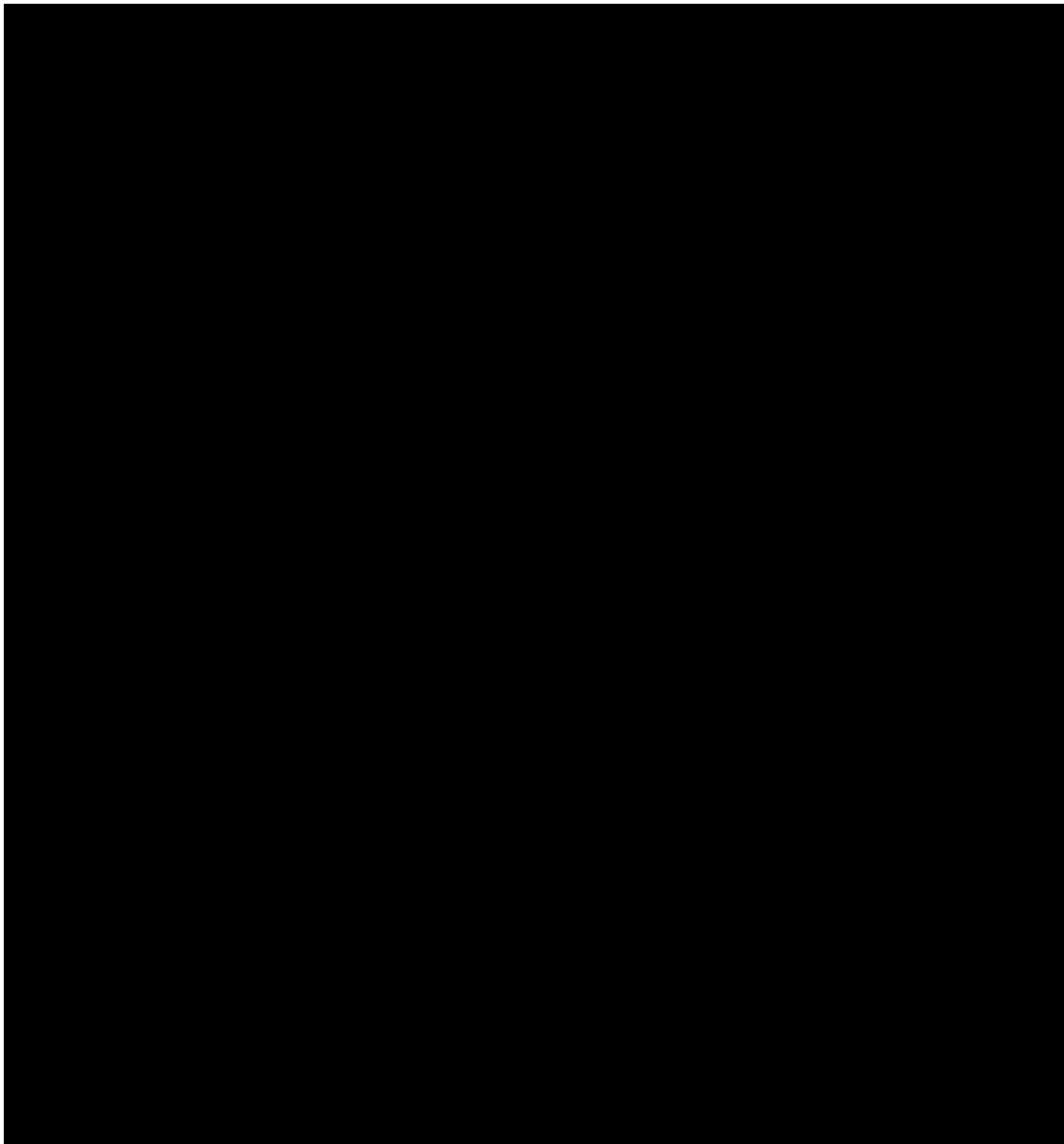
The BARS is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.

9.4.11 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements known as tardive dyskinesia, which can sometimes develop as a side effect of long-term treatment with antipsychotic medications. It is a 12-item scale to assess orofacial, extremity, and truncal movements as well as the overall severity, incapacitation, and the participant’s level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

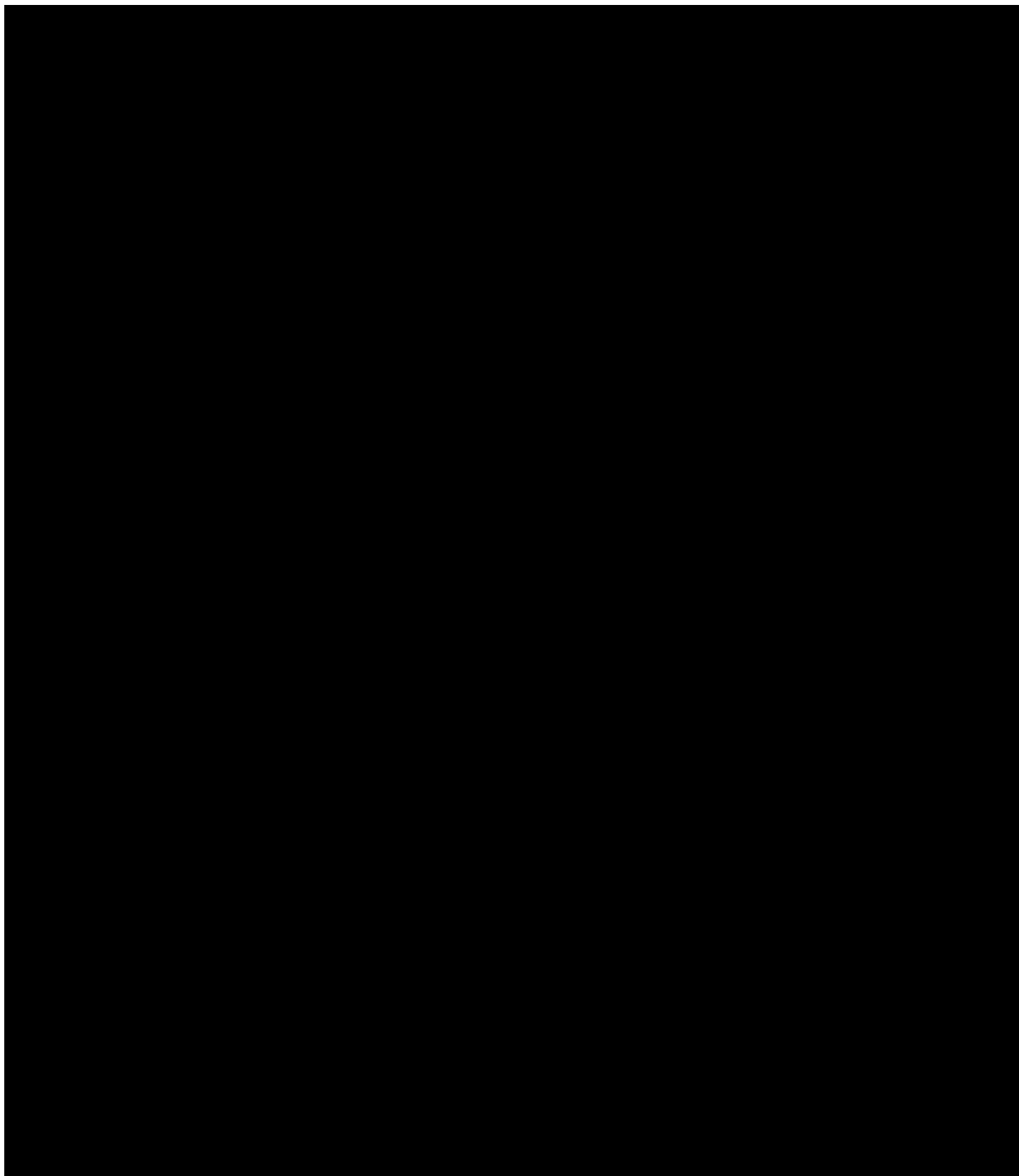
9.4.12 Other Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator or qualified designee per standard medical/clinical judgment.



9.6 Immunogenicity Assessments

Not applicable.



9.9 Other Assessments

9.9.1 *Mini International Neuropsychiatric Interview Version 7.0.2*

The MINI is a short structured diagnostic interview developed for DSM-5 psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical studies and epidemiology.

9.10 Healthcare Resource Utilization

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

All data will be listed, and summary tables will be provided.

10.1 Statistical Hypotheses

No statistical hypothesis testing will be performed.

10.2 Sample Size Determination

All analyses are descriptive only. The sample size determination is based on estimation rather than testing. Assuming a drop-out rate of approximately 25%, with 100 participants being enrolled in Cohort 1 and 75 participants being enrolled in Cohort 2, approximately 75 participants will complete the study in Cohort 1 and approximately 56 participants will complete the study in Cohort 2.

For the primary endpoint, assuming an incidence of TEAEs of 50% to 70%, the incidence of TEAEs per cohort can be estimated with a precision of at least $\pm 13\%$. This allows meaningful conclusions on the estimated TEAE rate.

For the secondary endpoints, assuming incidences of serious TEAEs of 5%, TEAEs leading to study discontinuation of 10% to 15% and incidences of pro- and anticholinergic TEAEs of 15%, the incidence of those TEAEs per cohort can be estimated with a precision of at least 6% to 9%. Serious TEAEs per cohort can be detected with at least 94% probability. This allows meaningful conclusions on the estimated rates for the secondary safety endpoints.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the informed consent and who meet the inclusion criteria and do not meet the exclusion criteria of the trial (screening failures are not considered to be part of the enrolled set).
Treated	All participants who received at least 1 dose of study intervention.
Period 1 Treated	All participants who received at least 1 dose of study intervention in Period 1 (Day 1 - Day 28).
Period 2 Treated	All participants who received at least 1 dose of study intervention in Period 2 (Day 29 - Day 56).

Defined Analysis Data Sets	Description
Safety Analysis Set	All treated participants in the respective analysis period.
Efficacy Analysis Set	All treated participants who had at least one efficacy assessment.
Per Protocol Set	All treated participants who had no major protocol deviations.

10.4 Statistical Analyses

The primary objective of the study is to assess the safety and tolerability of KarXT in adults with a DSM-5 diagnosis of schizophrenia in an inpatient setting during an initial slow titration of KarXT, administered BID on an empty stomach, followed by daily administration of KarXT administered BID with food. This study is a two-cohort open-label study collecting data for publication.

No inferential testing will be performed, and no p-values will be provided. Summary statistics for continuous variables will include N, mean, SD, minimum, median, and maximum. Summary statistics for discrete variables will be presented with counts and percentages.

This section provides a statistical analysis overview. More detailed statistical information will be provided in the SAP.

10.4.1 General Considerations

Participant disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized by cohort for the enrolled population. The distribution of enrollment by cohort and site will be provided.

Baseline and disease characteristics at baseline will be summarized by cohort for the treated population using appropriate descriptive statistics.

For the primary objective the main estimand is the incidence of TEAE from first dose of study intervention to the end of the safety follow-up in adults with a DSM-5 diagnosis of schizophrenia assuming a while on treatment strategy.

Table 10.4.1-1: Attributes of the Main Estimand for the Primary Objective

Estimand Attribute	Definition		
Treatment	KarXT slowly up-titrated and taken on an empty stomach for 4 weeks, followed by 4 weeks of KarXT treatment with food.		
Population	Participants with stable schizophrenia, who received at least one dose of treatment (Treated population).		
Variable	Treatment-emergent adverse events from baseline to end of safety follow-up		
Intercurrent Events	Event	Strategy	Description (or Rationale)
	Discontinuation of study intervention	While on treatment strategy	Treatment discontinuation is an intercurrent event and will be handled by while-on-treatment strategy. Specifically, all AEs occurring during study intervention are of interest.
Population-level Summary	Incidence of treatment-emergent adverse event from first dose of treatment to the end of the safety follow-up.		

Abbreviation: AE, adverse event; EoT, end of treatment.

10.4.2 Primary Endpoint(s)

The incidence of TEAEs will be summarized descriptively by cohort. The safety analysis set will be used for the analysis of the primary endpoint. Sensitivity analyses may be performed using the Per Protocol Set.

10.4.3 Secondary Endpoint(s)

The incidence of TEAEs will be summarized by cohort and study period (from first dose of treatment to Day 28, from Day 29 to EoT [Day 56]). Serious TEAEs, TEAEs leading to discontinuation, and pro- and anticholinergic TEAEs will be summarized descriptively by cohort overall and by study period (from first dose of treatment to Day 28, from Day 29 to EoT [Day 56], and from first dose of treatment to the end of the safety follow-up). The analyses will be performed on the safety analysis set. Sensitivity analyses may be performed on the Per Protocol set.

For all efficacy endpoints, the efficacy analysis set will be used. Baseline is defined as the last assessment prior to first dosing.

The change in PANSS total score, in PANSS positive score, in PANSS negative score and in PANSS negative Marder Factor score will be analyzed descriptively by cohort and assessment time point. Graphical displays showing the change from baseline over time will be provided.

The change from baseline in CGI-S score will be analyzed descriptively by cohort and assessment time point. Graphical displays showing the change from baseline over time will be provided.

10.4.5 Other Safety Analyses

All safety data will be listed and summarized for the Safety Analysis Set by cohort.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

All TEAEs, serious TEAEs, and TEAEs leading to discontinuation will be summarized by system organ class and preferred term. All analyses will be performed from first dose of study intervention to Day 28, from Day 28 to EoT (Day 56), and from first dose of study intervention until the end of the safety follow-up.

All AEs will be listed by participant, along with information regarding onset, duration, relationship, and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

Orthostatic vital signs, clinical laboratory data, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change from baseline values, as well as numbers of participants with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, body weight, BMI, and waist circumference.

10.4.6 Other Analyses

Not applicable.

10.5 Interim Analyses

Interim analyses may be performed after all participants in Cohort 1 have completed the 9-week treatment and safety follow-up periods. The final study analysis will be performed when all participants have completed the 9-week treatment and safety follow-up periods or discontinued early from the study. Additionally, optional data cuts at other time points will be planned, if required. Details of all planned analyses will be provided in the SAP.

11 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HCV	antibody to hepatitis C
APDs	antipsychotic drugs
AST	aspartate aminotransferase
AUC	area under the concentration vs time curve
BARS	Barnes Akathisia Rating Scale
BID	twice daily dose
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BPH	benign prostatic hyperplasia
bpm	beats per minute
BUN	urea nitrogen
CBC	complete blood count
CGI-S	Clinical Global Impression-Severity
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-suicide Severity Rating Scale
CTR	cardiothoracic ratio
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECGs	electrocardiograms

eCRF	electronic case report form
████	████████████████████
EOt	end of treatment
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase OR glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B
HCG	human chorionic gonadotropin
Hct	hematocrit
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HIV	human immunodeficiency virus
████	████████████████████
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IOCBP	individuals of childbearing potential
IP/IMP	investigational [medicinal] product
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	interactive response technologies
IU/L	international unit per liter
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LFT	liver function test
log	logarithm
LTE	long-term extension
MAOI	monoamine oxidase inhibitors
████	████████████████████
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview

mmHg	milliliters of mercury
NA	not applicable
NIH	National Institutes of Health
NMS	neuroleptic malignant syndrome
Non-IMPs	non investigational medicinal products
OL	open label
OLE	open label extension
PANSS	Positive and Negative Syndrome Scale
PE	physical examinations
PID	patient identification number
█	██████████
PR	partial response
PRN	as needed
PSA	prostate-specific antigen
PSDA	post study drug access
QRS	the interval between the beginning of the Q wave and the end of S wave in the electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's method
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse events
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
█	████████████████████
SNRI	serotonin and norepinephrine reuptake inhibitors
SoA	Schedule of Activities
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
█	██
UDS	urine drug screen
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a quality issue (eg, protocol deviation) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)

- European Regulation 536/2014 for clinical studies
- European Medical Device Regulation 2017/745 for clinical device research
- the IRB/IEC
- all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform participants of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

To honor this commitment and to evaluate population-specific signals, data on race and ethnicity data will be collected for this trial. A participant's race/ethnicity should be self-reported to the local study team and not assumed. These data will be documented by the study team in the eCRF, where permissible by local guidance, and will not be used as determinants of participant eligibility and/or continuation in the clinical trial. These data will be protected consistent with all other data collected during this trial.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyberattacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects.

Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

- 1) Responsibilities of IT Personnel
- 2) Securing the BMS Digital Infrastructure
- 3) Identity and Access Management
- 4) External Partner Connections
- 5) Cyber Threat Detection and Response
- 6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors)	Records or logs must comply with applicable regulations and guidelines and should include the following: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

The terms “participant” and “subject” refer to a person who has consented to participate in the clinical research study. Typically, the term “participant” is used in the protocol and the term “subject” is used in the Case Report Form (CRF).

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual who signs eCRFs electronically must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

Records collected throughout the study will be stored in the BMS clinical data management system for a duration of the life of the product plus 25 years.

RETURN OF STUDY INTERVENTION

For this study, study interventions (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study intervention containers, vials, and syringes, may be destroyed on site.

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal,

state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care providers, and researchers and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- National Coordinating Investigator
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on

significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

- 1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
- 2) Drafting the work or revising it critically for important intellectual content
- 3) Final approval of the version to be published
- 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Those who make the most significant contributions, as defined above, will be considered by the Sponsor for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.
Events <u>Meeting</u> the AE Definition
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. - Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. - New conditions detected or diagnosed after study intervention administration, even though the condition 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. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify “intentional overdose” as the verbatim term.
Events <u>NOT</u> 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).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTES below).
NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: A visit to the emergency department or other hospital department that does not result in admission. These visits should be evaluated for an occurrence of 1 of the other serious outcomes that would qualify as an SAE. • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life threatening or results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 : Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See [Section 9.2.5](#): Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment 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, will be considered and investigated. • The investigator will also consult the Investigator’s Brochure and/or product information for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (NOTE: Follow-up SAE reports must include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted promptly and not to exceed 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.

The required method for SAE data reporting is through the electronic Case Report Form (eCRF).

- The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).

In this case, the paper form is transmitted via email or confirmed fax transmission.

When paper forms are used, the original paper forms are to remain on site.

- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Fax Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 INDIVIDUALS OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to individuals of childbearing potential (IOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for participants, refer to [Section 6.1](#): Inclusion Criteria of the protocol. Only the contraceptive methods described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Individuals of Childbearing Potential (IOCBP)

An individual is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Individuals in the following categories are not considered IOCBP:

- Premenarchal
- Pre-menopausal individual with 1 of the following:
 - Hysterectomy
 - Bilateral salpingectomy
 - Bilateral oophorectomy
- Post-menopausal individual

A post-menopausal state is defined as 12 months of amenorrhea in an individual over the age of 45 years in the absence of other biological or physiological causes. In addition, individuals under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Individuals treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment when checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the individual can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require the use of alternative and/or additional contraceptive methods.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of < 1% per year when used consistently and correctly.^a

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)^b
 - Oral (birth control pills)
 - Intravaginal (rings)
 - Transdermal
- Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 7 days prior to initiation of study therapy.
- Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)^b
 - Oral
 - Injectable
- Progestogen-only hormonal contraception must begin at least 7 days prior to initiation of study therapy.

Highly Effective Contraceptive Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)^b
- Intrauterine device.
- Intrauterine system (IUS). (This method of contraception can only be used by participants in studies in which hormonal contraception is permitted by the study protocol.)^{b,c}
- Bilateral tubal occlusion.

- Vasectomized partner.

Having a vasectomized partner is a highly effective contraceptive method provided that the partner is the sole male sexual partner of the IOCBP and the absence of sperm has been confirmed. If not, an additional highly effective contraceptive method should be used.

A vasectomy is a highly effective contraceptive method provided that the participant is the sole male sexual partner of the IOCBP and the absence of sperm has been confirmed. If not, an additional highly effective contraceptive method should be used.

- Sexual abstinence.

Sexual abstinence is considered a highly effective contraceptive method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- IOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in [Section 2](#) of the protocol.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the IOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

^a Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

^b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to [Section 6.1](#): Inclusion Criteria and [Section 7.7.1](#): Prohibited and/or Restricted Treatments of the protocol.

^c IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to [Section 6.1](#): Inclusion Criteria and [Section 7.7.1](#): Prohibited and/or Restricted Treatments of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide.
- Cervical cap with spermicide.
- Vaginal sponge with spermicide.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by participants in studies in which hormonal contraception is prohibited.)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicide only.
- LAM.

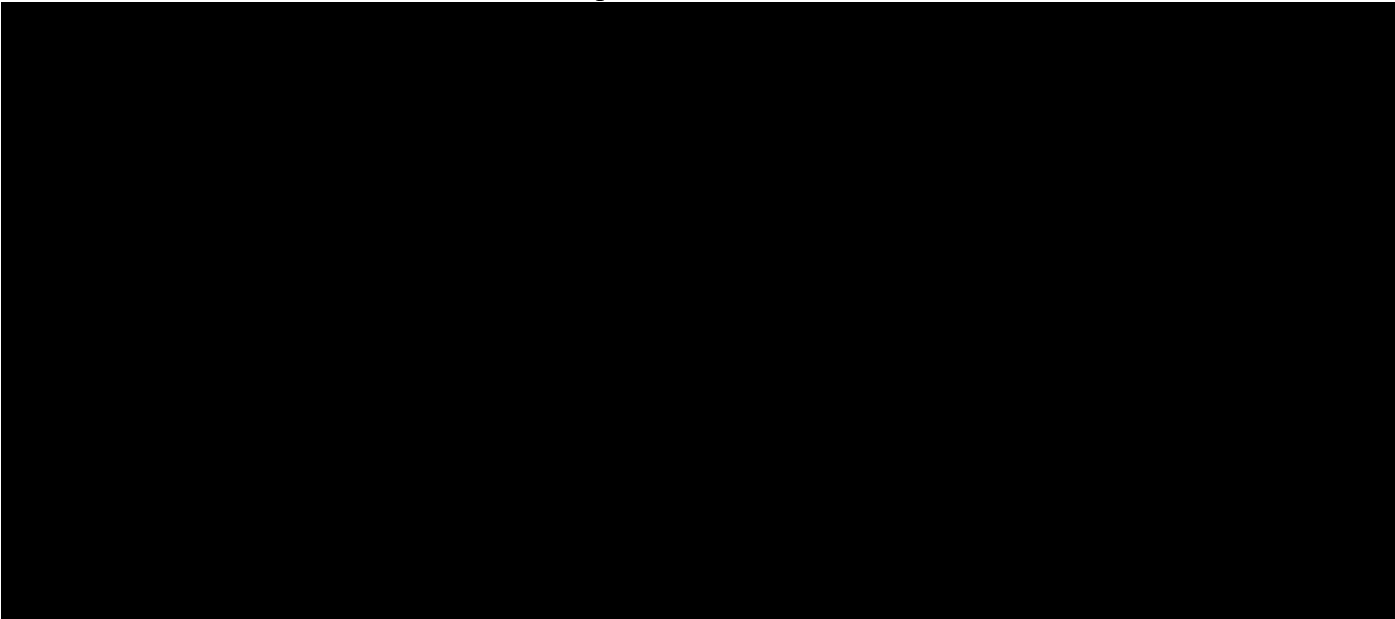
COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in [Section 9.2.5: Pregnancy of the protocol](#) and [Appendix 3](#).

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