CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults with DSM-5 Schizophrenia

Protocol Number: KAR-004

EudraCT Number: Not Applicable

CCI [redacted]

Investigational Product: KarXT (IND #: CCI [redacted])

Phase: Phase 2

Sponsor: Karuna Pharmaceuticals, Inc.
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Contract Research Organization: CCI [redacted]
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United States

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Version 3.0 Amendment 2
Version 2.0 Amendment 1
Version 1.0 Final

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults with DSM-5 Schizophrenia

Protocol Number: KAR-004

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council on Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

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2 STUDY PERSONNEL

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CCI

3 SYNOPSIS

Protocol Number:

KAR-004

Title:

A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults with DSM-5 Schizophrenia

Investigational Product:

KarXT

Study Centers:

Approximately 12 study centers in the United States

Phase:

Phase 2

Objectives:

Primary objective:

The primary objective of the study is to assess the efficacy of KarXT (a fixed combination of xanomeline and trospium chloride) (xanomeline 125 mg/trospium 30 mg twice daily [BID]) versus placebo in reducing Positive and Negative Syndrome Scale (PANSS) total scores in adult inpatients with a Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Secondary objectives:

The secondary objectives of the study are to assess overall safety and tolerability of KarXT in adult inpatients with a DSM-5 diagnosis of schizophrenia:

- To assess spontaneously reported adverse events (AEs) in subjects treated with KarXT versus placebo
- To assess spontaneously reported cholinergic symptoms in subjects treated with KarXT versus placebo
- To assess orthostatic vital signs in subjects treated with KarXT versus placebo
- To assess electrocardiogram (ECG) parameters in subjects treated with KarXT versus placebo
- To assess reduction of PANSS positive score in subjects treated with KarXT versus placebo
- To assess reduction of PANSS Marder Factor score in subjects treated with KarXT versus placebo
- To assess the pharmacokinetics (PK) of xanomeline and trospium following administration of KarXT in adult subjects with a DSM-5 diagnosis of schizophrenia
- To assess Clinical Global Impression-Severity (CGI-S) results in subjects with KarXT versus placebo

Study Design:

The study will be an inpatient study in adult subjects with DSM-5 schizophrenia. Subjects will be randomized to receive either placebo or KarXT (xanomeline 125 mg/trospium 30 mg BID) for a treatment

period of 5 weeks. Subjects will start on a lead-in dose of xanomeline 50 mg/trospium 20 mg 2 times per day (BID) for the first 2 days followed by xanomeline 100 mg/trospium 20 mg BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to xanomeline 125 mg/trospium 30 mg BID unless the subject is continuing to experience AEs from the previous dose increase of xanomeline 100 mg/trospium 20 mg BID. All subjects who were increased to xanomeline 125 mg/trospium 30 mg BID, depending on clinical response and tolerability, will have the option to return to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period. Dosing must not change after Visit 7 of the study and may be decreased for tolerability reasons no more than once during the study.

Number of Subjects:

A total of approximately 180 subjects planned to be randomized in a 1:1 ratio to either KarXT or placebo.

Treatment:

- Fixed dose Xanomeline 50 mg/Trospium 20 mg BID, oral
- Fixed dose Xanomeline 100 mg/Trospium 20 mg BID oral
- Fixed dose Xanomeline 125 mg/Trospium 30 mg BID oral
- Matching placebo BID oral

Study Duration:

Total study duration is up to 7 weeks, including a 7-day screening phase (up to a 7-day extension of the screening phase is allowed, if necessary) and a 5-week treatment period.

Inclusion Criteria:

1. Subject is aged 18-60 years, inclusive, at screening.
2. Subject 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 for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2.
3. Subject is experiencing an acute exacerbation or relapse of symptoms, with onset less than 2 months before screening.
    a. The subject requires hospitalization for this acute exacerbation or relapse of symptoms.
    b. If already an inpatient at screening, has been hospitalized for less than 2 weeks for the current exacerbation at the time of screening.
4. Positive and Negative Syndrome Scale total score between 80 and 120, inclusive.
    a. Score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale (P) items:
        i. Item 1 (P1; delusions)
        ii. Item 2 (P2; conceptual disorganization)
        iii. Item 3 (P3; hallucinatory behavior)
        iv. Item 6 (P6; suspiciousness/persecution)
5. There should not be a change (improvement) in PANSS total score between screening and baseline of more than 20%.
6. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 2 weeks before baseline.
7. Subjects taking a depot antipsychotic could not have received a dose of medication for at least 1 and a half injection cycles before baseline (eg, 3 or more weeks off for a 2-week cycle).
8. Subject is capable of providing informed consent.
    a. A signed informed consent form must be provided before any study assessments are performed.
    b. Subject must be fluent (oral and written) in English to consent
9. Subject is willing and able to be confined to an inpatient setting for the study duration, follow instructions, and comply with the protocol requirements.
10. Subject has a CGI-S score of ≥ 4 at screening and baseline visits.
11. Body mass index (BMI) must be ≥ 18 and ≤ 40 kg/m^2.
12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator.

13. Both females of child-bearing potential and males with partners of child-bearing potential must be willing to use a double-barrier method of birth control (ie, any double combination of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel) during the study and for 7 days after the last dose of study drug.
14. Subject has an identified reliable informant. An informant is needed at the screening and baseline visits as well as at the end of the study for relevant assessments. (Site staff may act as informant while the subject is an inpatient.) An informant may not be necessary if the subject has been the patient of the investigator for ≥ 1 year.

Exclusion Criteria

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening).
2. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results, to exclude patients with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on the liver function test results.
3. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
4. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months [redacted]
5. Has a DSM-5 diagnosis of moderate to severe substance abuse disorder (except tobacco use disorder) within the 12 months before screening (confirmed using MINI version 7.0.2 at screening), or current abuse as determined by urine toxicology screen or alcohol test. A screening subject 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. Use of cannabis at screening will result in screen failure with the allowance to rescreen at a later date if no moderate to severe substance use disorder is determined.
6. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and Columbia Suicide Severity Rating Scale (C-SSRS) as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or answers "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.
7. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.
8. Subjects cannot currently (within 2 weeks of baseline) be receiving oral antipsychotic medications, MAO inhibitors, anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for as needed anxiolytics (eg, lorazepam, chloral hydrate).
9. Pregnant, lactating, or less than 3 months postpartum. Sperm donation is not allowed for 90 days after the final dose of study drug.
10. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
11. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.
12. Subject 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) or required clozapine within the last 12 months.
13. Risk of violent or destructive behavior.
14. Current involuntary hospitalization or incarceration.
15. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 3 months of screening.

Primary Endpoint:

- Change in PANSS total score

Secondary Endpoints:

Efficacy Endpoints:

- Change in PANSS positive score
- Change in PANSS Marder Factor score
- Change in CGI-S score
- Percent of CGI-S responders (with CGI-S scale equal to 1 or 2)

Other Endpoints

CCI [redacted]

Safety Endpoints:

- Spontaneous AEs
- Orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate (beats/minute)
- Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, urinalysis, and drug screen
- 12-lead ECG
- Physical examination
- Suicidal ideation scale with the use of C-SSRS

Exploratory Endpoints:

CCI [redacted]

- Simpson-Angus Rating Scale
- Barnes Rating Scale for Akathisia
- Abnormal Involuntary Movement Scale
- Body weight, BMI, waist circumference

Study Population

All subjects who are randomized to the study will be included in the intent-to-treat (ITT) population.

All subjects who are randomized, receive at least 1 dose of study drug, and have a baseline assessment will be included in the modified intent-to-treat (MITT) population and will be used in the efficacy analysis.

All subjects who receive at least 1 dose of study drug will be included in the safety population and will be used in the safety analysis.

All subjects who are randomized, receive at least 1 dose of study drug and have at least 1 measurable serum concentration of study medication will be included in the PK population and will be used in the PK analysis.

Statistical Analysis:

The primary endpoint of the study is the change from baseline in PANSS total score at Week 5. It will be estimated using a mixed model for repeated measures. Additional sensitivity analysis may be performed on an observed case basis, using multiple imputation techniques, and classifying treatment dropouts as treatment failures. The sensitivity analyses of the primary endpoint will be specified in the statistical analysis plan.

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5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
MCC	microcrystalline cellulose
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of the normal range

6 INTRODUCTION

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.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States. population.[2] Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the United States is 5.1 per 1000 lives.[3] It is found equally in males and females, with males usually having an earlier onset of symptoms.[4]

Antipsychotic drug therapy (eg, risperidone, molindone, thioridazine, haloperidol, pimozide, trifluoperazine, clozapine, and fluphenazine) is the most common treatment option. All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. Current treatments are not effective for all subjects and also manifest unwanted side effects, such as weight gain, diabetes, and movement disorders. Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[5,6] There are five subtypes of muscarinic receptors (M1-M5). The therapeutic effect of muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[7] However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

Xanomeline tartrate, an agonist for muscarinic acetylcholine receptors, was developed during the 1990's and early 2000s by Eli Lilly and Company (Lilly) to treat Alzheimer's disease. Two Investigational New Drug (IND) applications were opened, one for an oral formulation and one for a transdermal formulation. Numerous clinical studies of the oral formulation were conducted in > 600 subjects, where significant improvements in cognition were seen. In addition, a randomized, double-blind, placebo-controlled study in 20 schizophrenic subjects showed a marked improvement in psychotic symptoms.[8] However, there was a high discontinuation rate with the studies done in Alzheimer's disease, mostly due to gastrointestinal side effects, orthostasis, and syncope attributed to muscarinic receptor agonism. Lilly hoped that the transdermal formulation might have an improved safety profile and tolerability, but though it helped somewhat, instead this formulation was associated with skin irritation associated with the transdermal preparation. Lilly decided to terminate work on xanomeline tartrate.

Karuna Pharmaceuticals (Karuna) is developing KarXT, a combination oral dosage form containing both xanomeline and trospium in the same capsule. In addition to exploring alternative doses of xanomeline, Karuna intends to explore the use of 30 mg of trospium twice daily (BID) in this study. Trospium is a marketed (10+ years) muscarinic antagonist that does not cross the blood brain barrier. It is well tolerated, with side effects limited to peripheral anticholinergic effects (eg, CCI dry mouth). The Sponsor aims to ameliorate the AEs associated with xanomeline muscarinic agonism by blocking the activation of peripheral muscarinic receptors with trospium chloride. It is proposed that this approach will reduce the dose-limiting, peripheral side effects associated with muscarinic agonism while allowing the activation of CNS muscarinic receptors.

The purpose of protocol KAR-004 is to test this combination dosage form as a BID regimen. A placebo arm is included to provide test sensitivity.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the US for the treatment of overactive bladder.

6.1 Background

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6.1.2 Summary of Relevant Clinical Studies

Refer to the IB for information regarding previous clinical studies conducted with xanomeline by Lilly, and studies KAR-001, KAR-002, and KAR-003 conducted by Karuna Pharmaceuticals.

To date, more than 600 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation) in 16 clinical studies conducted by Lilly, some for as long as 3 years.[8] Full details of these studies can be found in the most current version of the IB. In those studies, significant improvements in cognition and reduced psychotic symptoms were observed. In one large scale study of safety and efficacy in Alzheimer's subjects, an oral dosing regimen of 75 mg xanomeline tartrate thrice daily (TID) was associated with enhanced cognition and improvement in psychotic-like symptoms, relative to placebo. However, the discontinuation rate associated with this regimen was 58.6% (versus 34.5% on placebo), due primarily to GI side effects attributable to muscarinic receptor agonism. Lilly hoped that a transdermal formulation might alleviate some of these effects. However, their transdermal development efforts were not successful due to skin irritation associated with the transdermal preparation. These combined findings contributed to Lilly's decision to terminate work on the project.

An independent study of xanomeline in subjects with schizophrenia was reported in 2008.[9] In this pilot study, the effects of xanomeline were examined in 20 schizophrenia subjects utilizing a double-blind, placebo-controlled, 4-week study design. Outcome measures included the Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression scale, and tests designed to measure cognitive function. Subjects treated with xanomeline did significantly better than subjects in the placebo group on BPRS total scores and PANSS total scores (ie, 24-point change over placebo, $p = 0.04$). In the cognitive test battery, subjects in the xanomeline group showed improvements in measures of verbal learning and short-term memory function. These studies demonstrate the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

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6.1.3 Potential Risks and Benefits

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium.

Over 600 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation) in clinical studies. These early clinical studies, as well as 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, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. CCI

Trospium chloride has been marketed in the US for 12 years. Common anticholinergic side effects: dry mouth, CCI urinary hesitance, and worsening of narrow-angle glaucoma. For additional information, the package insert for Sanctura® (trospium chloride tablets for oral use) can be found in the IB.

Subjects assigned to active study drug may benefit by improvement in schizophrenic symptoms.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Objectives

7.1.1 Primary Objective

The primary objective of the study is to assess the efficacy of KarXT (a fixed combination of xanomeline and trospium chloride; xanomeline 125 mg/trospium 30 mg) versus placebo in reducing PANSS total score in adult inpatients with a Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

7.1.2 Secondary Objectives

The secondary objectives of the study are to assess overall safety and tolerability of KarXT in adult inpatients with a DSM-5 diagnosis of schizophrenia:

- To assess spontaneously reported AEs in subjects treated with KarXT versus placebo
- To assess spontaneously reported cholinergic symptoms in subjects treated with KarXT versus placebo
- To assess orthostatic vital signs in subjects treated with KarXT versus placebo
- To assess ECG parameters in subjects treated with KarXT versus placebo
- To assess reduction of PANSS positive score in subjects treated with KarXT versus placebo
- To assess reduction of PANSS Marder Factor score in subjects treated with KarXT versus placebo
- To assess the pharmacokinetics (PK) of xanomeline and trospium following administration of KarXT in adult subjects with a DSM-5 diagnosis of schizophrenia
- To assess Clinical Global Impression–Severity (CGI-S) scale results in subjects with KarXT versus placebo

7.2 Endpoints

7.2.1 Primary Endpoint

- Change in PANSS total score at Week 5

7.2.2 Secondary Endpoints

- Efficacy Endpoints:

- Change in PANSS positive score
- Change in PANSS Marder Factor score
- Change in CGI-S score
- Percent of CGI-S responders (with CGI-S scale equal to 1 or 2)

7.2.3 Other Endpoints

CCI [redacted]

- Safety Endpoints:
  - Spontaneous AEs
  - Orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate (beats/minute)
  - Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, urinalysis, and drug screen
  - 12-lead ECG
  - Physical examination
  - Suicidal ideation with the use of Columbia Suicide Severity Rating Scale (C-SSRS)
- Exploratory Endpoints:

  CCI [redacted]
  - Simpson-Angus Rating Scale
  - Barnes Rating Scale for Akathisia
  - Abnormal Involuntary Movement Scale (AIMS)
  - Body weight, body mass index (BMI), waist circumference

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This is a Phase 2, randomized, double-blinded, placebo-controlled, inpatient study to examine the efficacy, safety, and tolerability profile of KarXT in adult subjects diagnosed with DSM-5 schizophrenia who are in an acute exacerbation phase. Subjects will be randomized to oral KarXT (a novel, fixed dose combination of xanomeline and trospium) or placebo in a 1:1 ratio for a treatment period of 5 weeks. Treatment assignment to drug or placebo will be stratified by site. A total of approximately 180 subjects in approximately 12 US study sites are planned. Subjects who are randomized into the double-blinded treatment phase but discontinue/withdraw will not be replaced.

Screening of subjects will take place in 7 days or less before Day 1 (Days -7 to -1). Up to a 7-day extension of the screening phase is allowed, if needed.

At Screening, the interactive web response system (IWRS) will assign a unique subject identification number to the subject known as the Subject Number. This number will be associated with the subject throughout the study. Every subject who signs an informed consent form (ICF) must be entered into the IWRS regardless of eligibility in order to obtain a Subject Number. CCI [redacted]

The subjects will be randomized by study site. The treatment assignment will be determined by a randomization list prepared by the biostatistics group of CCI [redacted] and utilized in the IWRS. The 5-digit randomization number is used to identify the treatment (active or placebo) that will be assigned to the subject. A randomization number can only be assigned to one subject and cannot be reused once assigned.

Subjects will be flexibly dosed as per the protocol and the investigator's clinical judgment. Subjects will start on a lead-in dose of xanomeline 50 mg/trospium 20 mg BID for the first 2 days, followed by xanomeline 100 mg/trospium 20 mg BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to xanomeline 125 mg/trospium 30 mg BID, unless the subject is continuing to experience AEs from the previous dose increase of xanomeline 100 mg/trospium 20 mg BID. All subjects who were increased to xanomeline 125 mg/trospium 30 mg, depending on clinical response and tolerability, will have the option to return to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period. Dosing must not change after Visit 7 of the study and may be decreased for tolerability reasons no more than once during the study.

All enrolled subjects will have structured diagnostic interview sessions and questionnaires administered throughout the study. Analyses of change from baseline in diagnostic measures will be performed.

An Independent Safety Monitoring Committee (ISMC) will be responsible for reviewing on a periodic basis the safety data from this study and confirming that the study may continue.

8.1.1 Study Design

Phase:	Screening	Inpatient Treatment							End of Treatment
Day:	Day -7 to -1	Day 1	Day 3 ± 1 day	Day 7 ± 2 days	Day 8 ± 2 days	Day 14 ± 2 days	Day 21 ± 2 days	Day 28 ± 2 days	Day 35 − 2 days
Visit:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Xanomeline/ trospium (KarXT):	N/A	50 mg/20 mg BID	100 mg/20 mg BID	100 mg/20 mg BID	125 mg/30 mg BID (Option: 100 mg/20 mg BID)[a]	125 mg/30 mg BID (Option: 100 mg/20 mg BID)[a]	125 mg/30 mg BID (Option: 100 mg/20 mg BID)[a]	125 mg/30 mg BID (Option: 100 mg/20 mg BID)[b]	N/A
Comment:	Up to a 7-day extension to the screening phase is allowed.	2-day lead-in dose	Upward titration of dose		Upward titration of dose	Downward dose adjustment allowed according to clinical response/tolerability		No dose adjustment allowed (after Day 21)	

BID = twice daily.

a All subjects who were increased to xanomeline 125 mg/trospium 30 mg, depending on clinical response and tolerability, will have the option to return to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period.

b No dose adjustment will be allowed after Visit 7. All subjects will continue taking the doses chosen for xanomeline and trospium at Visit 7.

8.1.2 Schedule of Assessments

The schedule of planned study assessments is shown in the following flow chart.

Table 1. Schedule of Assessments

PROCEDURE	SCREENING PHASE	TREATMENT PHASE								
VISIT	**1 (Day -7 TO -1)[a]**	**2 (Day 1)**	**3 (Day 3 ± 1 day)**	**4 (Day 7 ± 2 days)**	**5 (Day 8 ± 2 days)**	**6 (Day 14 ± 2 days)**	**7 (Day 21 ± 2 days)**	**8 (Day 28 ± 2 days)**	**9/ET (Day 35 − 2 days)**	**Unscheduled Visit(s)[b]**
WEEKS PAST RANDOMIZATION	**NA**	**0**		**1**		**2**	**3**	**4**	**5**	
Written informed consent	X									
Collect demographic information (date of birth, gender, race)	X									
Pregnancy test (females of childbearing potential only)[c]	X[c]	X[c]							X[c]	
Urine drugs of abuse test and alcohol testing[d]	X									
Review of inclusion/exclusion criteria	X	X								
Subject eligibility verification process	X									
Medical, psychiatric, and medication history	X									
Complete physical examination[e]	X[e]								X[e]	
Spontaneous AEs and medical status[f]		X	X	X	X	X	X	X	X	X
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X
Height (Screening only) and body weight, BMI, waist circumference	X	X							X	
Orthostatic vital signs: blood pressure and heart rate[g]	X	X	X	X	X	X	X	X	X	X
Resting ECG (12-lead)[h]	X								X	
Blood samples for hematology, coagulation, and serum chemistry and urine sample for urinalysis[i]	X						X		X	X
[redacted] CCI										
Admission of subject to inpatient unit[k]	X									
Randomization/assignment of subject randomization #		X								
Determination of dose adjustment					X	X	X			X

PROCEDURE	SCREENING PHASE	TREATMENT PHASE								
VISIT	**1 (Day -7 TO -1)[a]**	**2 (Day 1)**	**3 (Day 3 ± 1 day)**	**4 (Day 7 ± 2 days)**	**5 (Day 8 ± 2 days)**	**6 (Day 14 ± 2 days)**	**7 (Day 21 ± 2 days)**	**8 (Day 28 ± 2 days)**	**9/ET (Day 35 − 2 days)**	**Unscheduled Visit(s)[b]**
WEEKS PAST RANDOMIZATION	**NA**	**0**		**1**		**2**	**3**	**4**	**5**	
Study drug provided (randomized, double-blind) and administered daily BID[l]		X	X	X	X	X	X	X		X
Blood samples for PK analysis[m]					X[m]			X[m]	X[m]	X[m]
MINI version 7.0.2.	X									
Positive and Negative Syndrome Scale (PANSS) for schizophrenia[n]	X	X				X		X	X	
C-SSRS[o]	X	X		X		X	X	X	X	X
CGI-S Scale	X	X		X		X	X	X	X	
CCI										
Simpson-Angus Rating Scale		X							X	
Barnes Rating Scale for Akathisia		X							X	
Abnormal Involuntary Movement Scale (AIMS)		X							X	

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; ID = identification; MINI = Mini International Neuropsychiatric Interview; PK = pharmacokinetic; QTcF = QT interval corrected by Fridericia.

a Up to a 7-day extension of the screening phase is allowed, if needed.

b Other assessments as needed.

c A serum pregnancy test for females of childbearing potential should be done at screening, and urine pregnancy tests should be done at other visits.

d If a subject leaves the unit, he/she should have a urine drug screen and test for alcohol (breathalyzer or blood alcohol level) upon returning to the unit.

e A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.

f Adverse events as reported by subjects or observed by clinical staff and occurs after dosing. One PK blood sample may be drawn if an AE is reported during a scheduled visit or if there is a dose adjustment or AE reported during an unscheduled visit (no multiple draws).

g Vital signs taken supine and standing after 2 minutes. Blood pressure includes systolic and diastolic blood pressure. Heart rate is beats/minute. During treatment, beginning with Visit 2, vital signs should occur 2 (± 1) hours after morning dosing. Orthostatic vital signs are only required after the AM dose of the specified visit days, but additional orthostatic vital sign monitoring is allowed at the PI's discretion. It would be acceptable, for example, to do orthostatic vital signs BID after dosing increases for a day or two for subjects where it seems warranted, but this shouldn't be done automatically.

h During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec).
i Refer to Section 10.1.3.1.4 for individual laboratory tests.

CCI [redacted]

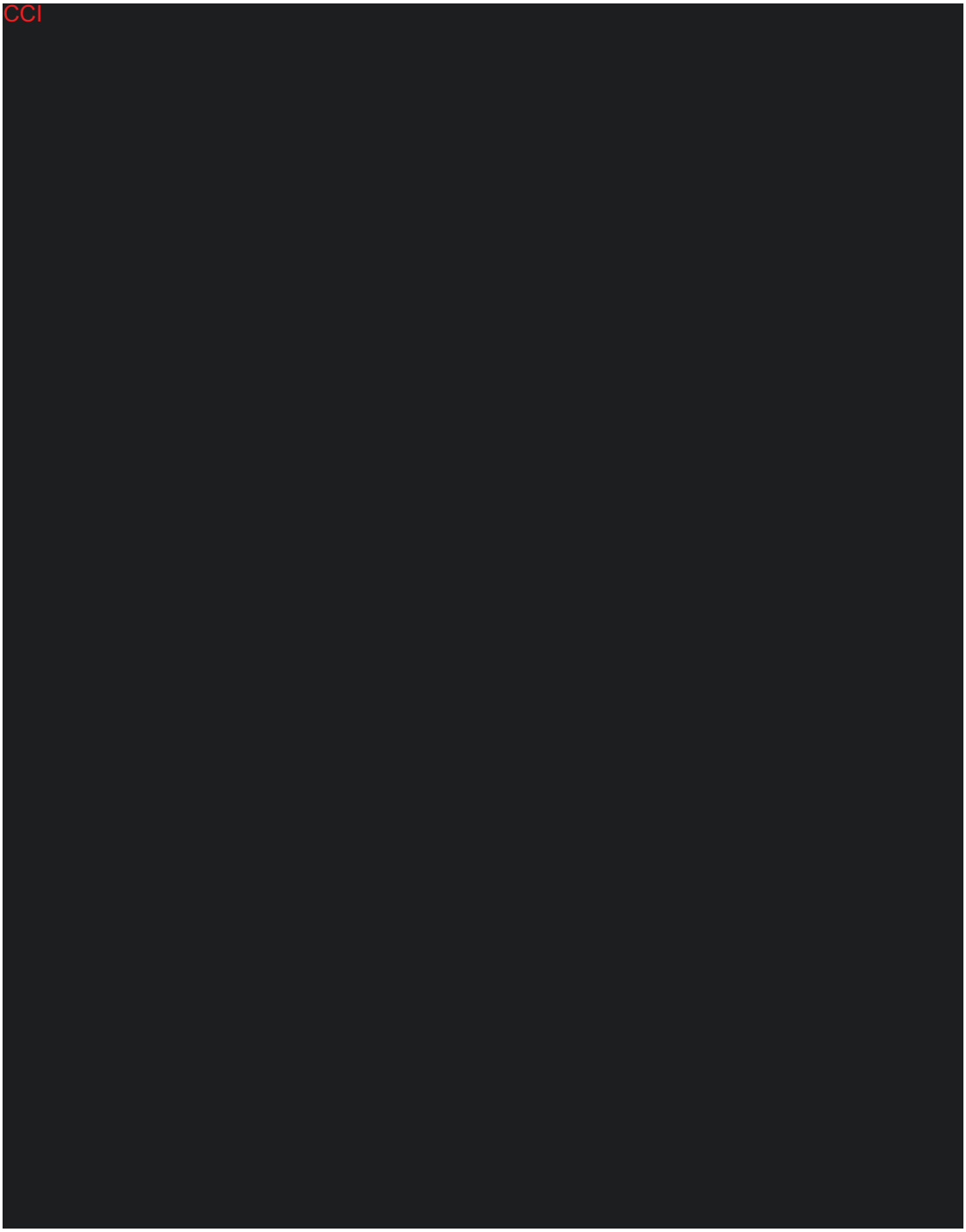
k If an eligible subject is not already an inpatient, the subject should be admitted to the inpatient unit.
l Starting on Day 1, study drug is administered daily BID by the study staff, with the last dose administered on the evening prior to Visit 9. If the morning dose is not feasible on Day 1, the first dose may be administered in the evening of Day 1; however, subjects must receive at least 4 doses of the 50 mg/20 mg BID before up-titrating the dose to the 100 mg/20 mg BID.
m For Visit 5/Day 8 and Visit 8/Day 28, 6 PK blood draws are required: before the morning dose, and at 1 hour ± 5 minutes, 2 hours ± 10 minutes, 4 hours ± 10 minutes, 8 hours ± 10 minutes, and 12 hours ± 10 minutes after the morning dose. For Visit 9/ET, a single PK blood sample should be drawn prior to discharge (preferably in the morning) for completed (and early termination) subjects. One PK blood sample may also be drawn if an AE is reported during a scheduled visit or if there is a dose adjustment or AE reported during an unscheduled visit (no multiple draws). For an Early Termination Visit that is related to an AE, the collection of a PK blood sample is not optional and should be drawn prior to discharge.
n It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. The PANSS assessment includes the Marder Factor.
o C-SSRS first time use lifetime, other times use "since last visit" version. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.

CCI [redacted]

[redacted]

8.2 Discussion of Study Design

8.2.1 Study Design



The use of placebo in subjects will allow the association of safety and efficacy outcomes unique to the KarXT group to be attributed to the active study drug. The double-blind design of the study will ensure that neither the subjects nor the study staff will know the treatment assignment to which a subject has been randomized and will mitigate bias on the conduct or outcome of the study.

The treatment period of 5 weeks is within the typical length of 4 to 6 weeks seen for psychiatric pharmaceutical studies. The CCI rat study CCI) supports the safety of KarXT given for 5 weeks in this study. The 5-week treatment period will allow the needed time for efficacy, safety, and cognitive changes to be observed.

8.2.2 Quality Management and Risk Evaluation

This protocol was evaluated to identify those processes and data that were critical to assure human subject protection and reliability of study results.

Predefined quality tolerance limits were established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the study, to identify systematic issues that could impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits will trigger an evaluation to determine if action is needed. Any important deviations from the predefined quality tolerance limits and remedial actions taken will be described in the clinical study report.

Risk control measures will be periodically reviewed to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

The following steps will be taken to ensure accurate, consistent, complete, and reliable data:

1. The Sponsor or designee will conduct an initiation meeting at the study site before the start of the study. The study protocol, procedures, and electronic case report forms (eCRFs) will be reviewed in detail and the study personnel will be trained to carry out the procedures defined in the protocol.

2. The investigator will be provided with a Study Site Binder for storing study related regulatory and study site documentation; eg, study logs and forms.
3. The investigator must review all eCRF entries for completeness and accuracy.
4. Periodic monitoring visits will be conducted on a regular basis by the Sponsor or designee in order to verify the accuracy of data entered on each eCRF against the raw data from source documents at the site. Items needing correction/clarification will be identified and brought to the attention of the study site personnel and principal investigator, and corrections will be made as appropriate.
5. The Sponsor or designee will perform a final review and data management of the eCRF. The study database will be validated using appropriate validation processes.
6. The Sponsor or designee may perform a regulatory audit of the study site, and may include a complete review of the overall study conduct, regulatory documentation, and selected subject eCRFs and source documents.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

A total of approximately 180 study subjects and approximately 12 sites in the United States are planned. Subjects who are randomized into the double-blind treatment phase but discontinue or withdraw will not be replaced.

8.3.2 Inclusion Criteria

To be eligible for enrollment, subjects must satisfy all of the following criteria:

1. Subject is aged 18-60 years, inclusive, at screening.
2. Subject 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 for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2.
3. Subject is experiencing an acute exacerbation or relapse of symptoms, with onset less than 2 months before screening.
    a. The subject requires hospitalization for this acute exacerbation or relapse of symptoms.
    b. If already an inpatient at screening, has been hospitalized for less than 2 weeks for the current exacerbation at the time of screening.
4. Positive and Negative Syndrome Scale total score between 80 and 120, inclusive, at screening.
    a. Score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale (P) items at screening:
        i. Item 1 (P1; delusions)
        ii. Item 2 (P2; conceptual disorganization)
        iii. Item 3 (P3; hallucinatory behavior)
        iv. Item 6 (P6; suspiciousness/persecution)

5. There should not be a change (improvement) in PANSS total score between screening and baseline of more than 20%.
6. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 2 weeks before baseline.
7. Subjects taking a depot antipsychotic could not have received a dose of medication for at least 1 and a half injection cycles before baseline (eg, 3 or more weeks off for a 2-week cycle).
8. Subject is capable of providing informed consent.
    a. A signed ICF must be provided before any study assessments are performed.
    b. Subject must be fluent (oral and written) in English in order to consent.
9. Subject is willing and able to be confined to an inpatient setting for the study duration, follow instructions, and comply with the protocol requirements.
10. Subject must have CGI-S score of ≥ 4 at screening and baseline visits.
11. Body mass index must be ≥ 18 and ≤ 40 kg/m^2
12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator.
13. Both females of child bearing potential and males with partners of child bearing potential must be willing to use a double-barrier method of birth control (ie, any double combination of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel) during the study and for 7 days after the last dose of study drug.
14. Subject has an identified reliable informant. An informant is needed at the screening and baseline visits as well as at the end of the study for relevant assessments. (Site staff may act as informant while the subject is an inpatient.) An informant may not be necessary if the subject has been the patient of the investigator for ≥ 1 year.

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criterion is applicable:

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening).
2. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results, to exclude patients with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on the liver function test results.
3. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
4. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months (see Appendix 17.2.1)

5. Has a DSM-5 diagnosis of moderate to severe substance abuse disorder (except tobacco use disorder) within the 12 months before screening (confirmed using MINI version 7.0.2 at screening), or current abuse as determined by urine toxicology screen or alcohol test. A screening subject 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. Use of cannabis at screening will result in screen failure with the allowance to rescreen at a later date if no moderate to severe substance use disorder is determined.
6. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and the C-SSRS as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or answers "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.
7. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.
8. Subjects cannot currently (within 2 weeks of baseline) be receiving oral antipsychotic medications, MAO inhibitors, anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics (eg, lorazepam, chloral hydrate) taken as needed.
9. Pregnant, lactating, or less than 3 months postpartum. Sperm donation is not allowed for 90 days after the final dose of study drug.
10. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
11. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.
12. Subject 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) or required clozapine within the last 12 months.
13. Risk of violent or destructive behavior.
14. Current involuntary hospitalization or incarceration.
15. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 3 months of screening.

8.3.4 Removal of Subjects from Therapy or Assessments

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IRB will be informed

about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the investigators, the IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IRB if it takes such an action.

8.3.5 Subject Withdrawal

Subjects who are randomized into the double-blind treatment phase but then discontinue or withdraw will not be replaced.

Subjects may withdraw from the study at any time as stated in the ICF (given to the subject at the time of enrollment) and without prejudice to further treatment. Subjects may be withdrawn or be discontinued from the study by the study investigator or the Sponsor for the following reasons:

1. Violation of entry criteria; ie, subjects who are enrolled but are later discovered not to meet entry criteria
2. Adverse event(s)
3. Protocol noncompliance (eg, if a study subject is off study drug for >5 days in a row).
4. Pregnancy (females of childbearing potential). Any study subject who becomes pregnant while participating in the study will be unblinded to study treatment randomization. If she is found to be on active treatment assignment, she will be followed until her pregnancy reaches term.
5. Development of suicidal or assaultive behavior
6. Alcohol or illegal drug use
7. Development of an intercurrent systemic illness requiring significant medical intervention or a clinically significant change in laboratory testing as per the investigator.
8. Sponsor’s decision to discontinue study
9. Subject withdraws consent
10. Subject has need for a medication prohibited by the protocol.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who leave the unit or are lost to follow-up. These efforts must be documented in the subject’s file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the study drug become known, making further

treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

The reason for withdrawal or discontinuation must be recorded on the subject's eCRFs. If a subject discontinues the study prematurely, for any reason, all procedures that would have been completed at the study discharge should be performed before subject study discontinuation, and the termination eCRF is to be completed.

All subjects withdrawn from the study because of an emergent adverse experience will continue to be followed until the AE(s) resolve or stabilize.

Pregnancy

No evidence of mutagenicity, or treatment effects on reproduction, fertility, or fetal parameters have been demonstrated in animals following administration of xanomeline, but there are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).

Therefore, participation of women of childbearing potential in this study must be willing to use a double-barrier method of birth control (ie, any double combination of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel) during the study and for 7 days after the last dose of study drug. Females of childbearing potential will have a serum pregnancy test at screening and a urine pregnancy test on Day 1 (before receiving xanomeline and/or trospium) and Day 35. Should a woman become pregnant or suspects she is pregnant while participating in this study, she should inform study staff and her primary care physician immediately.

Definition of women of childbearing potential: For the purpose of this study, a woman is considered of childbearing potential following menarche and until confirmed post-menopausal state, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Pregnant women are excluded from this study because the effects of xanomeline and trospium on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with xanomeline or trospium, women who are breastfeeding must not be enrolled in the study.

The effects of study drug on sperm are unknown. Men who agree to enroll in the study must agree to use a double-barrier method of birth control (ie, any double combination

of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel) and must agree to not impregnate a sexual partner during or for 90 days after the final dose of study drug. They must also agree to refrain from sperm donation for 90 days after the final dose of study drug.

Definition of fertile men (for female partners of male subjects): For the purpose of this study, a man is considered fertile unless permanently sterile by bilateral orchidectomy.

Subjects will be instructed that known or suspected pregnancy occurring during the study, in female subjects or female partners of male subjects, should be confirmed and reported to the investigator. Investigators will then withdraw pregnant female subjects from the study without delay. Upon discontinuation from the study, only those procedures that would not expose the pregnant female subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a female subject or female partner of a male subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Subjects who become pregnant during the study must discontinue study treatment. CCI [redacted] Pharmacovigilance must be notified of any female subject or female partner of a male subject that becomes pregnant while participating in this study. Although pregnancy is not an AE, all pregnancies must be followed to conclusion to determine their outcome. It is the responsibility of the investigator to report any pregnancy in a subject or subject's partner that occurs during the study by completing the Pregnancy Reporting Form.

Notification of the pregnancy should be submitted on the Pregnancy Reporting Form within 24 hours of awareness and reported using the same procedure as described for reporting SAEs (see Section 10.1.3.1.1). Spontaneous miscarriages, congenital abnormalities, and any premature termination of pregnancy will be reported as SAEs. Follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date.

The Pregnancy CRF will be included in the Safety Management Plan with instructions on how to complete it.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the subject has completed the study.

8.4 Investigational Products

8.4.1 Investigational Products Administered

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, one of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the free base equivalent of xanomeline and trospium according to the desired dosage strength. [redacted]

8.4.2 Identity of Investigational Products

Active study agents for each cohort will be in white, opaque, hard capsules. Placebo will be prepared in matching capsules, therefore an unblinded pharmacist will be required to dispense study agent at each dosing period. For the 2-day lead-in period, subjects randomized to active drug will receive capsule strength xanomeline 50 mg/20 mg trospium BID, followed by xanomeline 100 mg/trospium 20 mg BID for the remainder of Week 1. At the beginning of Week 2, dosing may be increased to xanomeline 125 mg/trospium 30 mg BID depending on clinical response and tolerability. Investigators have the option to return a subject to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period.

[redacted]

All investigational agents should be stored according to requirements.

8.4.3 Considerations for Subject Dosing

<u>Visit 2/Day 1 Randomization and Dosing</u>

- The first dose will be administered in the morning and the evening dose will be administered 12 ± 0.5 hours after the morning dose.

- In the event the above dosing regimen is not feasible, study sites may administer the first dose in the evening with continued dosing every 12 ± 0.5 hours. In this instance, the subject must still be administered 4 doses of the 50 mg/20 mg or placebo before dose escalation.

Visit 3/Day 3 on Weekends/Holidays

- When Day 3 occurs on a weekend, it is expected that the complete Visit 3 will be performed and subjects dose escalated on Day 3.

- If completion of the visit is not possible on Day 3, the ± 1-day visit window may be used. In this instance, the dose will not be up-titrated until the study visit occurs. In all cases, the subject must have had 4 doses of 50 mg/20 mg or placebo before up-titrating to 100 mg/20 mg or placebo.

Visit 5/Day 8 Dosing and PK considerations

- If dose escalation to the 125 mg/30 mg or placebo level is confirmed by investigator order on Visit 5/Day 8, that dose is to be administered in the morning to allow for serial PK blood draws per protocol.

- This may result in only 4.5 days of the 100 mg/20 mg or placebo dose, which is acceptable.

8.4.4 Packaging and Labeling

The study packaging will be performed by CCI Canada. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bulk supply bottles are labeled with the name of the drug, recommended storage conditions, the name and address of the manufacturer and the Investigational Use Statement ("Caution: New Drug – Limited by Federal [USA] Law to Investigational Use").

The labels for individual dosing prepared by the unblinded pharmacist will contain the Karuna protocol number, medication dosage form, subject number and initials, study day/date, blinded study dose level, date prepared, and preparer's initials.

8.4.5 Drug Product Accountability Procedures

Study drug accountability will be assessed periodically by the assigned unblinded study monitor.

8.4.6 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo with stratification by site.

At Screening, the IWRS will assign a unique subject identification number to the subject, known as the Subject Number. This number will be associated with the subject

throughout the study. Every subject who signs an ICF must be entered into the IWRS regardless of eligibility in order to obtain a Subject Number. CCI [redacted]

The subjects will be randomized by study site. The treatment assignment will be determined by a randomization list prepared by the biostatistics group CCI [redacted] and utilized in the IWRS. The 5-digit randomization number is used to identify the treatment (active or placebo) that will be assigned to the subject.

A randomization number can only be assigned to one subject and cannot be reused once assigned.

8.4.7 Selection of Doses in the Study

The lower lead-in doses for Days 1 to 2 and Days 3 to 7 allow the subject to adjust to the study drug before receiving a higher dose.

From the initial PK from the KAR-002 study as well as the more complete PK results from the first cohort of the KAR-003 study (all utilizing the new study formulation), it is clear that the AUC of xanomeline is roughly equivalent to that seen during the KAR-001 study, where the 75 mg xanomeline dose used in the earlier Lilly studies was used. Since it is believed that the efficacy of the compound relates to the exposure of the study drug in the subjects, it is believed that this dose should have roughly the same efficacy as had been seen in the earlier Lilly studies. Additionally, the first cohort of the KAR-003 study tolerated the 100 mg/20 mg BID dose reasonably well (after 2 days on 50 mg/20 mg BID). Thus, it seems quite reasonable for this to be the threshold (low) dose for the flex dose arm.

Tolerability issues were seen in the cohorts in KAR-003 receiving 150 mg BID xanomeline (whether on 20 or 40 mg BID of trospium); however, using 125 mg BID xanomeline paired with 40 mg trospium BID, fewer tolerability problems were observed. Thus, the results of the KAR-003 study point to the 125 mg BID of xanomeline dose as the “higher” dose that subjects can titrate up to on Day 8. The KAR-003 Dose Selection Committee, based on the presence of some anticholinergic AEs when subjects were dosed on 40 mg BID of trospium, decided to lower the trospium dose for the KAR-004 study to 30 mg BID for the higher dose for the flex dose arm.

8.4.8 Selection and Timing of Dose for Each Subject

Dosing will occur every 12 ± 0.5 hours each day, during waking hours. Trospium should be dosed on an empty stomach; ie, at least 1 hour before a meal and 2 to 3 hours after a meal.

KarXT and placebo are to be taken orally with a full glass of water.

Subjects will be evaluated for dose adjustments at Visits 5, 6, and 7 and at unscheduled visits. Subjects will start on a lead-in dose of xanomeline 50 mg/trospium 20 mg BID for the first 2 days, followed by xanomeline 100 mg/trospium 20 mg BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to xanomeline 125 mg/trospium 30 mg BID, unless the subject is continuing to experience AEs from the previous dose increase of xanomeline 100 mg/trospium 20 mg BID. All subjects who were increased to xanomeline 125 mg/trospium 30 mg, depending on clinical response and tolerability, will have the option to return to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period. Dosing must not change after Visit 7 of the study and may be decreased for tolerability reasons no more than once during the study.

8.4.9 Blinding

An IWRS will allocate treatment based on a prespecified randomization list, generated by CCI [redacted]. Active and placebo study drug will be provided to each site participating in the study. For each dose, study drug and packaging will be identical in size, shape, color, and appearance.

Study subjects, informants, investigators, site personnel involved in subject evaluation, and the Sponsor's medical monitor will be blinded to the subject treatment assignment. Both active study drug and placebo will be supplied as identical matching capsules. This prevents bias on the part of the study staff and the subject to influence the results of the study.

The Sponsor's authorized designee will generate and maintain the security of the randomization code. The blinding code will be broken early only when information is needed to maintain the health and well-being of subjects such as for treatment of an AE.

The reasons for any premature unblinding (either accidental or due to an SAE that appears related to the investigational product) will be properly documented in the study file. Unblinding according to the protocol will occur only after completion of the study.

A list of treatment numbers for each treatment group will be generated by the vendor selected by the Sponsor to perform this function, and the treatment prepared in accordance with this list. Numbers will not be reused regardless of the status of the use of the corresponding study drug.

The members of the ISMC will be unblinded as they review the safety data from the study. There will be an unblinded pharmacist to manage study drug inventory for each site and an unblinded study monitor for drug accountability and review of documentation of drug inventory.

If unblinding is necessary for the welfare of a subject who has experienced an AE, unblinding of study drug may occur for just that subject. If an AE is thought to be related to the study drug and poses a safety risk, the investigator must decide whether to stop investigational treatment and/or treat the subject. Subject withdrawal should be avoided, if possible. If discontinuation of treatment occurs, every attempt should be made to restart study drug if medically appropriate, whatever the duration of discontinuation. When a subject has an AE that requires that the investigator be unblinded, the investigator can obtain the treatment assignment from the IWRS system. The site is expected to notify the study medical monitor before breaking the study blind, unless it is in the subject's best interest if the blind is broken immediately. Note: in most circumstances it is not necessary to unblind a subject, even if an SAE has occurred. For many drugs there is no specific therapy for AEs. The appropriate course of action is to stop the investigational drug, and treat the signs and symptoms resulting from the AE.

8.4.10 Prior and Concomitant Therapy

8.4.10.1 Prior Medications

Subjects will be asked for all prior medications he/she were taking up to 6 months before the study, up to the time of the first dose of study medication on Day 1. All prior medications will be recorded on the eCRF.

8.4.10.2 Prohibited Medication/Therapy

During the study (ie, from the time of enrollment at the screening visit until study completion), subjects will refrain from the use of any new concomitant medications without the specific prior approval of the principal investigator. The administration of any other concomitant medications during the study period is prohibited without the prior approval of the principal investigator unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source documents and eCRF.

Within 2 weeks of baseline, subjects could not have taken oral antipsychotic medications, MAO inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate). Intramuscular antipsychotic medications taken before baseline should not have been taken within 1 and a half cycles from baseline (eg, 3 or more weeks off for a 2-week cycle). Please direct questions relating to prohibited medications to the assigned Medical Monitor.

Subjects are not to have alcohol or illegal drug abuse within the prior 12 months of screening (unless medical monitor provided approval at screening), or at any time during the study.

8.4.10.3 Rescue Medication

Subjects are allowed to take benzodiazepines (up to 6 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia. Subjects may also use nonbenzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid. CCI [redacted]

8.4.11 Treatment Compliance

Because this is an inpatient study, treatment compliance will be assured. All study drugs will be administered by study staff and recorded in the eCRF.

8.4.12 Supervised Outings

Subjects are not allowed to leave the study site or have day passes/outings unless they are accompanied by a staff member. Upon returning to the study site, the subject will have a urine drug screen and alcohol test (breathalyzer or blood alcohol level).

9 TIMING OF STUDY PROCEDURES

The planned study assessments are in Section 8.1.2.

9.1 Pre-treatment

9.1.1 Visit 1 (Screening Phase: Day -7 to Day -1)

Note: Written informed consent (IC) must be obtained before performing any study-related procedure, including screening evaluations.

Screening should be performed from Day -7 to Day -1. The screening phase is allowed to be extended up to an additional 7 days, if necessary.

Study candidates will be screened to assess eligibility for enrollment into the study. A screening log will be maintained for all consented study candidates. A screen failure is any study candidate who signs the IC and has completed the screening evaluation but does not qualify for the study or discontinues the study before study enrollment. The study candidate's initials, date screened, and reason(s) for screening failure must be recorded on the screening log.

During screening, the following procedures must be performed and recorded for each study candidate:

1. Obtain the study candidate's signed Informed Consent (IC) before the performance of any study-related procedures.
2. Collect demographic information (date of birth, gender, race) on the screening log.
3. Review inclusion/exclusion criteria to ensure eligibility.

4. Review the study candidate's medical and psychiatric history and prior and concomitant medications. Medical histories should include baseline symptoms, ongoing illnesses, other chronic conditions, surgical history, review of current and recently used (past 6 months) medications, as well as any other important information that may affect the eligibility of the subject.
5. Perform the MINI, version 7.0.2, a psychiatric evaluation to confirm if the study candidate meets the DSM-5 criteria for schizophrenia and does not meet psychiatric exclusionary criteria.
6. Administer the PANSS, CGI-S, Columbia Suicide Rating Scale (C-SSRS), CC CCI Study candidates must have a PANSS total score ≥ 80 to continue on to the study. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. CCI
7. Perform a complete physical examination (see Section 10.1.3.1.7 for required parameters).
8. Record height (in), weight (lb), and waist circumference measurements (in) and determine BMI.
9. Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
10. Perform a resting 12-lead ECG.
11. After the assessments above have been completed, collect blood samples for routine hematology (approximately 2 mL), coagulation (4.7 mL), serum chemistry (5 mL), serum pregnancy test for females of childbearing potential (5 mL), and urine for routine urinalysis (10 mL) (refer to Section 10.1.3.1.4 for required tests).
12. After the assessments above have been completed, collect a minimum of 10 mL of urine in a sterile plastic container for a urine drugs of abuse screening test (ie, National Institute of Drug Abuse [NIDA]-5). In addition, perform test to determine alcohol abuse (blood test [3.5 mL blood] or breathalyzer). Study candidates must be negative for these screening tests to proceed with further evaluation for study enrollment.
13. Subject eligibility verification process: independent diagnostic verification procedure and identity check using appropriate software/database. Verify eligibility.
14. Admit subject to inpatient unit.

9.2 Treatment Period

9.2.1 Visit 2 (Day 1; Study Enrollment - Randomization to Double-blind Study Treatment; Day 1)

1. Review concomitant medications.
2. Review inclusion/exclusion criteria to confirm eligibility.
3. Perform a urine pregnancy test (10 mL).

4. Record weight (lb) and waist circumference measurements and determine BMI.
5. Complete the PANSS, which must be ≥ 80. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. There should not be a change (improvement) in total PANSS score between screening and baseline of more than 20%. Study candidates must lack active suicidal ideation as determined by clinical assessment.
6. Complete the C-SSRS. Subjects cannot have suicidal ideation, as determined by clinical assessment and/or by answering "yes" to Items 4 or 5 on the C-SSRS at screening and/or baseline visits.
7. Complete the CGI-S, CCI , Simpson-Angus Rating Scale, Barnes Rating Scale for Akathisia, and AIMS. CCI

CCI

9. Randomize study subjects who meet these criteria to KarXT or placebo during this visit and assign a Subject Randomization#.
10. Begin administration of study drug
11. Inquire about AEs after dosing.
12. At 2 (± 1) hours after the first dose (if the first dose is not administered in the morning, after the evening dose), perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.2 Visit 3 (Day 3 ± 1 day; After 2 Days of Double-blind Study Treatment)

1. Inquire about AEs and changes in medical status since the last inquiry.
2. May draw 1 PK blood sample (3 mL) if an AE is reported.
3. Query study subject about concomitant medications.

CCI

5. Administration of study drug.
6. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.3 Visit 4 (Day 7 ± 2 days; After 1 Week of Double-blind Study Treatment)

1. Query the study subject regarding AEs and medical status, and concomitant medications and record changes in eCRF.
2. May draw 1 PK blood sample (3 mL) if an AE is reported.
3. Complete the CGI-S and C-SSRS.

CCI

5. Administration of study drug.
6. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.4 Visit 5 (Day 8 ± 2 days; After 8 Days of Double-blind Study Treatment)

1. Obtain 6 blood samples for PK analysis (3 mL each) after the morning dose.
2. Inquire about AEs and changes in medical status since the last inquiry.
3. Query study subject about concomitant medications.

CCI

5. Assess study subject tolerability to the study drug and adjust dose of randomized study drug based on clinical response and tolerability.
6. Administration of study drug.
7. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.5 Visit 6 (Day 14 ± 2 days; After 2 Weeks of Double-blind Study Treatment)

1. Query the study subject regarding AEs, medical status, and concomitant medications and record changes in eCRF.
2. May draw 1 PK blood sample (3 mL) if an AE is reported.
3. Assess study subject tolerability to the study drug and adjust dose of randomized study drug based on clinical response and tolerability, if required.
4. Complete the PANSS, CGI-S, and C-SSRS. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

CCI

6. Administration of study drug.
7. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.6 Visit 7 (Day 21 ± 2 days; After 3 Weeks of Double-blind Study Treatment)

1. Query the study subject regarding AEs, medical status, and concomitant medications and record changes in eCRF.
2. May draw 1 PK blood sample (3 mL) if an AE is reported.
3. Assess study subject tolerability to the study drug and adjust dose of randomized study drug based on clinical response and tolerability, if required.
4. Complete the CGI-S and C-SSRS.

CCI

6. Administration of study drug.
7. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
8. Collect blood samples for routine hematology (approximately 2 mL), coagulation (4.7 mL), serum chemistry (5 mL), and urine for routine urinalysis (10 mL).

9.2.7 Visit 8 (Day 28 ± 2 days; After 4-Weeks of Double-blind Study Treatment)

1. Query the study subject regarding AEs, medical status, and concomitant medications and record changes in eCRF.

2. Obtain 6 blood samples for PK analysis (3 mL each) after the morning dose.
3. Complete the PANSS, CGI-S, and C-SSRS. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

CCI [redacted]

5. Administration of study drug.
6. At 2 (± 1) hours after the morning dose, perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).

9.2.8 Visit 9 (Day 35 − 2 days; After 5 Weeks of Double-blind Study Treatment or Early Termination)

1. Query the study subject regarding AEs, medical status, and concomitant medications and record changes in eCRF.
2. Perform a complete physical examination.
3. Perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
4. Record weight (lb) and waist circumference measurements and determine BMI.
5. Perform a urine pregnancy test (10 mL).
6. Complete the PANSS, C-SSRS, CCI [redacted], CGI-S, Simpson-Angus Rating Scale, Barnes Rating Scale for Akathisia, and AIMS. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. CCI [redacted]

CCI [redacted]

8. Collect blood samples for: PK analysis, as possible (KarXT drug levels, 3 mL), and for routine hematology (2 mL), coagulation (4.7 mL), serum chemistry (5 mL), and urine for routine urinalysis (10 mL) (according to Section 10.1.3.1.4).
9. Perform a resting 12-lead ECG.
10. Verify that all tasks have been completed for the visit. Subjects will be discharged from the study following completion of laboratory sample collection, complete physical examination, urine pregnancy test, vital signs, and ECG. Subjects may be referred to their primary physician for follow-up as medically indicated.

9.2.9 Unscheduled Visits

1. Query the study subject regarding AEs, medical status, and concomitant medications and record changes in eCRF.
2. Collect blood samples for routine hematology (2 mL), coagulation (4.7 mL), serum chemistry (5 mL), and urine for routine urinalysis (10 mL) as needed (according to Section 10.1.3.1.4).
3. Assess study subject tolerability to the study drug and adjust dose of randomized study drug based on clinical response and tolerability, if required (unless visit is after Day 21).

4. May collect 1 blood sample for PK analysis (3 mL) if there was a dose adjustment or an AE reported.

CCI [redacted]

6. Administration of study drug, if appropriate.
   a. At 2 (± 1) hours after the morning dose (if dosed), perform orthostatic vital sign measurements: blood pressure (systolic and diastolic) and heart rate (beats/minute).
7. Complete the C-SSRS.
8. Other assessments may be performed at the discretion of the investigator.

9.3 Completion of Study and Lost to Follow-up

The study will be completed when all subjects have completed their study-related procedures in accordance with the protocol.

Every reasonable effort will be made to contact subjects who leave the facility and are lost to follow-up to obtain end of study information. Details regarding follow-up efforts should be documented in the subject's medical records/source documentation.

9.4 Duration of Treatment

The duration of treatment will be 5 weeks in addition to a screening time of up to 7 days, with a possible extension of up to an additional 7 days, if necessary.

10 EFFICACY, PHARMACOKINETICS, AND SAFETY ASSESSMENTS

The planned schedule of assessments is in Section 8.1.2.

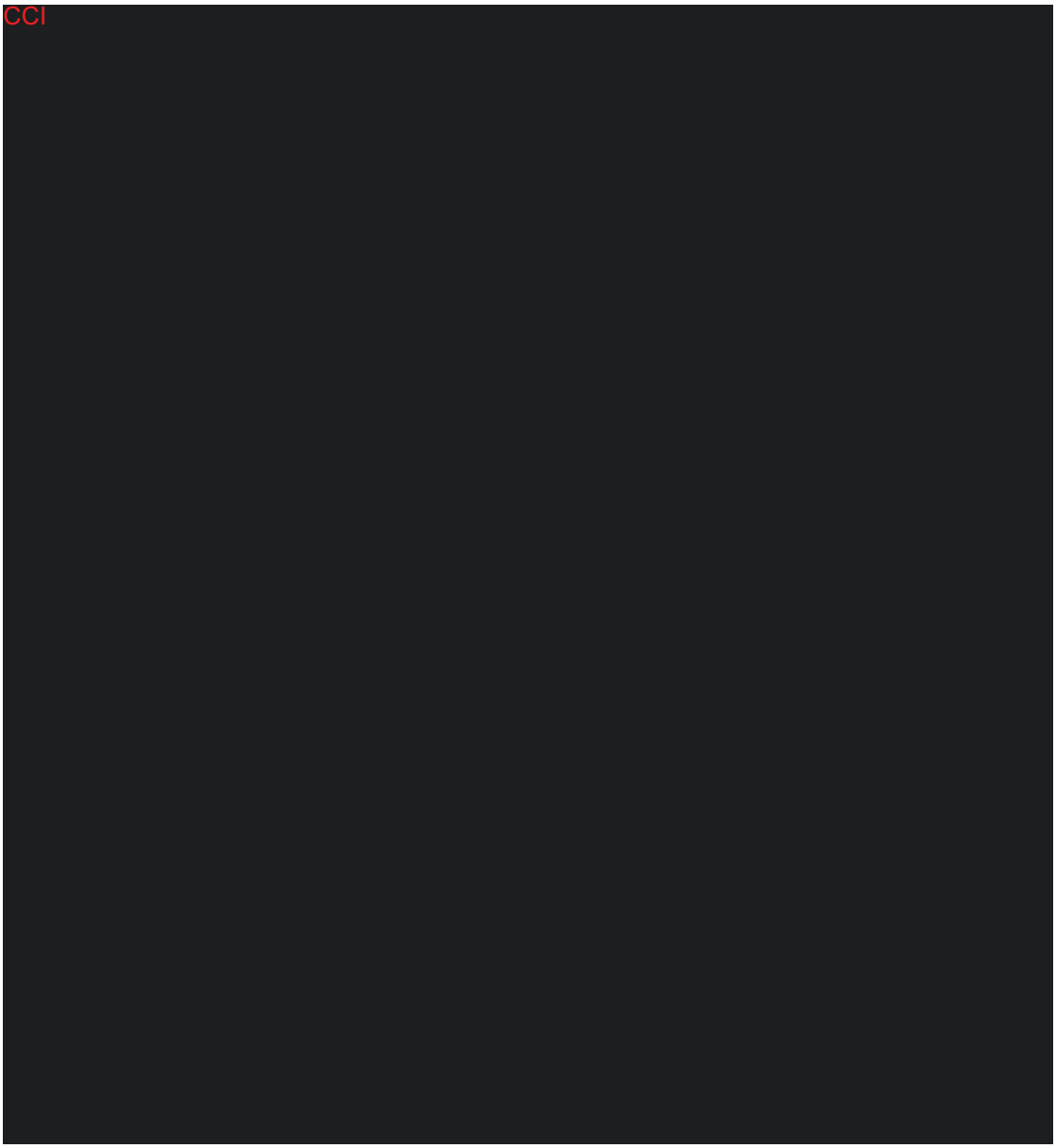
10.1 Efficacy, Pharmacokinetics, and Safety Assessments

10.1.1 Efficacy Variables

10.1.1.1 Positive and Negative Syndrome Scale

The PANSS including the PANSS Marder Factor, is a medical scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[10] The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects 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 scale assessments for all visits at which it is performed.



10.1.2 Pharmacokinetic Variables

10.1.2.1 KarXT Levels

Blood will be drawn for KarXT levels as indicated in Table 1.

Serial blood samples to measure plasma concentrations of xanomeline and trospium will be obtained on Visit 5/Day 8 ± 2 days (first dose of fixed titration period) and

Visit 8/Day 28 ± 2 days. Blood samples will be obtained at the following time points on these days:

- Before the morning dose and at 1, 2, 4, 8, and 12 hours after the morning dose. (Note: The 12 hour samples will be collected before administration of the evening dose.)

The 1 hour sample should be collected within ±5 minutes of the scheduled time. The 2, 4, 8, and 12 hour samples should be collected within ±10 minutes of their scheduled times. It is very important that the exact PK draw and dosing times are recorded in the eCRF, and also that PK samples are collected within the specified times of collection.

Note: A single PK sample should be drawn prior to discharge (preferably in the morning) at Visit 9/ET. In addition, one PK sample may be drawn if an AE is reported during a scheduled visit, or if there is a dose adjustment or AE reported during an unscheduled visit (no multiple draws). For Visit ET that is related to an AE, the collection of a PK blood sample is not optional and should be drawn prior to discharge.

Instructions for dividing, processing, and shipping PK samples will be provided in the CCI PK laboratory manual.

10.1.3 Safety Assessments

The methods of assessments of safety parameters are specified in Sections 10.1.3.1 to 10.1.3.1.9.9 and the timing is outlined in Table 1.

The principal investigator or the site sub-investigator has front-line primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of SAEs and timely review of other AEs reported during the study.

If at any time during the study a serious risk becomes evident, the study subject participation will be stopped and the principal investigator will also arrange for the participant's care to continue.

10.1.3.1 Adverse Events

Any clinically significant changes identified during the safety assessments conducted after the subject received the study drug must be documented as AEs.

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated

with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening need not be considered AEs.

In accordance with the protocol, the investigator and/or clinic staff will elicit AEs and inter-current illness during and at the end of the study period and these will be recorded on the appropriate page of the eCRF. Adverse events will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked?" The eCRF will be completed at the end of the study as soon as the results of the final lab tests are available.

The reporting period for AEs is the period immediately following the administration of study product on Visit 2/Day 1 and up to the time of discharge (Visit 9/Day 35) of the subject from the study.

Adverse events will be reported on the AE eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the study product, possible etiologies and whether the event meets criteria as a SAE and therefore requires immediate notification of the Sponsor, the IRB, and the FDA. If the event has not resolved at the end of the study reporting period it will be documented as still present on the eCRF. If an AE evolves into a condition that becomes "serious" it will also be reported as an SAE.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely:	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Very Likely/Certain:	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication
- Other, specify

Follow-up of Adverse Events

Subjects with AEs/SAEs will be treated if necessary and followed by the investigator until the event resolves or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. The investigator will provide or arrange for appropriate follow-up (if required) for subjects, and document the course of the subject's condition. Additional medical evaluation and treatment will be arranged as appropriate. Details of AE resolution must be documented in the eCRF.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.1.3.1.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect, cancer, or drug overdose.

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

See the IB for more details on AE and SAE Assessment Criteria and Reporting Responsibilities.

Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study, after the first known dose of investigational product, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be faxed or emailed **within 24 hours** for the attention of the CCI Safety & Pharmacovigilance department at:

Fax: CCI (primary) or
CCI (alternative)
SAE reporting email in case of fax failure: CCI

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The Sponsor and/or CCI will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/IRB approval/favorable opinion of the study. In addition, CCI, on behalf of the Sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.5.

10.1.3.1.2 Adverse Events of Special Interest

The AEs of special interest (AESIs) will be monitored. Adverse events of special interest are:

- Syncope/orthostasis

Adverse events of special interest (AESIs) should be recorded as AEs, and reported as SAEs when appropriate.

10.1.3.1.3 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (eg, IB for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The Sponsor and/or CCI shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the Sponsor.

Warnings and Precautions

Risk of Urinary Retention

Trospium chloride tablets should be administered with caution to subjects with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility

Trospium should be administered with caution to subjects with gastrointestinal obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease gastrointestinal motility and should be used with caution in subjects with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Controlled Narrow-angle Glaucoma

In subjects being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

Central Nervous System Effects

Trospium chloride is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations, and somnolence. Subjects should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise subjects not to drive or operate heavy machinery until they know how trospium chloride affects them. If a subject experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment

Trospium is substantially excreted by the kidney. The effects of moderate renal impairment on systemic exposure are not known but systemic exposure is likely increased. Therefore, anticholinergic adverse reactions (including dry mouth, CCI dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

10.1.3.1.4 Clinical Laboratory Evaluation

All laboratory tests will be performed by a Clinical Laboratory Improvement Amendments/College of American Pathologist (or equivalent) certified central clinical laboratory. The study site will receive all necessary supplies for the collection and processing of laboratory specimens.

Venous blood (approximately 12 to 20 mL) will be drawn for the tests listed below, according to the time points outlined in Table 1.

All laboratory assessments will be evaluated using normal ranges provided by the clinical laboratory. The investigator must review all laboratory reports and file a signed copy with each subject's chart. Changes in clinical laboratory test results judged to be normal or clinically non-significant by the physician responsible for all study related medical decisions will not be considered AEs. The normal range of values for all the laboratory evaluation is provided in Appendix 17.3. Any out-of-range (abnormal) clinically significant (in the opinion of the investigator) laboratory value that meets the criteria for an AE or SAE must be recorded on the AE page of the eCRF. When possible, the AE associated with the clinically significant laboratory abnormality rather than the laboratory value should be recorded (eg, hypokalemia, hyponatremia, anemia, etc.). A

laboratory test result that is out of normal range, but considered not clinically significant by the investigator will not be considered an AE.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the principal investigator and the Sponsor's medical monitor.

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Hematology (2 mL)

Hematology assessments will include measures of hemoglobin, hematocrit, mean cell volume, red blood cell count, white blood cell count with differential, and platelet count.

Clinical Chemistry (5 mL)

Serum chemistry tests will include measure of alkaline phosphatase, gamma-glutamyl-transferase, AST, ALT, Creatine kinase, lactate dehydrogenase, total bilirubin, total protein, cholesterol, triglycerides, urea nitrogen, uric acid, glucose, calcium, chloride, creatinine, inorganic phosphate, potassium, sodium, albumin, and bicarbonate.

Coagulation (4.7 mL)

Coagulation parameters will include prothrombin time, partial thromboplastin time, and fibrinogen.

Urinalysis

A minimum of 10 mL of urine will be obtained for the following tests: color/appearance, pH, glucose, specific gravity, ketones, protein, urobilinogen, occult blood, white blood

cells, microscopic.

10.1.3.1.5 Other Laboratory Variables

An NIDA-5 urine drug screen (10 mL; cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed at screening only.

Alcohol testing is performed using a breathalyzer or blood alcohol test (3.5 mL).

If a subject leaves the unit, he/she should have a urine drug screen test (10 mL) and test for alcohol (breathalyzer or blood alcohol test [3.5 mL]) upon returning to the unit.

Screening for pregnancy will be performed (serum beta-human chorionic gonadotropin [β-HCG] at Screening [5 mL], urine β-HCG at other visits [10 mL]).

10.1.3.1.6 Vital Signs

Orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate (beats/minute). Orthostatic vital signs are to be taken as specified in Table 1. During treatment, beginning with Visit 2, vital signs should occur 2 (± 1) hours after the morning dose. At investigator discretion, additional orthostatic vital signs are allowed to be conducted at other times as needed.

10.1.3.1.7 Physical Examination

Complete physical examination at screening include: body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination. A complete physical examination will be performed at Visit 9/ET.

10.1.3.1.8 Weight, Height, Body Mass Index, Waist Circumference

Height (screening only), weight, and waist circumference measurements will be obtained at visits as specified in Table 1. Body mass index should be calculated at these visits. All findings should be recorded in the eCRF.

10.1.3.1.9 Other Safety Assessments

10.1.3.1.9.1 Electrocardiogram

A resting 12-lead ECG will be used to obtain the following measurements: ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec).

10.1.3.1.9.2 Concomitant Medications

Subjects will be asked about any concomitant medications they are taking. All concomitant medications are recorded in the eCRF.

10.1.3.1.9.3 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.[11] 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 baseline/screening version will be completed; for all subsequent visits the "Since Last Visit" version of the C-SSRS will be administered.

10.1.3.1.9.4 Clinical Global Impression–Severity

The CGI-S is a rating scale used to measure illness and symptom severity in subjects with mental disorders and is used to rate the severity of a subject'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 subject 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 subjects.[12]

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

10.1.3.1.9.5 Simpson-Angus Rating Scale

The Simpson-Angus Scale 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.

10.1.3.1.9.6 Barnes Rating Scale for Akathisia

The Barnes Rating Scale for akathisia 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.[13]

10.1.3.1.9.7 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements know 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 subject's level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

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10.1.3.1.9.9 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.

10.1.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety data from the clinical study. This committee will be responsible, on a periodic basis, for confirming the safety of KarXT throughout the study, with particular focus on assessing for any new toxicities that might be involved with KarXT.

The reviews will be of unblinded data to allow a comparison of event rates and detection of safety signals across treatment groups to identify important safety information. The ISMC charter will contain the details of the types of data to be reviewed, the defined triggers for review, the minimum frequency of meetings (timed, if no triggers), and the communication plan for disseminating review recommendations.

10.1.5 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate and relevant to the disease condition.

10.1.6 Drug Concentration Measurements

Plasma samples will be analyzed for concentrations of xanomeline and trospium using a validated high performance liquid chromatography/tandem mass spectrometric method. The analysis will be performed by CCI [redacted]. The method requires a 50.0 µL human plasma aliquot containing K_2EDTA and allows for the simultaneous quantitation of xanomeline and trospium from the same sample.

11 STATISTICS

11.1 Statistical Analysis Plan

Full statistical considerations, table mock-ups and final analysis of efficacy, safety and PK data collected in this study will be outlined in a formal statistical analysis plan (SAP). This plan will be finalized before locking the database and unblinding of the final datasets.

11.2 Analysis Populations

11.2.1 Intent-To-Treat Population

Intent-to-treat (ITT) population is defined as subjects who are randomized to the study.

11.2.2 Modified Intent-To-Treat Population

Modified Intent-to-treat (mITT) population is defined as randomized subjects who receive at least 1 dose of study drug and have a baseline assessment. The mITT population will be used for efficacy analyses.

11.2.3 Safety Population

Safety population is defined as subjects who receive at least 1 dose of study drug. The safety population will be used for safety analyses.

11.2.4 Pharmacokinetic Population

Pharmacokinetic population is defined as randomized subjects who receive at least 1 dose of study drug and have at least 1 measurable serum concentration of study medication. PK population will be used for PK analyses.

11.3 Statistical Analyses

11.3.1 Subject Disposition

The number of subjects in each analysis population and the reasons for discontinuation will be summarized. In addition, subjects' status with regard to study treatment and follow-up will also be summarized.

11.3.2 Demographic and Other Baseline Characteristics

Subject disease and baseline characteristics will be summarized using frequency distribution or descriptive statistics as appropriate.

11.3.3 Efficacy Analyses

The primary endpoint of the study is the change from baseline in PANSS total score at Week 5. The difference between KarXT and placebo at Week 5 will be estimated using a mixed model for repeated measures (MMRM). The model will include the observed change from baseline PANSS total score at Week 2, Week 4, and Week 5 as the response. The treatment difference at Week 5 will be estimated using contrasts. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Site, age, gender, and baseline

PANSS total score will be used as covariates in the model. A method for pooling sites with small numbers of patients will be described in the SAP.

The sensitivity analyses of the primary endpoint will be specified in the Statistical Analysis Plan. Sensitivity analysis will include a method to handle missing data (eg, Analysis of Covariance with last observation carried forward or pattern mixture models using multiple imputation), alternative analysis populations (eg, patients completing the study or patients who have no major protocol deviations) and alternative statistical methods (eg, Analysis of Covariance models separately for each visit).

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The continuous secondary endpoints, including the change in PANSS positive score, change in PANSS Marder Factor score, CCI [redacted]

The categorical secondary endpoints, including percent of CGI-S responders, will be compared between the treatment groups (KarXT and placebo) using the Cochran-Mantel-Haenszel test stratified by baseline CGI-S score. A CGI-S responder is defined as a subject with CGI-S scale equal to 1 or 2.

11.3.4 Safety Analyses

The analysis of the safety data will focus on the comparison of KarXT and placebo. In addition, all safety data will be reported in listings.

Treatment emergent AEs (TEAEs) will be summarized by system organ class, preferred term, and treatment group. Descriptive statistics will be used to compare the overall incidence of TEAEs between the treatment groups.

Separate summaries will be generated for AESIs, tabulated by AESI category and preferred term using the categories as specified below:

- Syncope/orthostasis

Orthostatic vital signs, laboratory values, ECG parameters, and physical examinations will be summarized descriptively by time point and treatment group, including the changes from baseline as appropriate. Similar descriptive summaries will be provided for C-SSRS, Simpson-Angus Rating Scale, Barnes Rating Scale for Akathisia, AIMS, body weight, BMI, and waist circumference.

11.3.5 Pharmacokinetic Analyses

Pharmacokinetics results will be listed for all subjects who received active treatment. The profiles or time points obtained with protocol deviations affecting PK results will be flagged and may be excluded from summaries and analyses.

The data will be presented graphically and individual plots and summarized by actual treatment, visit and time point.

Pharmacokinetic parameters for xanomeline and trospium will be derived from plasma concentration data using non-compartmental methods. Actual time elapsed from dosing will be used to estimate all individual PK parameters. CCI [redacted] Additional parameters such as the elimination half-life will be determined if the data permit.

The effect of dose on PK and other inferential analyses for exposure-response relationship may be performed. The details will be described in the SAP. The noncompartmental analysis will be described as a part of final CSR.

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11.3.6 Interim Analyses

No interim analysis is planned for this study.

11.3.7 Handling of Missing Data

Several different methods to handle the missing data in efficacy assessments will be used.

  - For the primary efficacy analysis, likelihood-based modeling approach will be used to handle incomplete data. For this purpose, an MMRM will be applied.
  - Sensitivity analysis for the primary efficacy endpoint will be conducted using the last observation carried forward approach. In this analysis, the missing values will be replaced by the previous visit PANSS total score carried forward.
- Sensitivity analysis for the primary efficacy endpoint will be conducted using the Multiple Imputation approach; ie, by replacing each missing value with a set of plausible values that represent the uncertainty about the right value to impute.

11.4 Determination of Sample Size

Assuming a PANSS total score difference of 9 between drug and placebo and standard deviation of 18, a sample size of approximately 180 (90 evaluable subjects per arm) will result in a power of 91% for a 2-sided alpha of 0.05.

11.5 Protocol Deviations

All protocol deviations will be tracked in the eCRF/electronic data capture (EDC) system. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

The study site personnel and principal investigator must make all study records (including source data and documentation) available to US and International regulatory agency personnel, the IRB and the study Sponsor or designee, for the purposes of monitoring, auditing, inspection, and copying. In addition, disclosure of study information to third parties may be required by law.

12.2 Monitoring

The study will be monitored by the Sponsor or its designee on a regular basis throughout the study period. Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF and is administered study drug. Some data such as scale assessments and laboratory results will be maintained in the vendor systems.

In accordance with current Good Clinical Practice (cGCP) and International Council for Hamonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

12.3 Data Management and Coding

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be considered the source documents for the purposes of auditing the study. Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

CCI will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of CCI.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA Code of Federal Regulations (CFR) 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities for concomitant diseases and AEs and World Health Organization Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12.4 Quality Management and Risk Evaluation

Details are provided in Section 8.2.2.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

The accountability for the study drug at the study site rests with unblinded study monitors. These persons will maintain records of all the investigational products (drug and placebo), including their delivery and receipt, inventory at the site, use by each subject, and the destruction of unused study drug according to the directions of the Sponsor or designee. The investigators will assure that drug and placebo are used according to the protocol. The investigators will assure that the study drug and the records described in this paragraph will be stored in a locked area suitable for storage of pharmaceutical products, and in accordance with the conditions specified on the study drug label. Further, the investigators assure that the study drug and the records will be available for examination by the unblinded study monitor on periodic visits.

All unused study drug supplies and equipment will be destroyed according to directions of the Sponsor or designee at the end of the study.

On receipt of the study drug, an unblinded pharmacist at the study site will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The unblinded pharmacist will retain a copy of this receipt at the study center and it will be reviewed by the unblinded study monitor. The unblinded study monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the unblinded study monitor to ensure that the unblinded pharmacist has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The unblinded study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

The protocol, informed consent, and other written material given to the subjects, and any other relevant study documentation will be reviewed and approved by the governing IRB of the participating center before study initiation and/or before the study drug is released to the investigator, and the investigator will keep the IRB informed as to the progress of the study.

Modifications or changes to the protocol, the informed consent, or other study documentation may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted should be obtained.

The IRB must be informed by the principal investigator of informed consent changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only; on some specimen collection records, the subject's birth date may also appear. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA or the Sponsor of the clinical study.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the US regulatory authorities, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, the Guideline for GCP (ICH E6), the United States CFR governing the protection of human subjects (21CFR§50), IRBs (21CFR§56), the requirements for conducting clinical investigations (21CFR§312), and all applicable local, state and federal government regulations and laws.

14.4 Informed Consent

Written informed consent must be obtained before any protocol-specified procedures or interventions are carried out. Subjects will be counseled about the study before giving their written informed consent. The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, potential risks, and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. Subjects must be given ample opportunity to inquire about details of the study. The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. Written informed consent will be obtained from each subject before entry into the study. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records. The Informed Consent should be translated and certified into the local language of the respondent, as deemed necessary.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

The consent form must be approved by the IRB and be acceptable to the Sponsor. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each signed ICF must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the Sponsor or its designee. The subject should receive a copy of the signed and dated written ICF and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information, and reconsent will be obtained.

14.5 Conflict of Interest

The investigators will be partially paid by the Sponsor of this study for the study related expenses, but they will not profit from results, either positive or negative, with regard to

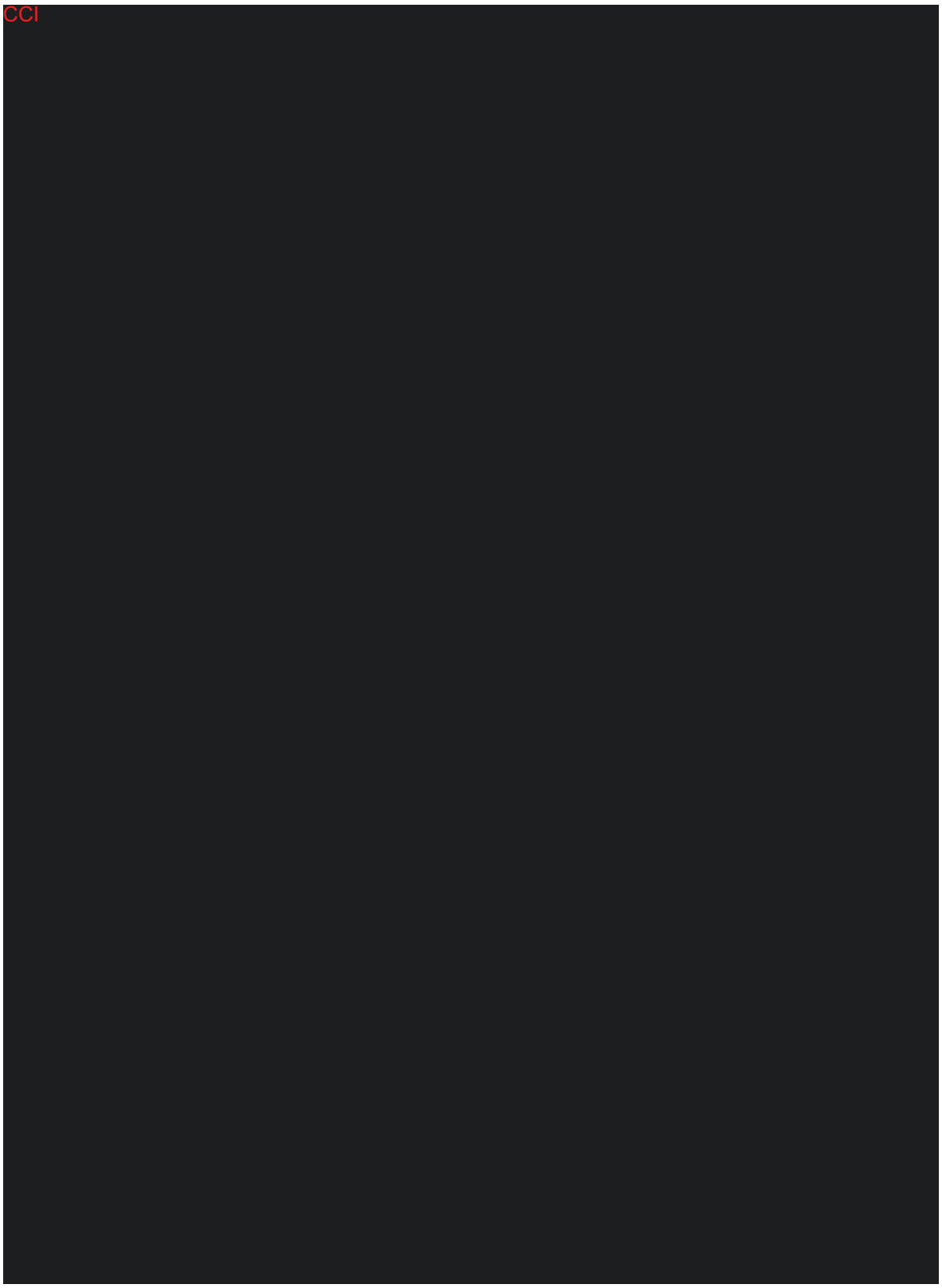
the product being evaluated. The investigators will not profit financially, should the product be marketed commercially.

14.6 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act [20], applicable to national and/or local laws and regulations on personal data protection.

The information on individual subjects arising from this study is to be considered confidential and transmitted to the Sponsor only in a form that will not permit identification of the individual. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject, and if requested, the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. Under informed consent, the subject shall understand that each participant is authorizing access to medical records as required for monitors, auditors, IRBs, and regulatory authorities. All records will be kept in a secure storage area with limited access.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