Official Title of Study:

An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia

NCT Number: NCT04820309

Document Date (Date in which document was last revised): 26 Sep 2023

1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia

Protocol Number: KAR-011

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 99 High Street Floor 26 Boston, MA 02110 Tel: (857) 449-2244 Email: info@karunatx.com
Protocol Version:	4.0
Protocol Date:	26 Sep 2023

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia

Protocol Number: KAR-011

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

Sponsor Signatory

[redacted]
Karuna Therapeutics

[redacted]
Date (DD-Mmm-YYYY)

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Karuna Therapeutics

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Date (DD-Mmm-YYYY)

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Karuna Therapeutics

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Date (DD-Mmm-YYYY)

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Contract Research Organization Signatory

[redacted]
Syneos Health

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Date (DD-Mmm-YYYY)

Biostatistician

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Veristat

[redacted]
Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia

Protocol Number: KAR-011

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and relevant International Council for Harmonisation (ICH) guidelines including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of KarXT, as described in this protocol and any other information provided by Karuna Therapeutics including, but not limited to, the current investigator's brochure.
- Prior to initiating the trial, I will provide the independent ethics committee (IEC)/institutional review board (IRB) all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Karuna Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about KarXT and of their delegated study-related duties and functions as described in the protocol. I will supervise these delegated persons or parties in the conduct of this trial.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Karuna Therapeutics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in De Novo Subjects With DSM-5 Schizophrenia
Protocol Number:	KAR-011
Investigators/Study Sites:	Approximately 60 sites in the United States
Phase of Development:	Phase 3
Objective(s):	**Primary Objective:** The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a Diagnostic and Statistical Manual-Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objective:** The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium following administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: • To evaluate the reduction in Positive and Negative Syndrome Scale (PANSS) total score • To evaluate the reduction in PANSS positive score • To evaluate the improvement in Clinical Global Impression-Severity (CGI-S) score • To evaluate the reduction in PANSS negative score • To evaluate the reduction in PANSS Marder Factor negative symptoms score • To evaluate the percentage of subjects who exhibit a 30% reduction in PANSS total score [redacted]
Study Endpoint(s):	**Primary Safety Endpoint:**

	The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs). **Secondary Endpoints:** **Safety:** The secondary safety endpoints of the study are: • Incidence of serious TEAEs • Incidence of TEAEs leading to withdrawal **Efficacy:** The secondary efficacy endpoints of the study are: • Change from baseline in PANSS total score at Week 52 • Change from baseline in PANSS positive score at Week 52 • Change from baseline in PANSS negative score at Week 52 • Change from baseline in PANSS Negative Marder Factor score at Week 52 • CGI-S score at Week 52 • Percentage of PANSS responders (a 30% reduction in PANSS total score) at Week 52 **Other Endpoints:** Other Safety endpoints: The other safety endpoints of the study are: • Spontaneously reported adverse events of special interest (AESIs) • Spontaneously reported anticholinergic and procholinergic symptoms • Change from baseline in Simpson-Angus Rating Scale (SAS) • Change from baseline in Barnes Akathisia Rating Scale (BARS) • Change from baseline in Abnormal Involuntary Movement Scale (AIMS) • Change from baseline in body weight, body mass index (BMI), and waist circumference • Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen) • Change from baseline in 12-lead electrocardiogram (ECG) • Change from baseline in physical examinations • Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS) Pharmacokinetic endpoint: • Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009 [redacted]

	[redacted]
Study Design:	This is a Phase 3, multicenter, 52-week, outpatient, open-label study to evaluate the long-term safety, tolerability, and efficacy of KarXT in de novo subjects, defined as those who did not have prior exposure to KarXT, who meet DSM-5 criteria for schizophrenia. The study consists of a screening phase of up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval), a baseline phase of up to 5 days, a 52-week open-label treatment phase, and a 7-day safety follow-up/end of study (EOS) visit following the last dose of KarXT for subjects who complete the treatment phase and those who prematurely discontinue from the study Screening Phase: A suitable number of subjects will be screened to enroll approximately 600 subjects (aged 18 to 65 years) with schizophrenia who are psychiatrically stable and can be adequately managed in an outpatient setting across approximately 60 study sites in the United States. The screening phase will last up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval). Baseline Phase: Subjects who meet the screening criteria will participate in a baseline period consisting of two separate visits. The start of the baseline period, Baseline Visit A, must be at least 3 days (and no more than 5 days) prior to Baseline Visit B. Subjects must continue to meet eligibility criteria throughout the baseline period to remain in the study. Treatment Phase: In this open-label study, all subjects will receive KarXT for up to 52 weeks. All subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium chloride) twice daily (BID) for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). At Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience adverse events (AEs) from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. [redacted]

	[redacted] Additional changes to KarXT dosing (eg, temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor. Interim visits, which can be conducted in-clinic or by telemedicine per investigator discretion, will occur between required in-clinic visits (see Schedule of Assessments Table 2). Additional Unscheduled study visits should be utilized as necessary to facilitate subject retention and ensure compliance with study objectives. Safety Follow-up/End of Study: A safety follow-up/EOS visit (Visit 30/Day 371±3 days) will be performed for all subjects after the last dose of KarXT. Independent Safety Monitoring Committee: An Independent Safety Monitoring Committee will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.
Study Criteria:	Inclusion Criteria: Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years, inclusive, at screening. 2. Subject is capable of providing informed consent. a. A signed informed consent form (ICF) must be provided before any study assessments are performed. b. Subject must be fluent (oral and written) in the language of the ICF to consent 3. 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 (MINI) for Schizophrenia and Psychotic Disorder Studies version 7.0.2. 4. The subject has not required psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 8-weeks of screening and is psychiatrically stable in the opinion of the investigator. 5. PANSS total score of ≤ 80 at screening and Baseline Visit B (Day 0). 6. CGI-S score of ≤ 4 at screening and Baseline Visit B (Day 0). 7. At the time of screening, or at any time within the 30 days prior to screening, the subject must have received an oral antipsychotic medication daily at a dose and frequency consistent with the drug label. 8. In the opinion of the investigator, it is clinically appropriate for the subject to discontinue current antipsychotic therapy and initiate experimental treatment with KarXT. 9. The subject is willing and able, in the opinion of the investigator, to discontinue all antipsychotic medications prior to baseline visit. a. Subjects should discontinue any antipsychotic medications prior to Baseline Visit A (Day -3). If clinically necessary, and in consultation with the medical monitor, antipsychotic medications may be continued through the baseline period up until the time

	of Baseline Visit B (Day 0). b. Antipsychotic down-taper, if clinically appropriate in the opinion of the investigator, may occur during the screening phase. 10. Subject has an identified, reliable informant willing and able to address some questions related to certain study visits, if needed. An informant may not be necessary if the subject has been the patient of the investigator for ≥1 year. [redacted] 13. BMI must be ≥18 and ≤40 kg/m^2. 14. Subject resides in a stable living situation and is anticipated to remain in a stable living situation for the duration of study enrollment, in the opinion of the investigator. 15. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1. 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). Exclusionary disorders include but are not limited to major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment. 2. The subject has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline. a. A 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. b. Subjects with a positive UDS for cannabis are permitted to enroll in the study provided that the subject's pattern of use is not indicative of a substance use disorder. 3. 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. 4. Subjects with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections

based on either medical history or liver function test results.

5. History or high risk of urinary retention, gastric retention, or narrow--angle glaucoma.
6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and 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.
8. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.

10. Subject has a history of treatment resistance to schizophrenia medications defined as:
    a. Failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) within the past 12 months, OR
    b. Having received clozapine within the past 3 years
11. Pregnant, lactating, or less than 3 months postpartum.
12. 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 opinion 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.
13. Subjects who have tested positive for coronavirus disease 2019 (COVID-19) within 2 weeks of screening.
14. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that preclude study participation.
15. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) within the 6 months before screening.

	16. Subjects with prior exposure to KarXT. 17. Risk of violent or destructive behavior. 18. Current involuntary hospitalization or incarceration. 19. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 30 days prior to screening.
Planned Sample Size:	Approximately 600 subjects (aged 18 to 65 years) are planned to be enrolled in this study.
Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium chloride) oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium chloride) oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium chloride) oral (Days 8 to 364, if tolerated)
Reference Therapy:	Not applicable.
Treatment Duration:	Total study duration is up to approximately 57 weeks, including a screening phase of up to 14 days with an extension of up to 7 days, a baseline phase of up to 5 days, a 52-week treatment phase and a 7-day follow-up/EOS phase.
Safety Assessments:	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; serious Aes (SAEs) and Aes leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; IPSS; and C-SSRS will be evaluated throughout the study as scheduled.
Efficacy Assessments:	PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits.
Pharmacokinetic Assessment:	Blood samples will be collected at scheduled visits for bioanalysis of plasma concentrations of xanomeline and trospium, and will be compared to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009.
[redacted]	
Statistical Methods and Planned Analyses:	Study Populations: Enrolled population: All subjects who have given informed consent for KAR-011 will be included in the Enrolled population. Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis. Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid PANSS assessment at baseline, and at least 1 postbaseline time point will be included in the mITT population and will be used in the efficacy analysis.

	PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT in the current study will be included in the PK population. The primary safety endpoint of the study is the incidence of TEAEs. Secondary safety endpoints are the incidence of serious TEAEs and the incidence of TEAEs leading to withdrawal of KarXT. The secondary efficacy endpoints are change from baseline to Week 52 in the PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, CGI-S score, and the percentage of PANSS responders at Week 52. [redacted] Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum, and maximum. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
CNS	central nervous system
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTS	clinical trial subject
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EOS	end of study
EOT	end of treatment
EPS	extrapyramidal symptoms
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GI	Gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IPSS	International Prostate Symptom Score

Abbreviation	Definition
IRB	Institutional Review Board
ISMC	Independent Safety Monitoring Committee
LFT	liver function test
[redacted]	[redacted]
MCC	microcrystalline cellulose
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	3 times daily
[redacted]	[redacted]
[redacted]	[redacted]
US	United States
VAS	visual analog scale
VCT	Verified Clinical Trials
vs	Versus
WOCBP	women of child bearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States (US) 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 drugs (APDs) are the mainstay of treatment for schizophrenia.[5] All currently available APDs act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, which include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[6, 7, 8] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[9, 10] Thus, there is a need for medications for schizophrenia that act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[11, 12] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[13] 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 [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but preferentially stimulates M1 and M4 receptors and binding to M1 and M4 receptors in the CNS, which is thought to be responsible for the drug's potential

therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M4 muscarinic agonist in vivo, measured by various second messenger assays.[14] Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate.[15]

Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement.

Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.[16, 17] Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in subjects who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus (vs) placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.[16, 17] In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.[18]

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

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline’s stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist that binds to and antagonizes all 5 muscarinic receptor subtypes.[19] It is a commonly used generic drug approved for over 10 years by the US Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.[19] Several human subject studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug’s quaternary ammonium structure.[20]

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Karuna Therapeutics (hereafter, Karuna) hypothesized that the addition of trospium would mitigate peripheral procholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation) and thus provide a strategy to allow xanomeline to be administered and stimulate brain muscarinic receptors with a decreased side effect burden. Phase 1 studies in healthy volunteers of this combination demonstrated that KarXT reduced these side effects by 46% compared to xanomeline alone.[21] Moreover, the remaining cholinergic AEs were generally

mild to moderate in severity and transient in nature, often lasting a few hours without recurrence and were generally single episode. In general, KarXT was well tolerated in healthy adult volunteers. These encouraging safety data prompted further work to assess KarXT for the treatment of schizophrenia and potentially other CNS disorders.

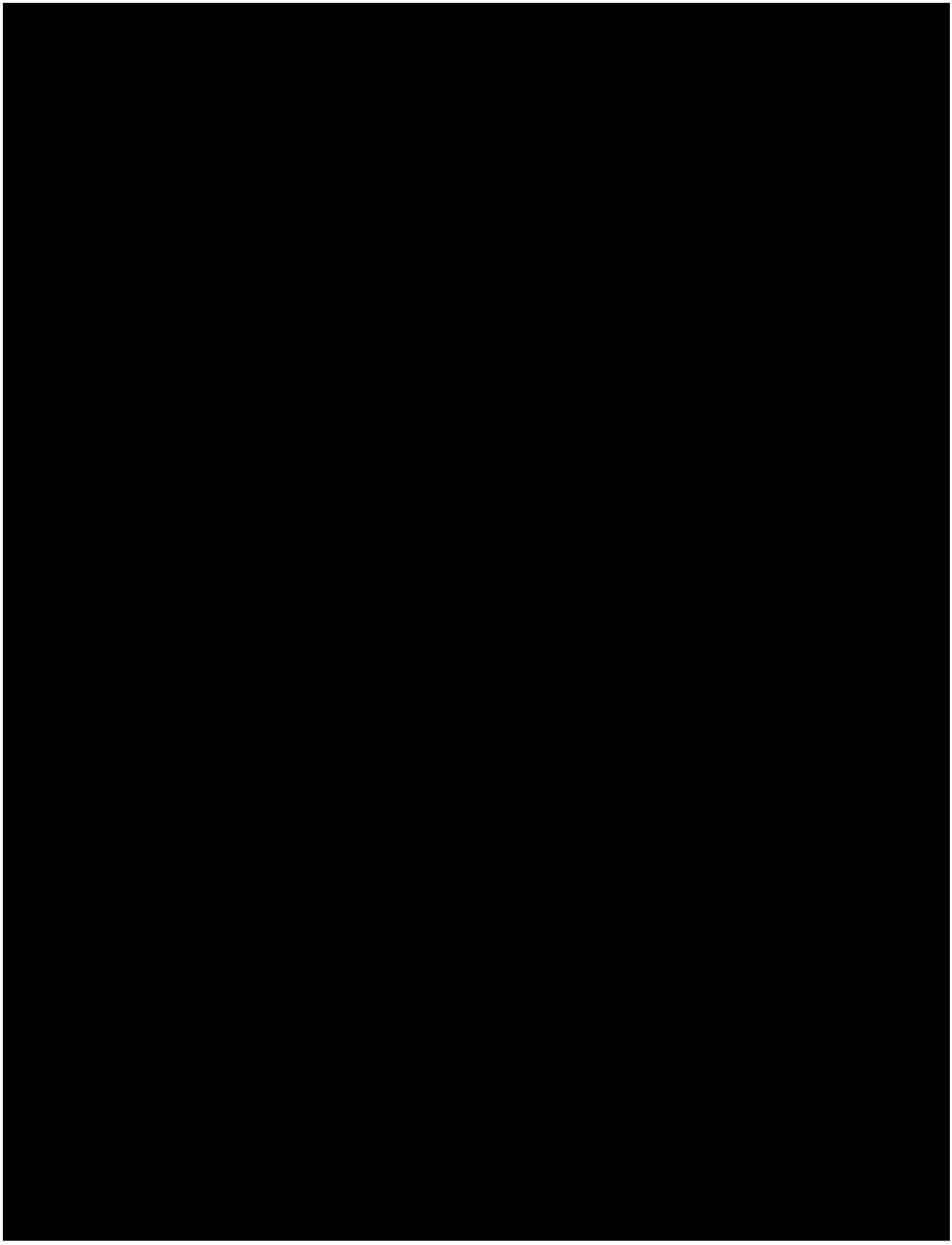
Karuna has recently completed an adequate and well-controlled, randomized, multicenter Phase 2, placebo-controlled, inpatient clinical trial of acute psychosis with schizophrenia in 182 adult subjects (KAR-004). KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) at 5 weeks compared to placebo ($p < 0.0001$), with statistical separation at each time point assessed (2, 4, and 5 weeks), and also demonstrated good overall safety and tolerability.

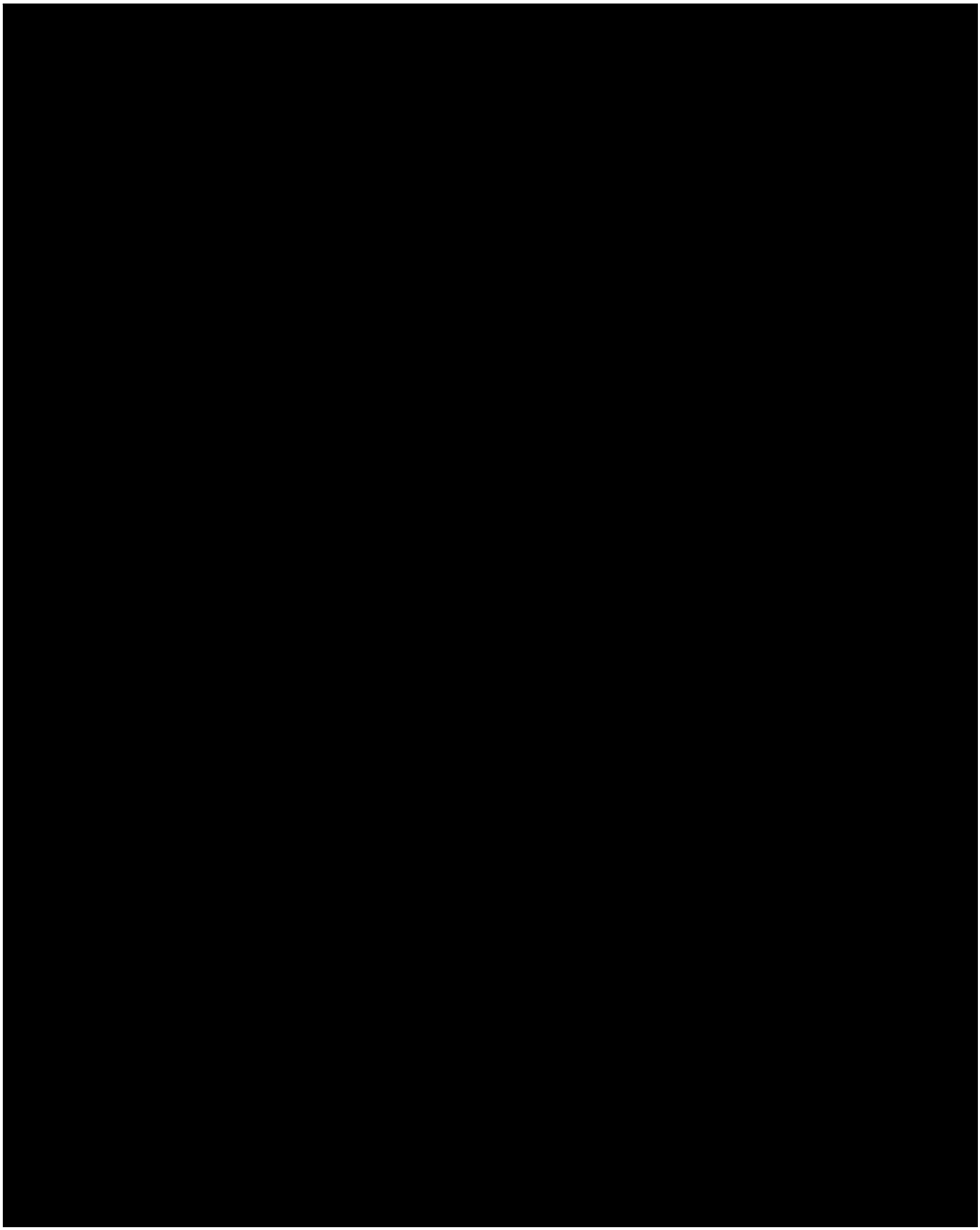
The purpose of the current study is to evaluate the long-term safety, tolerability, and efficacy of KarXT (xanomeline 125 mg/trospium chloride 30 mg) administered twice daily (BID) in adult outpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the United States and other regions of the world for the treatment of overactive bladder.

5.2.1 Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT Investigator's Brochure (IB).





[redacted]

5.2.2 Completed Clinical Studies

Refer to the IB for complete information regarding previous clinical studies conducted with xanomeline by Eli Lilly, and Studies KAR-001, KAR-002, KAR-003, and KAR-004 conducted by Karuna using xanomeline with trospium.

[redacted] In those studies, significant improvements in cognition and reduced psychotic symptoms were observed.

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008.[18] In this pilot study, the effects of xanomeline were examined in 20 subjects with schizophrenia utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric

Rating Scale 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 relative to placebo in some of the cognitive domains of verbal learning and short-term memory function. These studies demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

Study H2Q-EW-E001, conducted by Eli Lilly, had 36 male healthy volunteers in 4 groups of 9, who were administered escalating single doses of xanomeline tartrate in increments of 1, 5, 10, 25, 50, 75, 100, and 150 mg. Each group took 2 ascending doses of xanomeline tartrate and 1 dose of placebo in a single subject blind manner. There were no serious AEs (SAEs). AEs included watery diarrhea, nausea, dizziness, sweating, shivering, mild disorientation, increased blood pressure (BP), increase(s) in sitting and standing heart rate, slight increase in supine systolic BP, and postural hypotension.

The clinical experience with KarXT initiated by Karuna to date includes 3 completed Phase 1, clinical pharmacology studies in healthy volunteers (KAR-001, KAR-002, and KAR-003) and 1 completed Phase 2 study (KAR-004) in adult inpatients with DSM-5 schizophrenia.

The first study conducted by Karuna (KAR-001) was a Phase 1, double-blind, randomized, multiple-dose, pilot study comparing xanomeline administered alone to xanomeline administered in combination with trospium chloride in normal healthy volunteers. This study consisted of 2 arms, in which xanomeline was administered 3 times daily (TID), alone, at a total daily dose of 225 mg in 1 arm; the second arm received the same dose of xanomeline in combination with trospium chloride 20 mg administered BID, a total daily dose of 40 mg. Subjects were treated for 7 days. The goal was to determine if this dosing regimen would reduce the cholinergic side effects of xanomeline by coadministration of the muscarinic antagonist, trospium.

Overall, treatment with xanomeline 225 mg daily + trospium 40 mg daily administered over 7 days was considered safe and well tolerated. The results of key and supportive endpoints showed a numerical reduction (although not statistically significant) in visual analog scale (VAS) scores for cholinergic events for the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm. Specifically, consistent numerical reductions in VAS scores for the xanomeline + trospium treatment arm were observed for the supportive endpoints of maximum weekly individual VAS scores and mean daily maximum composite VAS scores.

Results of the clinician-administered scales were supportive of a reduction in vomiting, feelings of nausea, excess salivation, and sweating that interfered with daily activities in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP, or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes, which may have contributed to syncope and postural dizziness in those subjects. Two subjects

(both in the xanomeline-alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline-alone group.

The most commonly reported treatment-emergent AEs (TEAEs) in KAR-001 (≥20% of subjects in either treatment arm) were hyperhidrosis, salivary hypersecretion, nausea, dizziness postural, and diarrhea. Subject incidences of these 5 TEAEs was higher in the xanomeline-alone treatment arm (61.8%) compared to the xanomeline + trospium treatment arm (34.3%).

Overall, treatment with xanomeline 225 mg combined with trospium chloride 40 mg administered over 7 days was considered safe and well tolerated. The observed side effect profile was consistent with the known safety profile of xanomeline and trospium chloride. The incidence of TEAEs and cholinergic TEAEs was lower in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

[redacted]

All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. TEAEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium chloride, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium chloride appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT (125/30 BID) vs placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from a previous dose increase of 100/20 BID. A total of 182 subjects were enrolled and randomized (92 placebo; 90 KarXT). Of these subjects, 170 (87 [94.6%] placebo; 83 [92.2%] KarXT) received at least 1 dose of study drug and had at least 1 postbaseline PANSS assessment (modified intent-to-treat [mITT] population used for the efficacy analyses). Discontinuation rates were similar between the 2 treatment groups; 37 subjects discontinued the study early (19 [20.7%] placebo; 18 [20.0%] KarXT). The most common reason for early discontinuation was consent withdrawn (14 [15.2%] placebo; 14 [15.6%] KarXT) followed by AE (2 [2.2%] placebo; 3 [3.3%] KarXT).

TEAEs were reported in 43.3% of subjects in the placebo group and 53.9% of subjects in the KarXT group. The most commonly reported TEAEs were constipation, nausea, dry mouth,

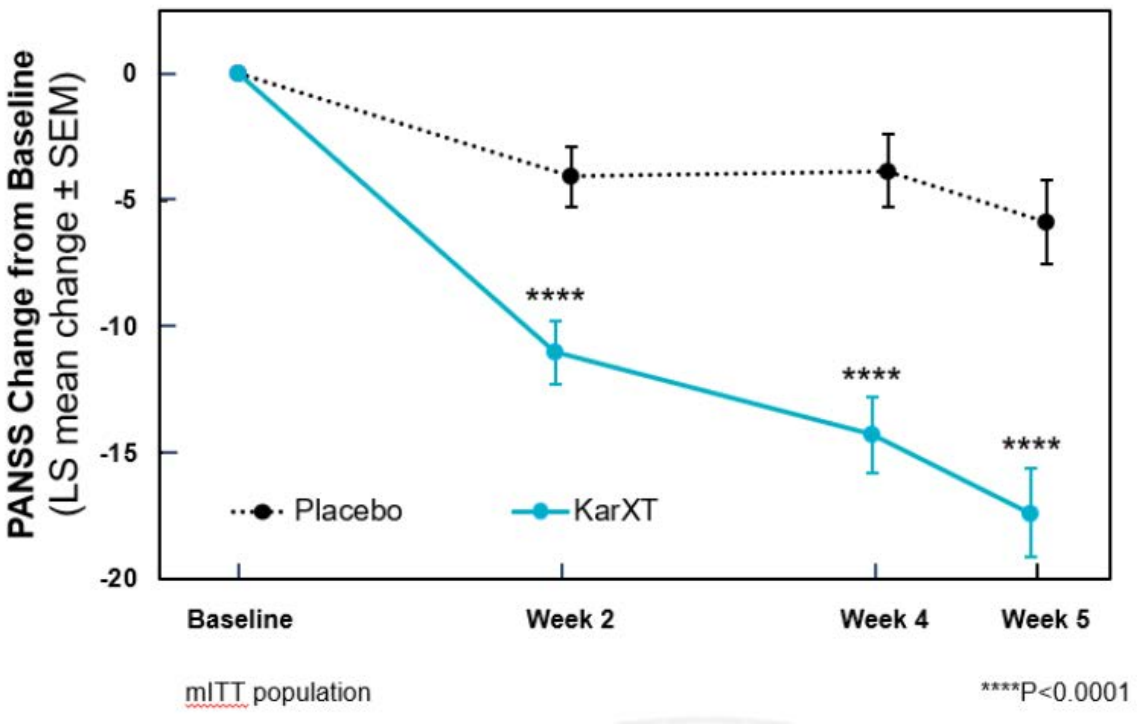
dyspepsia, and vomiting, and were more common (≥5% higher or twice that of placebo) in the KarXT group than in the placebo group.

There were 27.8% and 42.7% of subjects in the placebo and KarXT groups, respectively, who experienced at least 1 TEAE related to study drug. The most commonly reported study drug related TEAEs for the placebo and KarXT total groups were nausea, constipation, dry mouth, dyspepsia, and vomiting and were more common (≥5% higher or twice that of placebo) in the KarXT group than in the placebo group. The majority of the reported TEAEs were mild (27.8% placebo; 36.0% KarXT) or moderate (14.4% placebo; 16.9% KarXT) in severity. Two severe TEAEs were reported during the study. One subject in the placebo group had a severe TEAE of worsening schizophrenia symptoms, and 1 subject in the KarXT high dose group had a severe event of increased psychosis which was reported as an SAE possibly related to KarXT by the investigator. There were no other SAEs reported during the study and there were no deaths during the study.

The pattern and course of safety findings in KAR-004 were consistent with the known safety profile from earlier studies of both xanomeline monotherapy and xanomeline combined with trospium (KarXT). Even though the qualitative AE profile was consistent with earlier Phase 1 PK/safety studies in healthy volunteers, the relative tolerability burden was lower in this study of subjects with schizophrenia receiving KarXT than in the healthy volunteers. In addition, the safety and tolerability of KarXT was favorable and notably free of many common side effects associated with current APDs.

KarXT demonstrated statistically significant and clinically meaningful reduction in total PANSS score at all time points over 5 weeks compared to placebo (Figure 1). The primary efficacy endpoint result for the study (change from baseline in PANSS total score between the placebo group and the KarXT group at Visit 9/Week 5) showed a statistically significant decrease in PANSS total score ($p < 0.0001$). The statistically significant difference in change from baseline between the treatment groups was there at Visit 6/Week 2 ($p < 0.0001$) and continued to Visit 8/Week 4 and Visit 9/Week 5. Overall, the decrease from baseline in PANSS total score for the KarXT group was statistically significantly greater compared to the placebo group by treatment group for Visits 6, 8, and 9 ($p < 0.0001$).

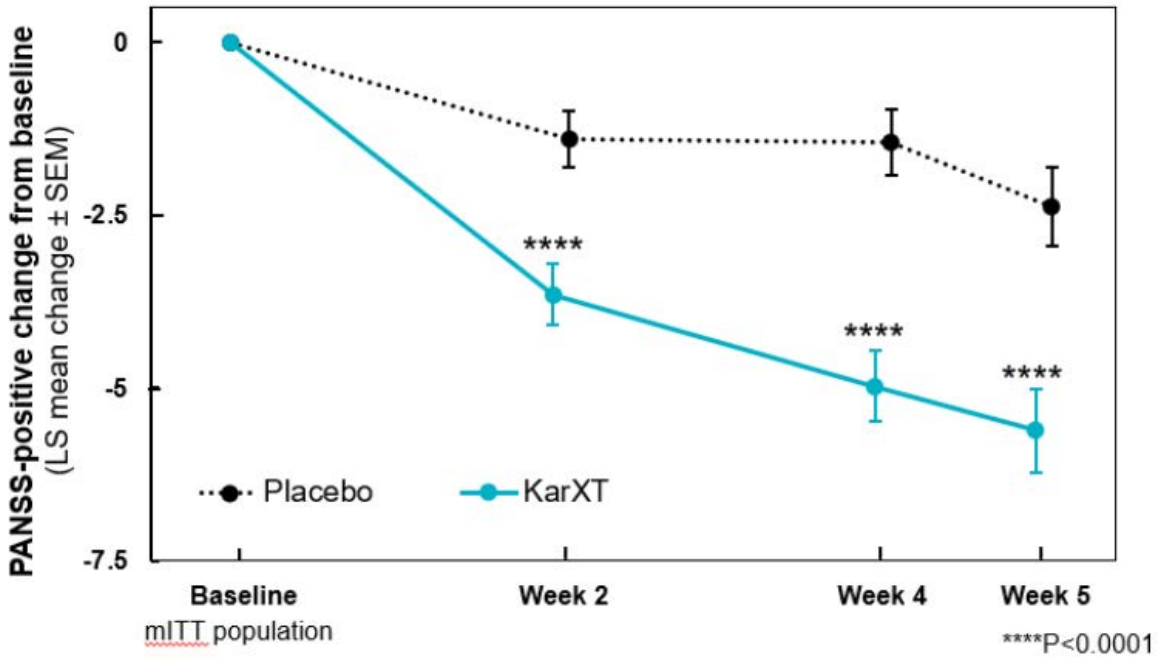
Figure 1. Change From Baseline in PANSS Total Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

A significant reduction in the secondary endpoint of PANSS-positive scores was observed ($p < 0.0001$) at Week 5 as well as the 2 earlier time points (ie, Weeks 2 and 4; see Figure 2).

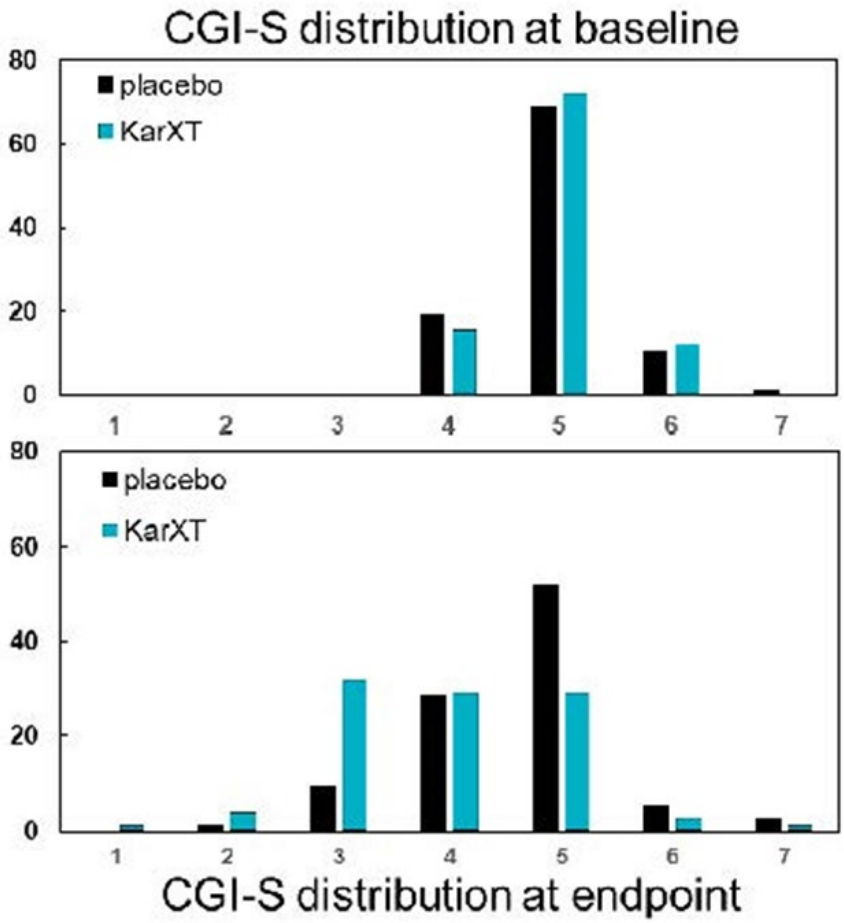
Figure 2. Change From Baseline in PANSS-Positive Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

As regards the Clinical Global Impression-Severity (CGI-S), subjects in the KarXT group overall significantly improved in ratings compared to placebo, with a p-value of <0.001 at Week 5. At Week 5, 8% of placebo subjects improved (decreased) their CGI-S ratings at least 2 levels vs 28.9% of KarXT subjects (see Figure 3).

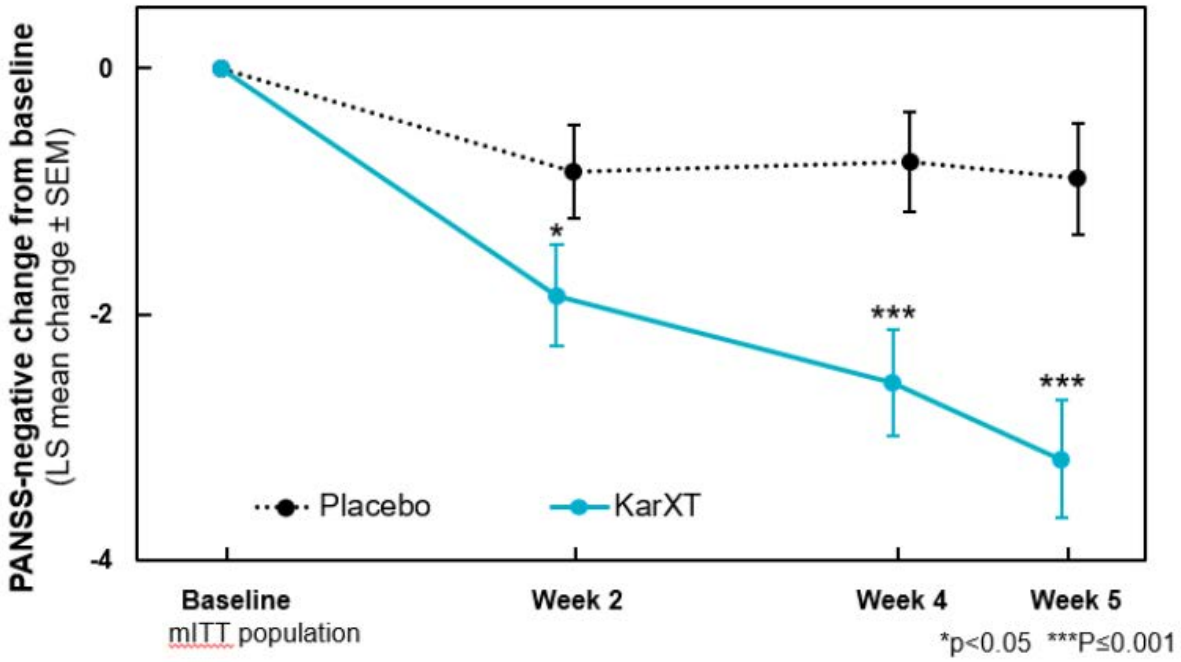
Figure 3. Change From Baseline in CGI-S (KAR-004)



Abbreviation: CGI-S = Clinical Global Impression–Severity.

A statistically significant reduction in the secondary endpoint of PANSS-negative score was observed ($p < 0.001$) at Week 5. Overall, the changes in the KarXT group were statistically significantly greater compared to the placebo group at Visits 6, 8, and 9 ($p < 0.001$). The least square mean improvement for the placebo group was 1.32 points at Week 5 (Visit 9) and the mean improvement for the KarXT group was 3.85 points leading to a mean difference of 2.53 points at Week 5 (Visit 9; see Figure 4).

Figure 4. Change From Baseline in PANSS-Negative Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

The overall safety/tolerability data were also fairly unambiguous; among the highlights:

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo:
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo:
  - The most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were severe and none led to discontinuations
  - One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE
  - No syncope or mean changes in BP were seen

  - A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after Week 2 was seen
  - One subject (on KarXT) was discontinued because of an elevated gamma-glutamyl transpeptidase (GGT)
  - There were no new safety findings associated with KarXT that have not been observed with either xanomeline alone or trospium alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available APDs for the treatment of schizophrenia
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and EPS
- Overall, the KAR-004 study results confirm and extend the antipsychotic benefit of xanomeline observed in past studies of xanomeline alone and the well-tolerated nature of KarXT. KAR-004 results support the continued development of KarXT into Phase 3 trials.

KAR-007 and KAR -009 had similar study designs and were modelled from the first pivotal study, KAR-004. Both KAR-007 and KAR-009 were Phase 3, randomized, double-blind, placebo-controlled trials to assess the efficacy, safety, and tolerability of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. Both KAR-007 and KAR-009 were identical, except KAR-007 enrolled subjects in the US only whereas KAR-009 enrolled subjects in Ukraine and the US. The primary objective of the studies was to assess the efficacy of KarXT (125/30 BID) vs placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects aged 18 to 65 years old received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks.

Both pivotal, Phase 3 studies met their primary endpoint. The primary endpoint in KAR-007 and KAR-009 was the change from baseline (CFB) in PANSS total score at week 5. In each of the studies, treatment with KarXT led to statistically significant improvements in PANSS total score at Week 5 compared with placebo ($p < 0.0001$ in each study). Cohen's d effect size was 0.61 in KAR-007 and 0.60 in KAR-009.

Secondary endpoints were analyzed based on a planned hierarchy in a fixed sequence and were typically in favor of KarXT. Treatment with KarXT led to statistically significant improvements relative to placebo in PANSS positive score at Week 5 in both studies ($p < 0.0001$ in each study). In KAR-007, the improvements in PANSS negative and PANSS Marder factor negative subscales were statistically significant in favor of KarXT versus placebo at Week 5 ($p \leq 0.0055$ and $p = 0.0022$, respectively). In KAR-009, the improvements in PANSS negative and PANSS Marder factor negative score at Week 5 was greater in KarXT than placebo but did not reach statistical significance at the 2-sided alpha level of 0.05 ($p = 0.1224$ and $p = 0.1957$, respectively). Analysis of the CFB in CGI-S in both studies demonstrated improvements in CGI-S scores at Week 5 in favor of KarXT versus placebo (statistically significant over placebo for KAR-007, and nominally significant over placebo albeit not formally tested in KAR-009). KAR-007 and KAR-009 included a Week 5 PANSS responder analysis as a secondary efficacy

endpoint (defined as an improvement from baseline of at least 30% at Week 5 in PANSS total score). The PANSS responder analysis showed that a greater proportion of subjects on KarXT achieved ≥ 30% improvement in PANSS total score at Week 5 compared to those on placebo in both KAR-007 (54.8% versus 28.3%, $p < 0.0001$) and KAR-009 (50.6% versus 25.3%, $p = 0.0056$).

KarXT was well-tolerated and safe in the Phase 3 studies, with the pattern and course of safety findings largely consistent with the known safety profile of KarXT. The most common TEAEs were associated with the procholinergic or anticholinergic effects of KarXT. The administration of KarXT was notably free of many common side effects associated with currently approved antipsychotic drugs.

KAR-008 is an ongoing Phase 3, multicenter, outpatient, open label extension (OLE) study designed to evaluate the long-term safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, which includes subjects who completed KAR-007 or KAR-009. Eligible subjects receive KarXT for up to 52 weeks. Enrollment in this study is complete (N=156).

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

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

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by subjects who were either “institutionalized” or studied in an “inpatient” hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs -5.9 placebo) at Week 5. KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all postrandomization time points (Weeks 2, 4, and, 5) with a calculated effects size (Cohen’s d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all postrandomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

[redacted] 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. The addition of trospium decreases

the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the United States for 19 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

Findings from one Phase 2 (KAR-004) and two Phase 3 (KAR-007 and KAR-009) pivotal placebo-controlled studies were similar. In all three clinical studies, administration of KarXT (100/20 and 125/30) for 5 weeks resulted in consistent, significant reductions in symptoms of schizophrenia in subjects with acute psychosis and CGI-S compared with placebo. The safety and tolerability of KarXT was consistent in 3 successive pivotal placebo-controlled studies (KAR-004, KAR-007 and KAR-009). The most common treatment-emergent adverse events (TEAEs) by preferred term in the KarXT treatment arm included nausea, dyspepsia, vomiting, constipation, headache, hypertension, diarrhea, and insomnia. KarXT was generally well tolerated and found to be safe in this patient population. KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies.

KAR-008 is an ongoing Phase 3, multicenter, outpatient, OLE study designed to evaluate the long-term safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, which includes subjects who completed KAR-007 or KAR-009.

In the current study, all subjects will receive KarXT for a period of approximately 52 weeks with the primary objective of assessing the long-term safety and tolerability profile of KarXT in an outpatient setting. All subjects will start with a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium chloride) BID for Days 1 to 2 and then the dose will be titrated to 100/20 BID for Days 3 to 7, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID starting on Visit 3 (Day 8), unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. [redacted]

Dosing will occur every 12±4.5 hours each day, during waking hours. KarXT should be dosed on an empty stomach: ie, at least 1 hour before a meal or 2 to 3 hours after a meal.

The current study is designed to demonstrate that long-term treatment with KarXT in adult subjects with schizophrenia is safe and tolerable.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objective

The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium following administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction in PANSS positive score
- To evaluate the improvement in CGI-S score
- To evaluate the reduction in PANSS negative score
- To evaluate the reduction in PANSS Marder Factor negative symptoms score
- To evaluate the percentage of subjects who exhibit a 30% reduction in PANSS total score

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint of this study is the incidence of TEAEs.

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The secondary safety endpoints of this study are:

- Incidence of serious TEAEs
- Incidence of TEAEs leading to withdrawal

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of the study are:

- Change from baseline in PANSS total score at Week 52
- Change from baseline in PANSS positive score at Week 52
- Change from baseline in PANSS negative score at Week 52
- Change from baseline in PANSS Negative Marder Factor score at Week 52
- CGI-S score at Week 52
- Percentage of PANSS responders (a 30% reduction in PANSS total score) at Week 52

6.2.3 Other Endpoints

6.2.3.1 Other Safety Endpoints

The other safety endpoints of the study are:

- Spontaneously reported adverse events of special interest (AESIs)
- Spontaneously reported anticholinergic and procholinergic symptoms
- Change from baseline in Simpson-Angus Rating Scale (SAS)
- Change from baseline in Barnes Akathisia Rating Scale (BARS)
- Change from baseline in Abnormal Involuntary Movement Scale (AIMS)
- Change from baseline in body weight, body mass index (BMI), and waist circumference
- Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen)
- Change from baseline in 12-lead ECG
- Change from baseline in physical examinations
- Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS)

6.2.3.2 Pharmacokinetic Endpoint

Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009.

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 3, multicenter, 52week, outpatient, open-label study to evaluate the long-term safety, tolerability, and efficacy of KarXT in de novo subjects, defined as not previously participated in a study of KarXT, who meet DSM-5 criteria for schizophrenia. The study consists of a screening phase of up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval), a baseline phase of up to 5 days, a 52-week open-label treatment phase, and a 7-day safety follow-up/end of study (EOS) visit following the last dose of KarXT for subjects who complete the treatment phase and those who prematurely discontinue from the study.

Screening Phase:

A suitable number of subjects will be screened to enroll approximately 600 subjects (aged 18 to 65 years) with schizophrenia who are psychiatrically stable and can be adequately managed in an outpatient setting across approximately 60 study sites in the United States. The screening phase will last up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval).

Baseline Phase:

Subjects who meet the screening criteria will participate in a baseline period consisting of two separate visits. The start of the baseline period, Baseline Visit A, must be at least 3 days (and no more than 5 days) prior to Baseline Visit B. Subjects must continue to meet eligibility criteria throughout the baseline period to remain in the study.

Treatment Phase:

In this open-label study, all subjects will receive KarXT for up to 52 weeks. All subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium chloride) BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). At Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. [redacted] Additional changes to KarXT dosing (eg, temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

Interim visits, which can be conducted in-clinic or by telemedicine per investigator discretion, will occur between required in-clinic visits (see Schedule of Assessments Table 2). Additional Unscheduled study visits should be utilized as necessary to facilitate subject retention and ensure compliance with study objectives.

All subjects will have structured diagnostic interview sessions and questionnaires administered throughout the study (see Schedule of Assessments Table 2). Analyses of change from baseline in diagnostic measures will be performed.

Safety will be assessed through spontaneously reported AEs including AESIs, procholinergic and anticholinergic symptoms, SAEs and AEs leading to discontinuation of KarXT, SAS, BARS, AIMS, body weight, BMI, waist circumference, orthostatic vital signs, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), 12-lead ECG, physical examination, IPSS and C-SSRS will be evaluated throughout the study as scheduled. Section 11 provides complete details on these safety assessments.

Efficacy will be assessed through PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits. Refer to Section 12 for more details.

Details on PK assessments are provided in Section 13 and include PK samples collected at scheduled visits.

[redacted]

A safety follow-up/EOS (Visit 30/Day 371±3 days) will be performed for all subjects after the last dose of KarXT.

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

Table 1 presents the Study Drug Dosing Scheme.

Table 1. Study Drug Dosing Scheme

Period:	Open-Label Treatment[a]							EOT/ET	EOS/UNS
Day:	Day 1	Day 3 +1 day	Day 8 ±1 day	Day 14 ±2 days	Day 28 ±3 days	Day 56 ±3 days	Days 70 to 350 ±3 days	Day 364 ±3 days	Day 371 ±3 days
Visit[a]:	Visit 1	Visit 2[f]	Visit 3[b]	Visit 4	Visit 5	Visit 7	Visits 8[c] to 28	Visit 29	Visit 30
Xanomeline/ trospium (KarXT)*:	50/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[d]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	N/A
Comment(s):	2-day lead-in dose	Upward titration of dose	Upward titration of dose						7 (±3) days after completion of the EOT or ET visit

Abbreviations: BID = twice daily; EOS = end of study; ET = early termination; EOT = end of treatment; N/A = not applicable; PI = principal investigator; UNS = unscheduled.

* All the KarXT doses are in mg xanomeline/mg trospium chloride.

a. At Visit 1 (Day 1) subjects will initiate dosing with KarXT BID independently at home. Visits 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 2, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits and can be conducted via telemedicine or on-site.

b. Subject to receive at least 8 doses of KarXT 100/20 before escalating to KarXT 125/30 dose.

c. After Visit 9/Day 84, required in-clinic visits will be conducted approximately every 4 weeks. Interim visits will be conducted between required in-clinic visits and can be conducted by telemedicine or in-clinic per investigator discretion (see Schedule of Assessments Table 2 for further details).

d. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID.

e. [redacted]. Additional changes to KarXT dosing (eg, temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

f. Visit 2/Day 3 is an interim visit and can be conducted via telemedicine or in-clinic per investigator discretion.

7.2 Discussion of Study Design

The KarXT clinical development program includes this open-label study to evaluate the long-term safety, tolerability, and efficacy data for KarXT in de novo subjects, defined as those who did not have prior exposure to KarXT, who meet the DSM-5 criteria for schizophrenia.

The dosing plan for this study has been established and follows the earlier studies. All eligible subjects will receive the same lead-in doses of KarXT (KarXT 50/20 BID). Dosing will be titrated to 100/20 BID on Visit 2 (Day 3) and further titrated to 125/30 BID on Visit 3 (Day 8), unless the subject continues to experience AE(s) from the previous dose increase of KarXT.

During the study, all subjects who are increased to the highest dose of KarXT, depending on tolerability, will have the option to return to the next lower dose of KarXT (100/20 BID). [redacted]

Interim visits, which can be conducted in-clinic or by telemedicine per investigator discretion, will occur between required in-clinic visits (see Schedule of Assessments Table 2). Additional Unscheduled study visits should be utilized as necessary to facilitate subject retention and ensure compliance with study objectives.

A 52-week treatment phase is considered to be sufficient to demonstrate the long-term safety and tolerability of KarXT. A sample size of approximately 600 subjects is also determined to be an appropriate number of evaluable subjects to assess the long-term safety of KarXT administration. Section 5.2 details the nonclinical and clinical background information available on KarXT, including dose rationale.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed the study treatment, including the EOS visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

7.4 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 and tolerability data from the clinical study. [redacted]. This committee will be responsible, on a periodic basis, for confirming the safety and tolerability of KarXT throughout the study, with particular focus on assessing for any new or long-term toxicities that might be involved with KarXT.

The reviews will allow a comparison of event rates and detection of safety signals, and 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.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is aged 18 to 65 years, inclusive, at screening.
2. Subject is capable of providing informed consent.
    a. A signed informed consent form (ICF) must be provided before any study assessments are performed.
    b. Subject must be fluent (oral and written) in the language of the ICF to consent
3. 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 (MINI) for Schizophrenia and Psychotic Disorder Studies version 7.0.2.
4. The subject has not required psychiatric hospitalization, acute crisis intervention, or other increase in level of care due to symptom exacerbation within 8 weeks of screening and is psychiatrically stable in the opinion of the investigator.
5. PANSS total score of ≤ 80 at screening and Baseline Visit B (Day 0).
6. CGI-S score of ≤ 4 at screening and Baseline Visit B (Day 0).
7. At the time of screening, or at any time within the 30 days prior to screening, the subject must have received an oral antipsychotic medication daily at a dose and frequency consistent with the drug label.
8. In the opinion of the investigator, it is clinically appropriate for the subject to discontinue current antipsychotic therapy and initiate experimental treatment with KarXT.
9. The subject is willing and able, in the opinion of the investigator, to discontinue all antipsychotic medications prior to baseline visit.
    a. Subjects should discontinue any antipsychotic medications prior Baseline Visit A (Day -3). If clinically necessary, and in consultation with the medical monitor, antipsychotic medications may be continued through the baseline period up until the time of Baseline Visit B (Day 0).
    b. Antipsychotic down-taper, if clinically appropriate in the opinion of the investigator, may occur during the screening phase.
10. Subject has an identified reliable informant willing and able to address some questions related to certain study visits, if needed. An informant may not be necessary if the subject has been the patient of the investigator for ≥ 1 year.
11. [redacted]
12. [redacted]

13. BMI must be ≥ 18 and ≤ 40 kg/m^2.
14. Subject resides in a stable living situation and is anticipated to remain in a stable living situation for the duration of study enrollment, in the opinion of the investigator.
15. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1.

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8.2 Exclusion Criteria

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

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening). Exclusionary disorders include but are not limited to major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and posttraumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment.
2. The subject has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline.
    a. A 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.
    b. Subjects with a positive UDS for cannabis are permitted to enroll in the study provided that the subject's pattern of use is not indicative of a substance use disorder.
3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, GI, 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.
4. Subjects with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test (LFT) results.
5. History or high risk of urinary retention, gastric retention, or narrow--angle glaucoma.
6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months
7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and 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.

8. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.
9. [redacted].
10. Subject has a history of treatment resistance to schizophrenia medications defined as:
    a. Failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) within the past 12 months, OR,
    b. Having received clozapine within the past 3 years
11. Pregnant, lactating, or less than 3 months postpartum.
12. 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 opinion 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.
13. Subjects who have tested positive for coronavirus disease 2019 (COVID-19) within 2 weeks of screening.
14. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that preclude study participation.
15. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) within the 6 months before screening.
16. Subjects with prior exposure to KarXT.
17. Risk of violent or destructive behavior.
18. Current involuntary hospitalization or incarceration.
19. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 30 days prior to screening.

8.3 Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements and therefore do not enroll (screen failures) may be allowed to rescreen up to 1 time in consultation with the medical monitor. Participants who screen failed due to elevated LFTs are not eligible for rescreening.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early (after receiving at least 1 dose of the study drug) from the study will be asked to return to the study site within 7 (±3) days of the EOT or ET visit to complete EOS assessments as indicated in the Schedule of Assessments (Table 2).

In the event that a subject discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of investigator's clinical judgement; the reason for subject withdrawal will be noted on the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders them ineligible for further treatment according to the inclusion/exclusion criteria (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a subject is off KarXT for >7 consecutive days])
- violation of entry criteria (ie, enrolled subjects who are later discovered not to meet eligibility criteria)
- development of suicidal or assaultive behavior
- alcohol abuse or illegal drug use
- pregnancy, as indicated in Section 11.7.8.
- Sponsor's decision to discontinue study

Subjects who withdraw 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 are lost to follow-up. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center. These efforts must be documented in the subject's file. Subjects with AEs ongoing at EOS 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 KarXT become known, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.4.1 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, WOCBP in this study must be willing to use a highly effective method of birth control (see APPENDIX 1 for a list of acceptable highly effective methods of contraception) during the study and for 30 days after the last dose of KarXT. WOCBP will have a urine pregnancy test at Screening, Baseline Visit B (Day 0) and thereafter, as designated at other scheduled visits (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result.

Pregnant women are excluded from this study because the effects of KarXT 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 KarXT, women who become pregnant must discontinue KarXT immediately.

The effects of KarXT on sperm are unknown. Male subjects whose sexual partners are WOCBP must agree to use a highly effective method of birth control (see APPENDIX 1 for a list of acceptable highly effective methods of contraception) and must not impregnate a sexual partner during treatment with or for 30 days after the last dose of KarXT. They must also agree to refrain from sperm donation for 30 days after the last dose of KarXT.

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of KarXT. The investigator must notify the Sponsor or their designee of any female

subject or female partner of a male subject that becomes pregnant while participating in the study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Only those procedures that would not expose the pregnant female patient to undue risk will be performed. See Section 11.7.8 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a Pregnancy Reporting Form will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAEs (Section 11.7.4).

8.5 Completion of the Study or 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 are lost to follow-up to obtain EOS information. Details regarding follow-up efforts are to be documented in the subject's medical records/source documentation.

8.6 Study Termination

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.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, 1 of which is loaded with xanomeline tartrate and the other is loaded with trospium chloride. In addition to the active ingredients, the xanomeline beads contain microcrystalline cellulose (MCC), ascorbic acid, and talc. In addition to MCC, trospium beads contain lactose monohydrate and talc. The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsules. For the 2-day lead-in period (Days 1 and 2), subjects will receive capsule strength KarXT 50/20 mg BID for a total daily dose of 100/40 mg, followed by 100/20 mg BID for a total daily dose of 200/40 mg for the remainder of Week 1 (Days 3 to 7). At the beginning of Week 2 (Day 8), dosing may be increased to 125/30 mg BID for a total daily dose of 250/60 mg, depending on tolerability. Investigators have the option to return a subject to KarXT 100/20 mg BID for the remainder of the treatment period. [redacted]

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor (see also Section 9.4).

KarXT 50/20 mg is composed of 33.4% xanomeline tartrate, 8.7% trospium chloride, excipients 39.8% MCC, 17.3% lactose monohydrate, 0.3% ascorbic acid, and 0.5% talc in a size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsule.

KarXT 100/20 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid, and 0.5% talc in a size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsule.

KarXT 125/30 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid, and 0.5% talc in a size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements as specified on the Investigational Product label.

9.1.2 Packaging and Labeling

The study packaging and labeling will be performed by Catalent Pharma Solutions, located in Philadelphia, Pennsylvania. All packaging and labeling operations will be performed according

to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Blister packaged investigational product is 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 (or United States) law to investigational use."

Further details on the investigational product label will be provided in the Pharmacy Manual.

Complete details on study medication dispensing can be found in the Pharmacy Manual.

9.1.3 KarXT Storage

KarXT must be stored at room temperature 15 °C to 25 °C.

9.1.4 KarXT Retention

KarXT must be retained until completion or termination of the study. All unused and used KarXT must be destroyed at the site or returned to a drug-destruction facility for destruction, as specified by Sponsor through written authorization. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal and/or return to drug destruction facility are documented and maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

The first dose of KarXT will be administered in the morning of Day 1 and the last dose will be administered in the morning of end of treatment (EOT) Visit (Day 364). KarXT should be administered daily BID on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal). Administration of KarXT will be supervised by study site personnel (during in-clinic visits) and [redacted] monitor administration of KarXT in between clinic visits to ensure compliance [redacted].

9.2.1 Day 0/Baseline Visit B

- Sites will provide the subjects with a titration blister card wallet containing sufficient KarXT doses for the first week of study participation. Subjects will be instructed to begin self-administration of KarXT BID in the morning of Day 1.
- For all KarXT doses, the first dose is to be self-administered in the morning and the evening dose will be self-administered at 12 (±4.5) hours after the morning dose.
- Remind the subject to return the titration blister card wallet at their next visit.

9.2.2 Visit 1/Day 1 Dosing

- Initiate BID dosing with KarXT 50/20.
- All subjects should receive 4 doses of KarXT 50/20 before dose escalation to KarXT 100/20 BID. Subjects should contact the investigator in the event they did not take all 4 doses of KarXT 50/20 during the first 2 days of dosing.

9.2.3 Visit 2/Day 3 Dosing

- Initiate BID dosing with KarXT 100/20.
- All the subjects should receive at least 8 doses of KarXT 100/20 before dose escalation to KarXT 125/30 BID. Subjects should contact the investigator in the event they do not take at least 8 doses of KarXT 100/20 during the first week of dosing.
- Remind the subject to return the titration blister card wallet at their next visit.

9.2.4 Visit 3/Day 8 Dosing

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order, site staff will provide subjects with a single 125/30 maintenance blister card wallet.
- The first dose of 125/30 is to be self-administered in the evening at home by the subject. If the subject has not yet received their morning dose of KarXT at the time of the study visit, the subject should receive their first dose of KarXT 125/30 at the time of the study visit.
- A single PK sample should be drawn at Visit 3/Day 8, and the dose of KarXT and time of most recent dosing should be recorded.
- Remind the subject to return the maintenance blister card wallet at their next visit.

In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, dispense a single 100/20 maintenance blister card wallet.

9.2.5 Visit 4/Day 14 Dosing

- If dose of KarXT 125/30 BID was confirmed by investigator order, site staff will provide subjects with two 125/30 maintenance blister card wallets, which will provide sufficient doses until the subject's next study visit.
- A single PK sample should be drawn at Visit 4/Day 14, and the dose of KarXT and time of most recent dosing should be recorded.
- Remind the subject to return the maintenance blister card wallets at their next visit.

In the event that the subject was not escalated to KarXT 125/30, in accordance with investigator order, sites should provide subjects with two 100/20 maintenance blister card wallets.

9.2.6 Visits 5 to 8 (Days 28 to 70) Dosing

- At each study visit, site staff will provide subjects with two 125/30 or 100/20 maintenance blister card wallets based on the investigator-confirmed dose in order to provide sufficient quantities of KarXT until the subject's next clinic visit.
- Remind the subject to return the maintenance blister card wallets at their next visit.

9.2.7 Visits 9 to 29 (Days 84 to 364) Dosing

- At each scheduled in-clinic study visit, site staff will provide subjects with four 125/30 or 100/20 maintenance blister card wallets based on the investigator-confirmed dose in order to provide sufficient quantities of KarXT until the subject's next clinic visit.
- For Days 84, 168, and 280, a single PK sample will be collected and the dose of KarXT and time of most recent dosing should be recorded.
- Remind the subject to return the maintenance blister card wallets at their next in-clinic visit.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

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 ICF must be entered into the IWRS regardless of eligibility in order to obtain a Subject Number. This 9-digit number will consist of a 3-digit study code and a 3-digit site identification, followed by a 3-digit number assigned sequentially within each site, starting at [redacted].

9.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

9.4 Dosage Modification

Subjects will self-administer KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.1.1).

Additional changes to KarXT dosing (eg, temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

[redacted]

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study subjects.

Administration of KarXT will be supervised by study site personnel (during in-clinic visits) and [redacted] monitor administration of KarXT in between clinic visits to ensure compliance [redacted]. KarXT will be dispensed in prepackaged blister card wallets. The titration wallet will contain 10 days of dosing with 2 days of 50/20 KarXT BID and 8 days of 100/20 KarXT BID. After titration, subjects will receive 1 or more wallets each containing 8 days of BID doses of 125/30 or 100/20 KarXT based on the investigator-confirmed dose. Subjects will be advised to return the blister card wallets to the site staff at each in-clinic visit for drug accountability.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Investigational product will not be destroyed or returned to the Sponsor or designee until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Subjects will be asked to confirm all prior medications they were taking up to 6 months before the study, up to the time of consent. All prior medications will be recorded on the eCRF.

Restricted prior therapies are provided below.

All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

During the study (i.e., from the time consent until study completion [EOS]), subjects should refrain from the use of any new concomitant medications without the approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

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

[redacted]

Note: Please direct questions relating to prohibited medications to the medical monitor.

9.6.2 Concomitant Medications for Anxiety and/or Sleep Aid

Subjects are allowed to take [redacted]

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Section 11, Section12, Section 13, and Section 14 for additional details regarding safety, efficacy, PK, [redacted] assessments, respectively.

COVID-19 testing will be completed in accordance with clinical site standard operating procedures. If a subject tests positive for COVID-19 during the study, they may be quarantined as needed and any scheduled visits should be rescheduled or conducted by telemedicine at the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as outlined in Section 11.7.4.

Table 2. Schedule of Assessments

DAY	Day -17 to Day -4	Day -3 to Day -1	Day 0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK				1			2	4	6	8	10	12	14	16	18	20	22	24
VISIT	**Screening[1]**	**Baseline Visit A[2]**	**Baseline Visit B**	**1**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	C	C	C		I	C	C	C	C	C	C	C	I	C	I	C	I	C
PROCEDURE																		
Written informed consent	X																	
Collect demographic information (date of birth, age, sex, race, ethnicity)	X																	
Subject eligibility verification process	X																	
Medical, psychiatric, and medication history	X																	
Urine pregnancy test (WOCBP only)[c]	X		X			X	X	X	X	X	X	X		X		X		X
Urine drugs of abuse and alcohol testing[d]	X	X				X	X	X	X	X	X	X		X		X		X
Review of inclusion/exclusion criteria	X	X																
Height, body weight, BMI, waist circumference[e]	X	X					X	X	X	X	X	X		X		X		X
Complete physical examination[f]	X																	
Targeted physical examination[g]		X	X			X	X	X	X	X	X	X		X		X		X

DAY	Day -17 to Day -4	Day -3 to Day -1	Day 0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK				1			2	4	6	8	10	12	14	16	18	20	22	24
VISIT	**Screening[1]**	**Baseline Visit A[2]**	**Baseline Visit B**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	C	C	C		I	C	C	C	C	C	C	C	I	C	I	C	I	C
PROCEDURE																		
Spontaneous AEs[h]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[i]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[j]	X	X	X			X	X	X	X	X	X	X		X		X		X
Resting ECG (12-lead)[k]	X						X							X				
Blood samples for clinical laboratory tests[l]	X						X	X			X			X				X
Blood sample for viral serology[m]	X																	
[redacted]																		
Functional constipation inquiry[n]		X[b]				X	X	X	X	X	X	X		X		X		X
Determination of dose titration						X												
PK blood draw[o]						X	X					X						X
MINI	X																	
PANSS[p]	X		X			X		X		X		X		X		X		X
C-SSRS[q]	X	X	X			X	X	X	X	X	X	X		X		X		X
[redacted]																		

DAY	Day -17 to Day -4	Day -3 to Day -1	Day 0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK				**1**			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Screening[1]**	**Baseline Visit A[2]**	**Baseline Visit B**	**1**	**2[a]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	C	C	C		I	C	C	C	C	C	C	C	I	C	I	C	I	C
PROCEDURE																		
CGI-S scale	X		X			X	X	X		X		X		X		X		X
[redacted]																		
SAS		X[b]				X		X						X				
BARS		X[b]				X		X						X				
AIMS		X[b]				X		X						X				
[redacted]																		
KarXT dispensed[s]			X			X	X	X	X	X	X	X		X		X		X
Subject self-administration of KarXT BID using [redacted]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
IPSS[w]														X		X		X

Table 2 Schedule of Assessments (Continued from Visits 16 to 30)

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ET)**	**30 (EOS/UNS)[3]**
TYPE OF VISIT	I	C	I	C	I	C	I	C	I	C	I	C	I	C	C
PROCEDURE															
Urine pregnancy test (WOCBP only)[e]		X		X		X		X		X		X		X	X
Urine drugs of abuse and alcohol testing[d]		X		X		X		X		X		X		X	X
Body weight, BMI, waist circumference[e]		X		X		X		X		X		X		X	X
Complete physical examination[f]															X
Targeted physical examination[g]		X		X		X		X		X		X		X	
Spontaneous AEs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[3]
Review of concomitant medications[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[3]
Vital signs: BP and HR[j]		X		X		X		X		X		X		X	X
12-lead resting ECG[k]		X						X						X	
Blood samples for clinical laboratory tests[l]				X				X				X		X	
[redacted]															
Functional constipation inquiry[n]		X		X		X		X		X		X		X	X
PK blood draw[o]								X							
PANSS[p]				X				X				X		X	X
C-SSRS[q]		X		X		X		X		X		X		X	X[3]
CGI-S scale		X		X		X		X		X		X		X	X
[redacted]															

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ET)**	**30 (EOS/UNS)[3]**
TYPE OF VISIT	I	C	I	C	I	C	I	C	I	C	I	C	I	C	C
PROCEDURE															
[redacted]															
SAS		X						X						X	X
BARS		X						X						X	X
AIMS		X						X						X	X
KarXT dispensed[s]		X		X		X		X		X		X			
Subject self-administration of KarXT BID [redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]															
IPSS[w]		X		X		X		X		X		X		X	X

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BID = twice daily; BP = blood pressure; C= Clinic visit; [redacted]; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; [redacted]; ECG = electrocardiogram; [redacted] EOS = end of study; EOT = end of treatment; ET = early termination; HR = heart rate; I = Interim visit; IPSS = International Prostate Symptom Score, MINI = Mini International Neuropsychiatric Interview; [redacted]; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; [redacted]; [redacted] QTcF = QT interval corrected by Fridericia; SAS = Simpson-Angus Rating Scale; [redacted]; UNS = unscheduled visit; WOCBP = women of childbearing potential.

1. Up to a 7-day screening extension can be granted with medical monitor approval
2. Baseline Visit A must be completed no less than 3 days and no more than 5 days before Baseline Visit B.
3. Unscheduled (UNS) visits may be conducted as needed to facilitate retention and ensure compliance with study objectives. UNS visits must include at a minimum a review of concomitant medications, assessment of any new or ongoing AEs, and a C-SSRS. Other assessments may be performed as needed.

a. At Visit 2/Day 3, and beginning again on Visit 10/Day 98 and every 4 weeks thereafter, interim visits will be completed between the required in-clinic visits. Interim visits will be conducted by site staff and can be completed using telemedicine (audio only, or audio + video) or in-clinic, per investigator discretion.
b. This procedure may be completed at either Baseline Visit A or Baseline Visit B.
c. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of positive urine pregnancy test result, a serum sample should be sent to central laboratory for confirmation of the result.
d. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or urine alcohol level) will be performed locally at scheduled visits. A sample should be sent to the central lab at screening. Thereafter, if positive, with the exception of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
e. Height is recorded at screening only.
f. 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.
g. A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations, which will be performed as clinically indicated at any study visit.
h. AEs as reported by subjects or observed by clinical staff and occurs after dosing. For interim visits, spontaneous AEs will be collected by telemedicine.
i. For interim visits, concomitant medications will be collected by telemedicine.
j. Vital signs measurements should be taken at scheduled in-clinic visits, while the subject is supine and standing after 2 minutes. Includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. During clinic visits, orthostatic vital signs should occur 2 (±1) hours after morning dosing whenever possible.
k. ECG should be obtained within 1 to 2 hours after the morning dose and before blood withdrawal for any safety laboratory tests whenever possible. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained.
l. Refer to Section 11.6 for individual laboratory tests. For urinalysis, a urine dipstick will be performed locally. In the event of abnormalities, the sample will be sent to the central laboratory for full microscopic urinalysis.
m. All subjects must have the following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, HIV-1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.
n. Functional constipation inquiry: At specified visit, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see APPENDIX 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
o. PK blood samples will be collected on Days 8, 14, 84, 168, and 280. On Day 8 the PK sample should be drawn within 1 to 2 hours post-dose whenever possible. Note: In cases of dose reduction, re-escalation, or re-titration, an additional PK sample may be collected per investigator discretion in consultation with the medical monitor.

p. It is recommended that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed, except for the screening visit (MINI conducted first). The PANSS assessment includes the Marder Factor.

q. C-SSRS past 12-months version will be utilized at screening; the "since last visit" version will be conducted at all other scheduled study visits. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.

[redacted].

s. See Pharmacy Manual for details on KarXT dispensing and compliance evaluation.

[redacted]

w. IPSS will be administered monthly only in male subjects ≥45 years of age at the time of signing the informed consent. IPSS assessment administration will start from Visit 11 (at the time of this amendment, study enrollment has been completed, and all enrolled subjects have completed Visit 9).

10.1 Informed Consent

Informed consent forms must be approved for use by the reviewing IRB. Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject and/or caregiver.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 2). Section 11.6 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where KarXT is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 2).

Safety assessments are described in Section 11 and include spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; 12-lead ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); physical examination; and C-SSRS.

Efficacy assessments are described in Section 12 and include PANSS and CGI-S scores.

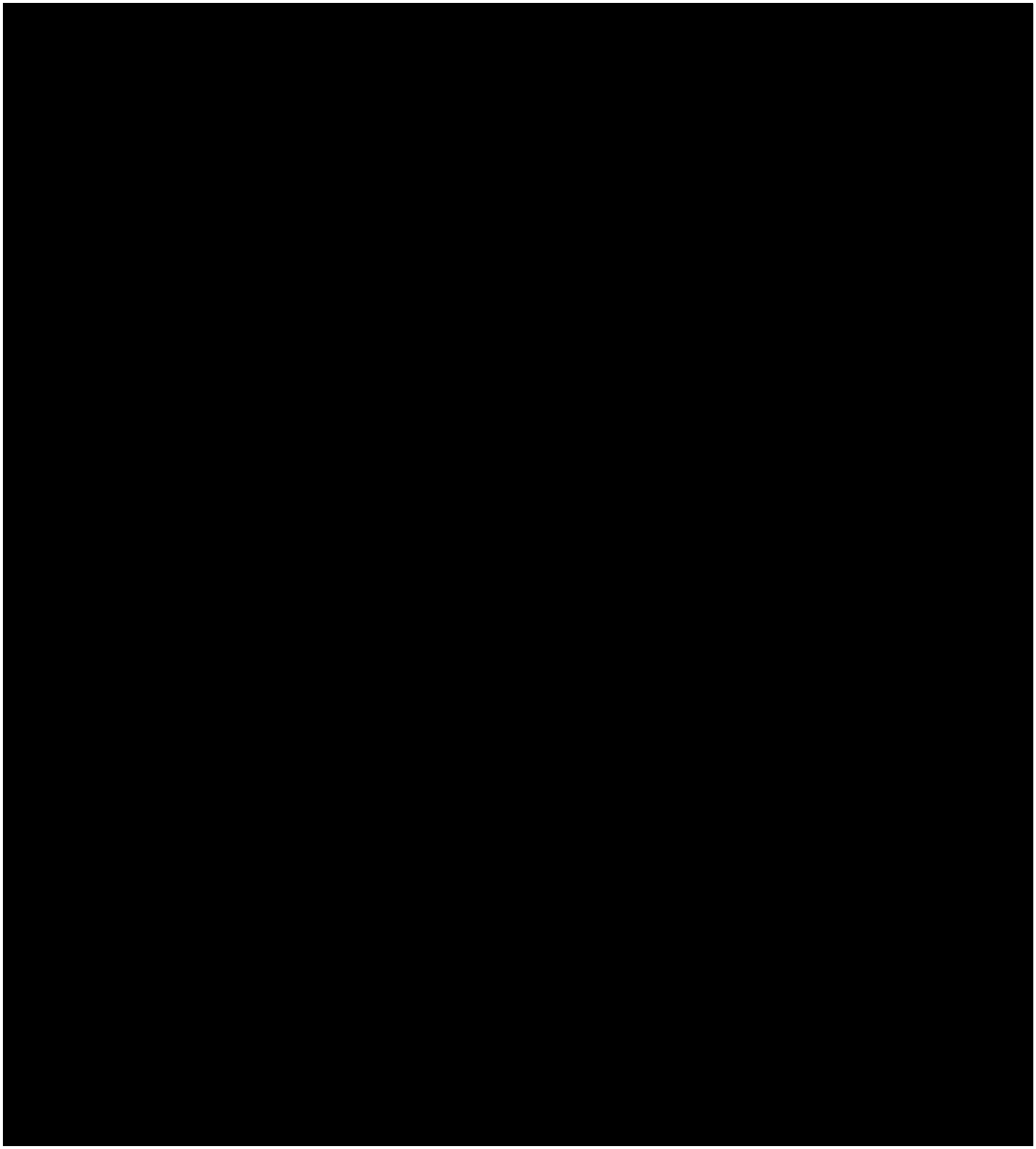
PK assessments are described in Section 13.

[redacted]

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit should include at a minimum the C-SSRS and an assessment of concomitant medications and any new or ongoing adverse events. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the medical monitor.

Study discontinuation procedures are described in Section 8.4 and Section 8.6.

[redacted]



11 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms, SAEs and AEs leading to discontinuation of KarXT, SAS, BARS, AIMS, body weight, BMI, waist circumference, orthostatic vital signs, 12-lead ECG, IPSS, clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, and drug screen], physical examination, and C-SSRS) will be performed at protocol-specified- visits, as specified in the Schedule of Assessments (Table 2).

11.1 Demographics, Medical History, and Psychiatric History

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

Medical, psychiatric, and medication history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all baseline symptoms, ongoing illnesses, other chronic conditions, and surgical history at screening. Medical history will also include history of drug, substance, or alcohol abuse/dependence within 1 year before Screening.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.7. All changes not present at the time of consent or described in the past medical history and identified as clinically significant must be recorded as AEs.

11.2 Vital Signs

Orthostatic vital signs (systolic and diastolic BP and heart rate measurements) will be evaluated at the in-clinic visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured supine and standing after 2 minutes. BP measurements are to be taken in the same arm for the duration of the study. During treatment orthostatic vital signs should occur 2 (±1) hours after morning dosing, whenever possible.

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

11.3 Complete/Targeted Physical Examination

A complete physical examination (body temperature, 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) will be performed at visits as specified in Table 2. Physical examinations will be performed by a physician or qualified designee.

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

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

Height (screening only), weight, and waist circumference measurements will be obtained at visits as specified in Table 2. BMI should be calculated at these visits. All findings should be recorded in the eCRF.

11.5 Electrocardiograms

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

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

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

11.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2).

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urinalysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol HDL LDL Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
HbA1c (glycated Hb test)		
[redacted]		

Coagulation	**Serology[a]**
PT Activated PTT Fibrinogen	HBV HCV HIV

Pregnancy test: A urine pregnancy test for WOCBP should be performed per the Schedule of Assessments (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to central laboratory to confirm the result.
Full and microscopic urinalysis: Chemical exam: SG, pH, bilirubin, urobilinogen, protein, glucose, ketone, hemoglobin, leukocyte esterase, nitrite. Microscopic exam: RBCs, WBCs, epithelial cells, bacteria, yeasts, parasites, casts, crystals

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; Hb = hemoglobin; HBV = Hepatitis B; Hct = hematocrit; HCV = Hepatitis C; HDL = high density lipoprotein; HIV = Human Immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SG = specific gravity; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] The following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, HIV 1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.

Venous blood of approximately 12 to 20 mL will be withdrawn for the tests listed above at scheduled time points as per Table 2.

A minimum volume of 10 mL of urine will be obtained to perform urinalysis (if abnormalities observed on dipstick) and urine drug screen at scheduled time points as per Table 2.

Blood and urine samples (microscopic analysis, when indicated) will be analyzed at a central laboratory facility. Urine samples will first be analyzed at investigator site by dipstick. If the results of the dipstick indicates abnormalities to be further investigated, the sample will be sent to the central laboratory and a microscopic analysis will be performed. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed in the medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for the drug-induced liver toxicity (detailed in Section 11.7.5), during the study.

Other Laboratory Assessments:

- A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick at the scheduled visits. A sample should be sent to the central lab at screening. Thereafter, if positive, with the exception of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
- Alcohol testing will be performed using a breathalyzer or urine alcohol test.

[redacted]

11.7 Adverse Events

11.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at the time of consent, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at the time of consent will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted in the AE eCRF during the rest of the study. Clinically significant vital signs and laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period and these will be recorded in the appropriate page of the eCRF. AEs 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.

Each AE is to be documented in the eCRF with reference to date of onset, duration, frequency, severity, relationship to KarXT, action taken with KarXT, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented in the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time of consent until EOS. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to KarXT are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to KarXT

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to KarXT if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE = adverse event.

11.7.2 Adverse Events of Special Interest

LFT elevations as outlined in 11.7.5 inclusive of drug-induced liver injury (DILI) and symptomatic orthostasis including syncope (a transient loss of consciousness or fainting) is to be captured as an AESI and reported as such. Non symptomatic orthostasis will not be reported as an AESI. Any such AESI due to any cause, whether or not related to KarXT, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using email.

11.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (however, hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an SAE; the details of such hospitalizations must be recorded in the medical history or physical examination page of the eCRF),
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.7.4 Serious Adverse Event Reporting

An SAE occurring from the time of informed consent until EOS must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to KarXT, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using email.

Catalyst Clinical Research Pharmacovigilance email address: **Safety@catalystcr.com**

The event must be recorded in the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of

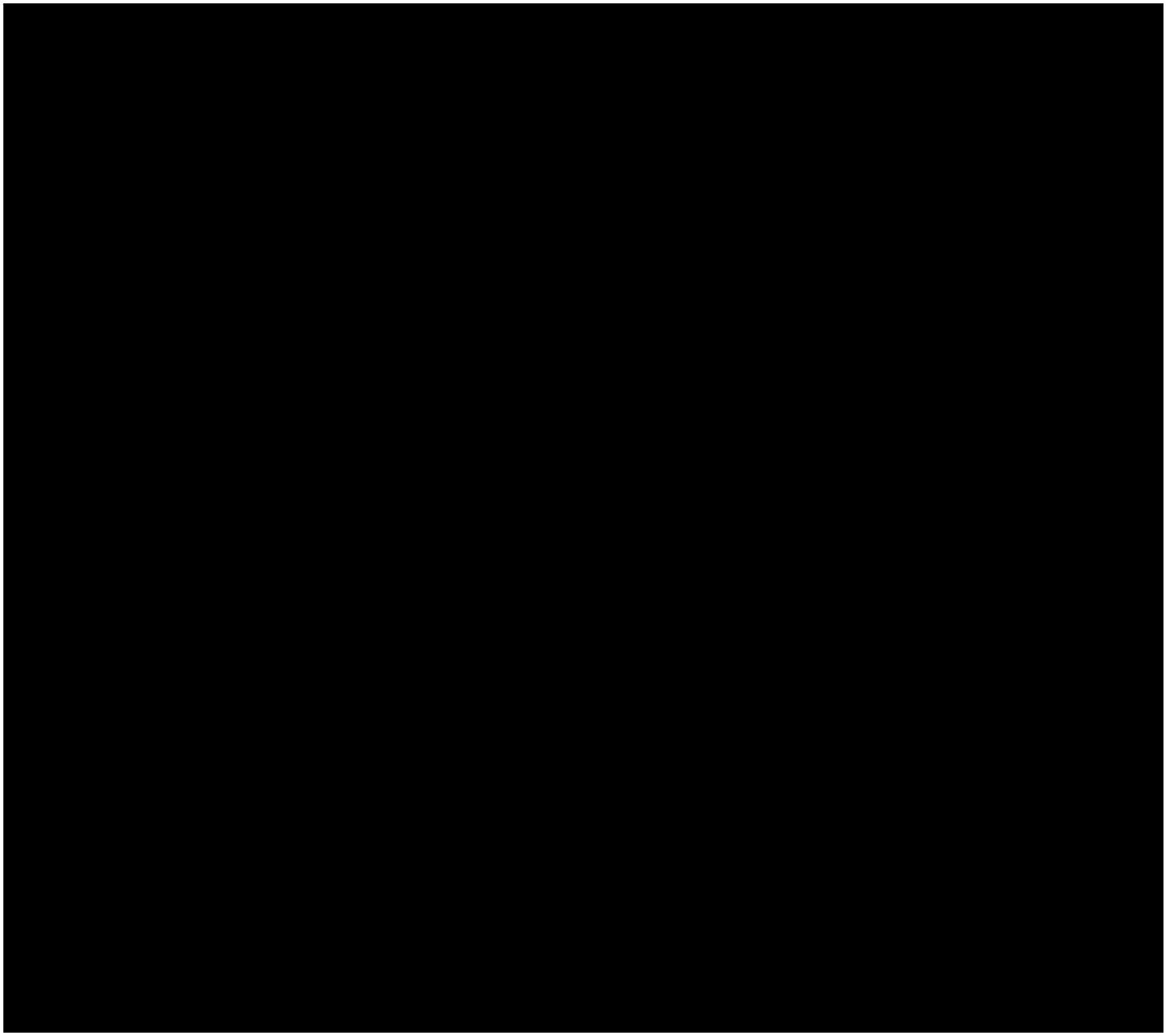
becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to KarXT or procedures.

After EOS, any SAE that the Investigator considers related to study drug must be reported to Catalyst Clinical Safety or the Sponsor/designee.

11.7.5 Drug-Induced Liver Injury

Drug-Induced Liver Injury (DILI) should be reported as an AESI anytime the subject exhibits:



11.7.6 Trial Discontinuation Criteria Other than DILI and Pregnancy

11.7.6.1 Individual Stopping Criteria

Based on NCI CTCAE v5.0, study drug will be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs other than DILI AEs (see Section 11.7.5) will be at the discretion of the investigator.

11.7.6.2 Trial Stopping Rules

The safety and tolerability aspects of KarXT will be overseen by an ISMC. The ISMC will meet periodically and review the unblinded data and will be responsible for advising the sponsor on ways to safeguard the interests of the clinical study subjects. The committee is expected to recommend sponsor whether to:

a. Continue the clinical study without modification; or
b. Continue the clinical study with modification (listing the specific modifications recommended); or
c. Terminate the study.

11.7.7 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB or package insert of generic trospium)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the Independent Ethics Committee (IEC)/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

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 GI obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease GI 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 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, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

Elevation of liver enzymes:

Elevated liver enzymes have been reported in previous studies of xanomeline alone in AD patients. It is notable, however, that the hepatic enzyme elevations were not observed in the Phase 1 studies in healthy volunteers and that the LFT elevations observed in the Phase 2 schizophrenia study (KAR-004) with KarXT (a combination of xanomeline and trospium) were quite limited in contrast to the effects observed with xanomeline in the elderly Alzheimer's population. Moreover, even in the AD patients who experienced more hepatic enzyme elevations, the data demonstrate reversibility even with continued xanomeline treatment in those patients where there was sufficient follow-up data. Importantly, there were no Hy's law cases or elevations in total bilirubin to a value of >2 × upper limit of reference range in either the xanomeline or KarXT datasets.

11.7.8 Pregnancy

WOCBP must have a negative pregnancy test at Screening and Baseline Visit B (Day 0).

The investigator must notify the Sponsor (or designee) of any female subject or female partner of a male subject that becomes pregnant while participating in the study. Any known cases of pregnancy will be reported until the subject completes or withdraws from the study.

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than 30 days after completion of the pregnancy.

If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of KarXT. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed.

If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event. This event is considered as an SAE.

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a 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.

11.7.9 Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT (total daily dose greater than 250/60 mg).

Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in BP with or without bradycardia, and severe anxiety and panic may occur.

Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Epinephrine 0.1 to 1.0 mg subcutaneous may be of value in overcoming severe cardiovascular or bronchoconstrictor responses.

AEs associated with overdoses should be reported in the eCRF.

11.8 Simpson-Angus Rating Scale

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

11.9 Barnes Akathisia Rating Scale

The BARS is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.[23]

11.10 Abnormal Involuntary Movement Scale

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

11.11 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.[24] 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.

11.12 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass.[25] The stool is often hard and dry.[26] Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement.[27] The normal frequency of bowel movements in adults is between 3 per day and 3 per week.[25] Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, APPENDIX 2.[28]

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and has been shown to be a useful tool in clinical practice and research.[29] A sample Bristol Stool Form Scale is located in APPENDIX 2.

As a measure of anticholinergic effects, at all in-clinic visits, subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample, nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools, pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation.[27, 30]

Treatment of constipation depends on the underlying cause and the duration that it has been present. For the purposes of constipation complaints during a clinical trial, the use of laxatives of a bulk forming agent, osmotic agent, stool softener, or lubricant type may be used.

As definitions of constipation are typically based on a history of at least a week, site physician discretion will be allowed for initiation of such treatments.

11.13 International Prostate Symptom Score (IPSS)

The Internal Prostate Symptom Score (IPSS) is administered by a clinician [38]. The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 (not at all) to 5 (almost always). The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic)[39].

The questions assess following urinary symptoms: (1) Incomplete emptying, (2) frequency, (3) intermittency, (4) urgency, (5) weak stream, (6) straining and (7) Nocturia.

Question 8 of the IPSS refers to the patient's perceived quality of life. The score on question 8 is not included in the total score calculation.

If a subject has an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 during the treatment period, the subject should be referred to a urologist. The urologist, in collaboration with the study Investigator and the medical monitor, should determine whether the subject should be discontinued from study treatment and/or the study. Study drug should be temporarily interrupted until the subject is seen by the urologist.

12 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

12.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[31] 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 scheduled assessments for all visits at which it is performed, except during screening when the MINI should be conducted first.

12.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It 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.[32]

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

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

On Days 8, 14, 84, 168, and 280, a single sample will be collected during the subject's regularly scheduled study visit (see Table 2). On Day 8 the PK sample should be drawn within 1 to 2 hours post-dose whenever possible.

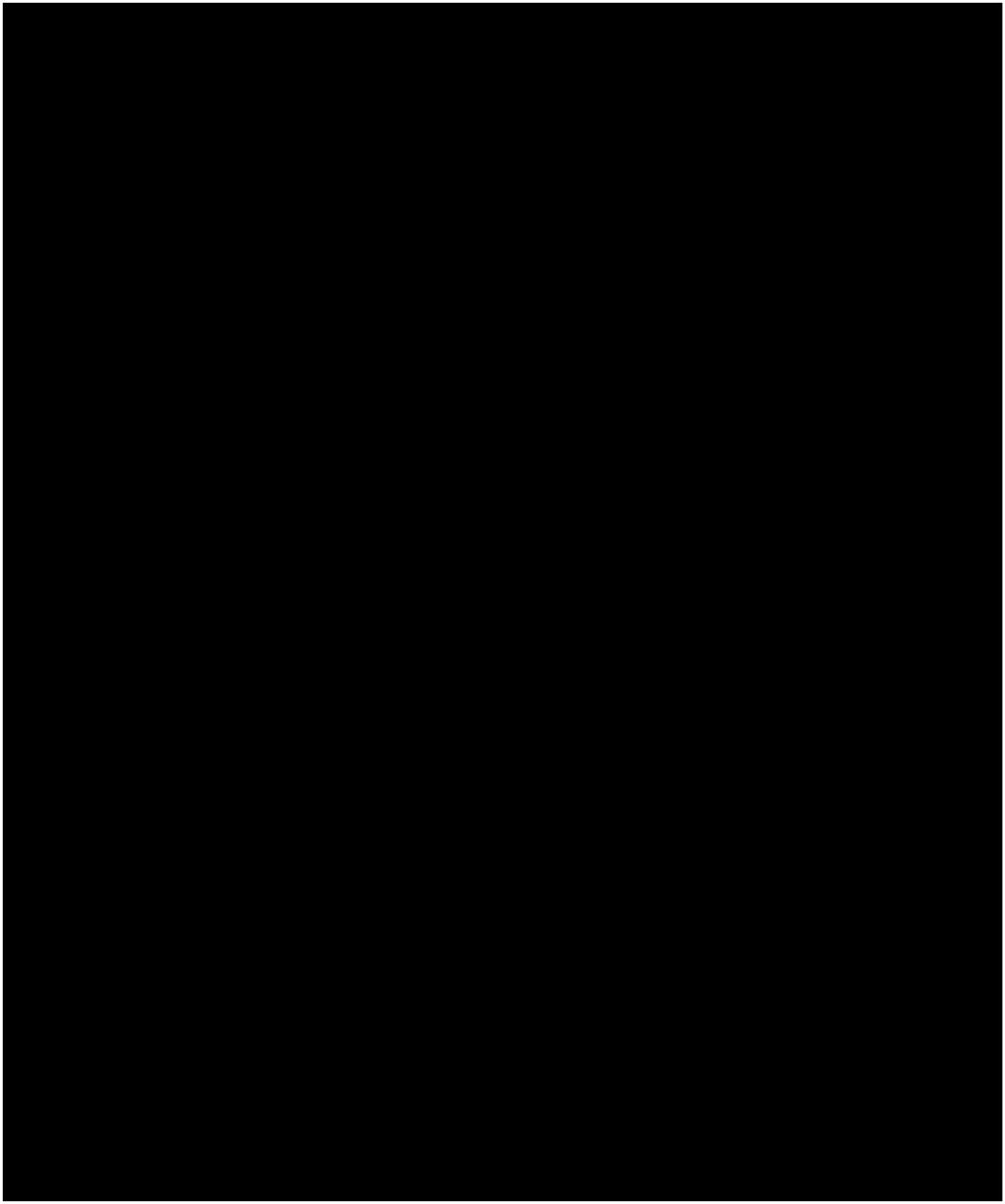
Approximately 4 mL of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

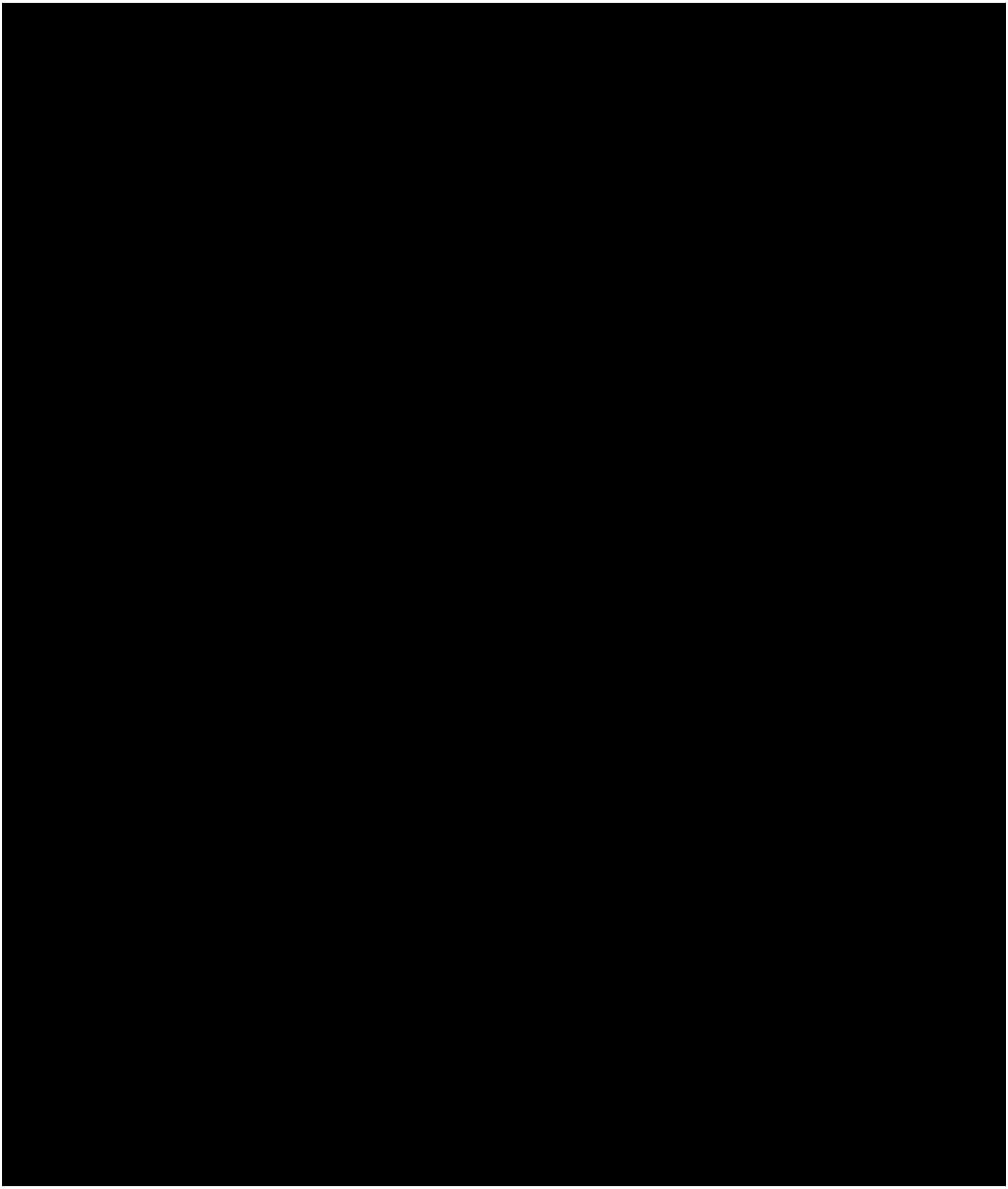
A single PK sample may be drawn if a relevant/significant AE is reported or if there is a dose adjustment. For ET that is related to an AE, collection of PK blood sample at the ET visit is recommended.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Bioanalysis of Trospium and Xanomeline

The plasma concentration of trospium and xanomeline in PK samples will be measured using a validated bioanalytical method. Details of the method validation and sample analysis will be included with the final clinical study report.





[redacted]

15 STATISTICAL ANALYSIS

An SAP will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using Statistical Analysis System ® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group.

Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum, and maximum. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

15.1 Determination of Sample Size

No formal sample size calculations were done. A sample size of up to 600 was deemed sufficient to provide 6- and 12-month safety data on subjects exposed to KarXT.

15.2 Analysis Populations

Enrolled population: All subjects who have given informed consent for KAR-011 will be included in the Enrolled population.

Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis.

mITT population: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid PANSS assessment at baseline, and at least 1 postbaseline time point will be included in the mITT population and will be used in the efficacy analysis.

PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT in the current study will be included in the PK population.

15.3 Safety Analysis

Safety endpoints will be summarized for all subjects in the Safety population.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. The incidence of TEAEs (defined as events with an onset date on or after the first dose of KarXT) will be summarized by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset,

duration, relationship and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

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

15.4 Efficacy Analysis

Efficacy analyses will be summarized based on the mITT population. The summaries described in this section will provide data on maintenance of effect of open-label KarXT over 52 weeks. Tabular presentations will display descriptive statistics for baseline and change from baseline study results by scheduled visit.

Responder efficacy variables (PANSS responders) will be summarized descriptively.

Continuous efficacy variables based on the change from baseline (PANSS, CGI-S) will be summarized using descriptive statistics by scheduled visit. Tabular presentations will display descriptive statistics for the baseline and change from baseline results by scheduled visit. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time.

15.5 Pharmacokinetic Analysis

The PK evaluation will rely on an existing population PK model for KarXT in subjects with schizophrenia. The plasma concentrations of xanomeline and trospium measured in this study will be overlaid onto distributions of concentrations predicted by the population PK model developed from KAR-007 and KAR-009 data. Percentages of measured concentrations in the current study that lie within, above, and below the 90% prediction interval of concentrations predicted by the model will be calculated.

Details of the PK analysis will be described in the SAP.

[redacted]

15.7 Interim Analysis

No interim analysis is planned for this study.

15.8 Handling of Missing Data

[redacted]

Additional methods of missing data imputation may be explored and will be outlined in the SAP.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and all applicable local, state and federal government regulations and laws.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets, and other subject facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if she becomes pregnant during the course of the study or within 7 days of the last dose of KarXT.

Subject Registry:

Clinical trial registries, such as clinical trial subject (CTS) database (CTS database) and Verified Clinical Trials (VCT), seek to reduce duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the informed consent for the study, the investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

At the beginning of screening visit, following consent execution and subject number assignment and before other study procedures, site staff that have received training and login information access (www.subjectregistry.com) to the database will enter the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts will be generated and should be printed for source documentation. The report will detail each protocol violation detected and specific washout period dates where applicable.

Throughout the study, tracking of actively enrolled subjects will continue based on updates by coordinators in the interactive response system. At the last subject contact, CTS database and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on IWRS.

16.2 Data Handling

Any data to be recorded directly in the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported in the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel in eCRFs for transmission to the Sponsor. Data in eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's secure internet website, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Data recorded on source documents will be transcribed into 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.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the KAR-011 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits may include on-site or remote visits and may also utilize periodic telephone contacts. The investigators will assure them and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor or its designee will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. Syneos Health will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

- All protocol deviations will be tracked in the Clinical Trial Management 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.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will

be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception (eg, hormonal or double barrier method of birth control, or intrauterine device) beginning >30 days before receiving study drug on Day 1 and continuing until 30 days after the last dose of study drug. If oral contraceptives are used, the subject must have been on a stable dose for ≥6 months.

A woman of child-bearing potential (WOCBP) is any woman who has experienced menarche and is not yet postmenopausal unless she is permanently sterile (i.e. hysterectomy, bilateral salpingectomy, bilateral tubal ligation, or bilateral oophorectomy). Women who have experienced menarche but are not yet postmenopausal, and who are permanently sterile by one of the methods described above are not required to undergo pregnancy testing at study visits, and it is not considered a protocol deviation to skip pregnancy testing for these individuals.
A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- double barrier method consisting of a physical (e.g., condom, diaphragm) and chemical barrier (e.g., spermicide)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant while on study treatment or for 30 days after the last dose. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

APPENDIX 2. FUNCTIONAL CONSTIPATION INQUIRY

1 ROME III Diagnostic Criteria for Constipation and Irritable Bowel Syndrome with Constipation

Symptoms ≥3 months; onset ≥6 months before diagnosis

Functional Constipation	IBS-C
Must include ≥ 2 of the following: • Straining[a] • Lumpy or hard stools[a] • Sensation of incomplete evacuation[a] • Sensation of anorectal obstruction/blockage[a] • Manual maneuvers to facilitate defecation (eg, digital evacuation, support of the pelvic floor)[a] • <3 defecations/week	IBS: Recurrent abdominal pain/discomfort ≥ 3 days/month for the past 3 months, associated with ≥ 2 of the following: • Improvement with defecation • Onset associated with change in stool frequency • Onset associated with change in stool form
• Loose stool rarely present without use of laxatives	IBS is subtyped by predominant stool pattern • IBS-C: hard or lumpy stools[b] ≥ 25% of defecations; loose or watery stools[c] < 25% of defecations[d]
• Insufficient criteria for IBS-C	

Abbreviation: IBS-C = irritable bowel syndrome with constipation.

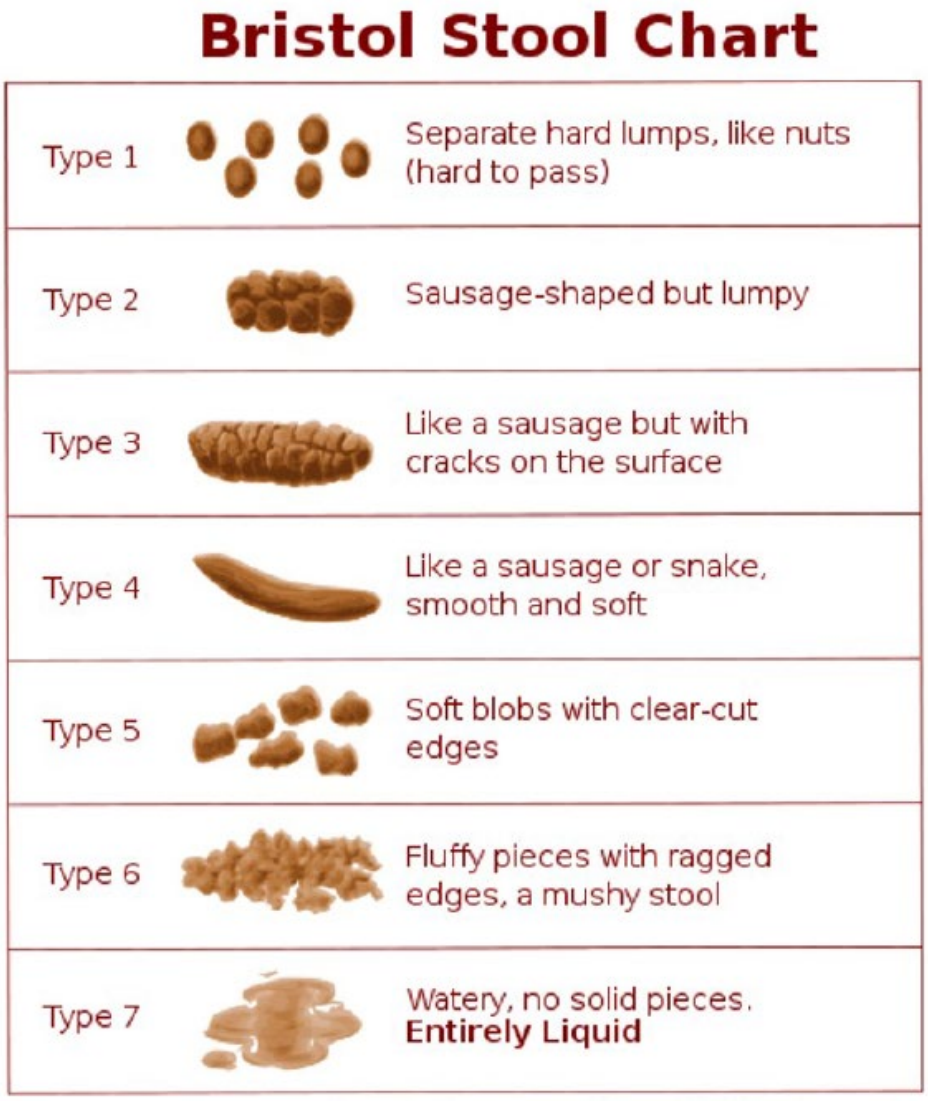
[a] ≥ 25% of defecations.

[b] Bristol Stool Form Scale 1–2: separate, hard lumps like nuts (difficult to pass); or lumpy, sausage-shaped stool.

[c] Bristol Stool Form Scale 6–7: fluffy pieces of stool with ragged edges; mushy stool; or watery without solid pieces (entirely liquid).

[d] In the absence of use of antidiarrheals or laxatives (Longstreth GF et al. *Gastroenterology.* 2006;130:1480-1491, C3 p.1486).

2 Bristol Stool Form Scale



1. TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

The major revisions to **Protocol KAR-011 v4.0** include changes to include the International Prostate Symptom Score (IPSS) assessment, schedule of assessments, updated Phase 3 study status, administrative and minor editing changes that do not affect the content or conduct of the protocol have been incorporated.

Bolded text indicates new content and ~~strike-through~~ shows deleted text. Only the changed text in a section will be shown. Changes to the reference section are not documented. The administrative and minor editing are not elaborated on in this document but are found in the tracked change document that accompanies this summary of revisions.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis, Title Page, Sponsor Signature Page, Header	~~13 December 2021~~, and-Protocol version ~~3.0~~	**26-September-2023,** and Protocol version **4.0**	Corrected date and version to v4.0 issue
Synopsis/Study Design/ Section 7.2	De novo subjects, defined as ~~not previously participated in a study of KarXT~~, who meet DSM-5 criteria for schizophrenia.	De novo subjects, defined as **those who did not have prior exposure to KarXT,** who meet DSM-5 criteria for schizophrenia.	To be consistent with exclusion criteria number 16, updated de novo subject's definition.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis/Safety assessments/Section 7.1/ Section 11/Section 15.3	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; serious AEs (SAEs) and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled.	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; serious AEs (SAEs) and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; **IPSS**; and C-SSRS will be evaluated throughout the study as scheduled.	[redacted], monthly reporting of IPSS assessment for male subjects ≥ 45 has been added to safety assessments.
List of Abbreviations		**IPSS: International Prostate Symptom Score**	Updated abbreviations list.
Section 5.2.2	~~Two randomized, double-blind, placebo-controlled Phase 3 trials (KAR-007 and KAR-009) are planned in which the subjects will be exposed to either KarXT or placebo (1:1) for a period of up to 5 weeks. Also, a Phase 3 open-label, roll-over trial (KAR-008) is planned in which the subjects rolled over from KAR-007 and KAR-009 will be treated with KarXT for a period of up to 52 weeks in an outpatient setting.~~	**KAR-007 and KAR -009 had similar study designs and were modelled from the first pivotal study, KAR-004. Both KAR-007 and KAR-009 were Phase 3, randomized, double-blind, placebo-controlled trials to assess the efficacy, safety, and tolerability of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. Both KAR-007 and KAR-009 were identical, except KAR-007 enrolled subjects in the US only whereas KAR-009 enrolled subjects in Ukraine and the US. The primary objective of the studies was to assess the efficacy of KarXT (125/30 BID) vs placebo in reducing PANSS total scores in adult inpatients with a**	Added KAR-007 and KAR-009 study status and results.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		DSM-5 diagnosis of schizophrenia. Subjects aged 18 to 65 years old received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. **Both pivotal, Phase 3 studies met their primary endpoint. The primary endpoint in KAR-007 and KAR-009 was the change from baseline (CFB) in PANSS total score at week 5. In each of the studies, treatment with KarXT led to statistically significant improvements in PANSS total score at Week 5 compared with placebo ($p < 0.0001$ in each study). Cohen's d effect size was 0.61 in KAR-007 and 0.60 in KAR-009.** **Secondary endpoints were analyzed based on a planned hierarchy in a fixed sequence and were typically in favor of KarXT. Treatment with KarXT led to statistically significant improvements relative to placebo in PANSS positive score at Week 5 in both studies ($p < 0.0001$ in each study). In KAR-007, the improvements in PANSS negative and PANSS Marder factor negative subscales were statistically significant in favor of KarXT versus placebo at Week 5 ($p \leq 0.0055$ and $p = 0.0022$, respectively). In KAR-009, the improvements in PANSS negative and PANSS Marder factor negative score at Week 5 was greater in KarXT than placebo but did not reach statistical significance at the 2-sided alpha level of 0.05 ($p = 0.1224$ and $p = 0.1957$, respectively). Analysis of the CFB in CGI-S in both studies demonstrated improvements in CGI-S scores at Week 5 in**	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		favor of KarXT versus placebo (statistically significant over placebo for KAR 007, and nominally significant over placebo albeit not formally tested in KAR-009). KAR-007 and KAR-009 included a Week 5 PANSS responder analysis as a secondary efficacy endpoint (defined as an improvement from baseline of at least 30% at Week 5 in PANSS total score). The PANSS responder analysis showed that a greater proportion of subjects on KarXT achieved ≥ 30% improvement in PANSS total score at Week 5 compared to those on placebo in both KAR-007 (54.8% versus 28.3%, p < 0.0001) and KAR 009 (50.6% versus 25.3%, p = 0.0056). **KarXT was well-tolerated and safe in the Phase 3 studies, with the pattern and course of safety findings largely consistent with the known safety profile of KarXT. The most common TEAEs were associated with the procholinergic or anticholinergic effects of KarXT. The administration of KarXT was notably free of many common side effects associated with currently approved antipsychotic drugs.** **KAR-008 is an ongoing Phase 3, multicenter, outpatient, open label extension (OLE) study designed to evaluate the long-term safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, which includes subjects who completed KAR-007 or KAR-009. Eligible subjects receive KarXT for up to 52 weeks. Enrollment in this study is complete (N=156).**	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 5.3	[redacted]		
	Trospium chloride has been marketed in the United States for ~~12~~ years.	Trospium chloride has been marketed in the United States for **19** years.	
	~~In a Phase 2 (KAR-004) clinical study, KarXT (100/20 and 125/30) significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common TEAEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. All the reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.~~	**Findings from one Phase 2 (KAR-004) and two Phase 3 (KAR-007 and KAR-009) pivotal placebo-controlled studies were similar. In all three clinical studies, administration of KarXT (100/20 and 125/30) for 5 weeks resulted in consistent, significant reductions in symptoms of schizophrenia in subjects with acute psychosis and CGI-S compared with placebo. The safety and tolerability of KarXT was consistent in 3 successive pivotal placebo-controlled studies (KAR-004, KAR-007 and KAR-009). The most common treatment-emergent adverse events (TEAEs) by preferred term in the KarXT treatment arm included nausea, dyspepsia, vomiting, constipation, headache, hypertension, diarrhea, and insomnia. KarXT was generally well tolerated and found to be safe in this patient population. KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to**	Updated safety findings from completed Phase 3 studies (KAR-007 and KAR-009) and provided a status update from ongoing OLE study (KAR-008).

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		current therapies. **KAR-008 is an ongoing Phase 3, multicenter, outpatient, OLE study designed to evaluate the long-term safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, which includes subjects who completed KAR-007 or KAR-009.**	
Section 11.7.2	~~AESIs will be monitored and include orthostasis and~~ LFT elevations **as outlined in 11.7.5** inclusive of drug-induced liver injury (DILI) **and symptomatic orthostasis including syncope (a transient loss of consciousness or fainting) is to be captured as an AESI and reported as such.**	**LFT elevations as outlined in 11.7.5** inclusive of drug-induced liver injury (DILI) **and symptomatic orthostasis including syncope (a transient loss of consciousness or fainting) is to be captured as an AESI and reported as such. Non symptomatic orthostasis will not be reported as an AESI. Any such AESI due to any cause, whether or not related to KarXT, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using email.**	Updated criteria for AESI to include Syncope and DILI, and clarified reporting requirements.
Section 11.7.5		**Drug-Induced Liver Injury (DILI) should be reported as an AESI anytime the subject exhibits:** [redacted]	Updated section to clarify when DILI should be reported as an AESI.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 11.7.9	Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). ~~Atropine sulfate should be available for intravenous or intramuscular administration. Several doses ranging from 0.5 to 2.0 mg may be required~~. Epinephrine 0.1 to 1.0 mg subcutaneous may ~~also~~ be of value in overcoming severe cardiovascular or bronchoconstrictor responses.	Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Epinephrine 0.1 to 1.0 mg subcutaneous may be of value in overcoming severe cardiovascular or bronchoconstrictor responses.	Clarified language to be consistent with IB.
Section 11.13		**The Internal Prostate Symptom Score (IPSS) is administered by a clinician [38]. The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 (not at all) to 5 (almost always). The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic) [39].** **The questions assess following urinary symptoms: (1) Incomplete emptying, (2) frequency, (3) intermittency, (4) urgency, (5) weak stream, (6) straining and (7) Nocturia.** **Question 8 of the IPSS refers to the patient's perceived quality of life. The score on question 8 is not included in the total score calculation.** **If a subject has an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 during the treatment**	[redacted], monthly reporting of IPSS assessment for male subjects ≥ 45 has been added to this protocol. This section describes the IPSS assessment and follow-up.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		period, the subject should be referred to a urologist.The urologist, in collaboration with the study Investigator and the medical monitor, should determine whether the subject should be discontinued from study treatment and/or the study. Study drug should be temporarily interrupted until the subject is seen by the urologist.	
Section 15.4	Responder efficacy variables (PANSS responders) will be summarized descriptively. ~~Responses will be derived relative to the acute study baseline assessments~~.	Responder efficacy variables (PANSS responders) will be summarized descriptively.	The omitted sentence is not applicable to this trial.
Appendix 1	~~A woman is considered to be WOCBP following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy [22]. Female subjects who are postmenopausal, which is defined as 12 consecutive months with no menses without an alternative medical cause, must have been postmenopausal for >1 year if they wish to not use contraceptives. Postmenopausal status must be confirmed by a test of the subject's follicle-stimulating hormone (FSH) level which must be elevated and consistent with postmenopausal levels (ie, >40 IU/L); otherwise, these subjects must agree to use contraceptives listed below.~~	**A woman of child-bearing potential (WOCBP) is any woman who has experienced menarche and is not yet postmenopausal unless she is permanently sterile (i.e. hysterectomy, bilateral salpingectomy, bilateral tubal ligation, or bilateral oophorectomy). Women who have experienced menarche but are not yet postmenopausal, and who are permanently sterile by one of the methods described above are not required to undergo pregnancy testing at study visits, and it is not considered a protocol deviation to skip pregnancy testing for these individuals.**	Updated language to clarify the contraception guidelines of WOCBP.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	~~Female subjects who are surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) will not need to undergo the FSH level test.~~		

Summary of Changes to Table 2 (Schedule of Assessment)

Change	Rationale
Added IPSS assessment at **Visit 11, Visit 13, Visit 15, Visit 17, Visit 19, Visit 21, Visit 23, Visit 25, Visit 27, Visit 29, and End of Study/unscheduled Visit.**	[redacted], implemented monthly reporting of IPSS assessment for male subjects ≥ 45 at these visits.
w. IPSS will be administered monthly only in male subjects ≥45 years of age at the time of signing the informed consent. IPSS assessment administration will start from Visit 11 (at the time of this amendment, study enrollment has been completed, and all enrolled subjects have completed Visit 9).	Added footnote to clarify the IPSS administration specifications.

1. TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

The major revisions to **Protocol KAR-011 v3.0** include changes to inclusion criteria, schedule of assessments, and number of sites and subjects. Administrative and minor editing changes that do not affect the content or conduct of the protocol has been incorporated.

Bolded text indicates new content, ~~strike-through~~ shows deleted text. Only the changed text in a section will be shown. An ellipsis, or series of dots (…), is used to indicate that unchanged text before and/or after the addition or revision is not shown. For changes that affect multiple sections of the protocol, the change is listed once at the first instance below, and each subsequent protocol section incorporating that change is also listed at that point. Changes to the reference section are not documented. The administrative and minor editing are not elaborated on in this document but are found in tracked change document, that accompanies this summary of revisions.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis, Title Page, Sponsor Signature Page, Header	~~31 August 2021~~	**20-December-2021**	Corrected date to v3.0 issue
Synopsis/ Investigators/Study Sites	Approximately ~~40~~ sites in the United States	Approximately **60** sites in the United States	Change in total number of study participants will require more study sites.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]	[redacted]	[redacted]	[redacted]
Synopsis / Study Endpoints / Secondary Endpoints / Efficacy **Section 6.2.2.2**	Percentage of PANSS responders (a 30% ~~change~~ in PANSS total score) at Week 52	Percentage of PANSS responders (a 30% **reduction** in PANSS total score) at Week 52	Response is defined as a reduction in PANSS scores (i.e., 30% worsening is not response)
[redacted]			

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]	[redacted]		[redacted]
Synopsis / Study Design / Screening Phase **Section 7.1**	A suitable number of subjects will be screened to enroll approximately ~~400~~ subjects (aged 18 to 65 years) with schizophrenia who are psychiatrically stable and can be adequately managed in an outpatient setting across approximately ~~40~~ study sites in the United States. The screening phase will last up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval) ~~and will end upon the start of the study baseline phase~~	A suitable number of subjects will be screened to enroll approximately **600** subjects (aged 18 to 65 years) with schizophrenia who are psychiatrically stable and can be adequately managed in an outpatient setting across approximately **60** study sites in the United States. The screening phase will last up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval).	Study size increased to ensure adequate 6 and 12 month exposures. Unnecessary text removed.
Synopsis / Study Design / Baseline Phase **Section 7.1** **Table 2**	Subjects who meet the screening criteria will participate in a baseline period consisting of two separate visits ~~and lasting no more than 5 days during which, subjects will complete 3 days of at home assessments~~ [redacted].	Subjects who meet the screening criteria will participate in a baseline period consisting of two separate visits. **The start of the baseline period, Baseline Visit A, must be at least 3 days (and no more than 5 days) prior to Baseline Visit B. Subjects must continue to meet eligibility criteria throughout the baseline period to remain in the study.**	Clarification of baseline period duration and requirements
Synopsis / Study Design / Treatment Phase **Section 7.1** **Section 7.2** **Table 2**	~~Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. Interim visits will be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits as needed to facilitate subject retention and ensure compliance with study objectives. Additional unscheduled study visits may be conducted as needed.~~	**Interim visits, which can be conducted in-clinic or by telemedicine per investigator discretion, will occur between required in-clinic visits (see Schedule of Assessments Table 2). Additional Unscheduled study visits should be utilized as necessary to facilitate subject retention and ensure compliance with study objectives.**	Clarification of interim visits and their use.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis / Study Criteria / Inclusion Criteria **Section 8.1**	2. 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	2. Subject is capable of providing informed consent. a. A signed informed consent form **(ICF)** must be provided before any study assessments are performed. **b.** Subject must be fluent (oral and written) in **the language of the ICF to consent**	Permit use of non-english ICF for native Spanish speakers
Synopsis / Study Criteria / Inclusion Criteria **Section 8.1**	5. PANSS total score of ≤ 80 at screening 6. CGI-S score of ≤ 4 at screening	7. PANSS total score of ≤ 80 at screening **and Baseline Visit B (Day 0).** 8. CGI-S score of ≤ 4 at screening **and Baseline Visit B (Day 0).**	Ensure participants remain stable and safe to manage in outpatient setting
Synopsis / Study Criteria / Inclusion Criteria **Section 8.1**	~~7.~~ At the time of screening, ~~the subject must be receiving an oral antipsychotic medication daily as maintenance therapy.~~ [redacted]	**7.** At the time of screening, **or at any time within the 30 days prior to screening, the subject must have received an oral antipsychotic medication daily at a dose and frequency consistent with the drug label.**	Subjects who have recently discontinued treatment may be eligible if current meeting all other stability criteria.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis / Study Criteria / Exclusion Criteria **Section 8.2**	1. The subject has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months a. A 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. b. Subjects ~~who test~~ positive for cannabis ~~at screening~~ may be permitted to enroll ~~in consultation with the medical monitor~~ if the subject's pattern of use is not indicative of a substance use disorder.	**2.** The subject has a history of moderate to severe alcohol use disorder or a substance (other than nicotine or caffeine) use disorder within the past 12 months **or a positive urine drug screen (UDS) for a substance other than cannabis at screening or baseline.** a. A 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. b. Subjects **with a** positive **UDS** for cannabis **are** permitted to enroll **in the study** subject's pattern of use is not indicative of a substance use disorder.	Clarified that UDS will be utilized to assess use of non-protocol permitted substances. Additional discussion w/ medical monitor not required for cannabis provided the subject does not meet criteria for a substance use disorder
Synopsis / Study Criteria / Exclusion Criteria **Section 8.2**	19. Participation in another clinical study in which the subject received an experimental or investigational drug agent within ~~3 months of~~ to screening.	19. Participation in another clinical study in which the subject received an experimental or investigational drug agent within **30 days prior** to screening.	30 days deemed sufficient to ensure subject safety

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis / Sample Size **Section 7.2**	Approximately ~~400~~ subjects (aged 18 to 65 years) are planned to be enrolled in this study.	Approximately **600** subjects (aged 18 to 65 years) are planned to be enrolled in this study.	Sample size increased to ensure study objectives
Table 1 **Section 8.4**	7 (±3) days after ~~the last dose or for ET from the study or UNS~~	7 (±3) days after **completion of the EOT or ET visit**	Clarified EOS study takes place w/in 7 days of ET or EOT visit
Table 1 / Footnote a	At Visit 1 (Day 1) subjects will initiate dosing with KarXT BID independently at home. Visits ~~2~~, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits ~~and should be conducted by telemedicine.~~	Visits 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits **2,** 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits and **can be conducted via telemedicine or on-site.**	Visit 2 made interim (see below); all interim visits may be completed on-site or via telemedicine per investigator discretion
Table 1 / Footnote c	~~Beginning~~ after Visit 9/Day 84, ~~interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks.~~	After Visit 9/Day 84, **required in-clinic visits will be conducted approximately every 4 weeks. Interim visits will be conducted between required in-clinic visits and can be conducted by telemedicine or in-clinic per investigator discretion (see Schedule of Assessments Table 2 for further details)**.	Clarified use of interim visits

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Table 1 / Footnote f Table 2		**Visit 2/Day 3 is an interim visit and can be conducted via telemedicine or in-clinic per investigator discretion.**	Visit 2 changed to interim to reduce study burden and increase investigator flexibility to meet study objectives
Section 9.2.4, 9.2.5	If dose escalation to the KarXT 125/30 level is confirmed by investigator order ~~on Visit 3/Day 8~~, site staff will provide subjects with a single 125/30 maintenance blister card wallet.	If dose escalation to the KarXT 125/30 level is confirmed by investigator order, site staff will provide subjects with a single 125/30 maintenance blister card wallet.	Dose is confirmed by investigator order at each study visit.
Section 9.6.1	Subjects will be asked to confirm all prior medications they were taking up to 6 months before the study, up to the time of ~~the Baseline Visit A (Day -3)~~. All prior medications will be recorded on the eCRF.	Subjects will be asked to confirm all prior medications they were taking up to 6 months before the study, up to the time of **consent**. All prior medications will be recorded on the eCRF.	Prior medications are those taken prior to consent
Section 9.6.1	During the study (ie, from the time of ~~enrollment at the screening visit~~ until study completion (EOS), subjects should refrain from the use of any new concomitant medications without the approval of the investigator.	During the study (i.e., from the time **consent** until study completion [EOS]), subjects should refrain from the use of any new concomitant medications without the approval of the investigator.	Clarified conmeds should be managed from time of consent

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 11.1 **Section 11.7.1**	All changes not present at ~~baseline~~ or described in the past medical history and identified as clinically significant must be recorded as AEs.	All changes not present at the **time of consent** or described in the past medical history and identified as clinically significant must be recorded as AEs.	AE collection begins upon signed consent
Section 11.6 **Table 2**	A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick at the scheduled visits.	A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick at the scheduled visits. **A sample should be sent to the central lab at screening. Thereafter, if positive, with the exception of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.**	Urine drug screen (UDS) samples only need to be sent to central lab at screening for eligibility review and thereafter only if the on-site test is positive for a substance other than cannabis. Negative results reported by on-site UDS.
Section 11.7.4	An SAE occurring from the time ~~the first dose of KarXT is administered, during the study, or within 1 week of stopping the treatment~~ must be reported…	An SAE occurring from the time **of informed consent until EOS** must be reported… **After EOS, any SAE that the Investigator considers related to study drug must be reported to Catalyst Clinical Safety or the Sponsor/designee.**	Clarified SAEs occurring at any time during the study must be reported. Any SAEs the investigator becomes aware of after EOS must be reported

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			
Appendix 1	Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception ~~(eg, hormonal or double barrier method of birth control or intrauterine device)~~ beginning >30 days before receiving study drug…	Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception beginning >30 days before receiving study drug…	Double barrier is not highly effective; all study approved contraception methods are listed within appendix 1

Summary of Changes to Table 2 (Schedule of Assessment)

Change	Rationale
Removal of AE collection at Visit 1/Day 1	Visit 1/Day 1 reflects only the beginning of at-home dosing with KarXT and any AEs reported will be assessed and collected on an ongoing basis from the time of consent

[redacted]

Removal of vital signs, constipation inquiry, and C-SSRS at Visit 2/Day 3	Visit 2/Day 3 changed to interim visit
[redacted]	
Removed PANSS assessment at Visit 4, Visit 17, Visit 21, Visit 25	These additional assessments are unnecessary to meet study objectives and increase participant burden.
[redacted]	

[redacted]

KAR-011 Summary of Changes of Amendment 2

Page 1

Updated Karuna Therapeutics address

Updated Protocol Date

Section 2, Synopsis

Synopsis was updated to reflect content changes in the protocol as noted for each section below.

6.1.2 Secondary Objective

Updated to integrate last bullet into general statement

The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium following administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction in PANSS positive score
- To evaluate the improvement in CGI-S score
- To evaluate the reduction in PANSS negative score
- To evaluate the reduction in PANSS Marder Factor negative symptoms score
- To evaluate the percentage of subjects who exhibit a 30% reduction in PANSS total score

6.2.2.2 Efficacy Endpoints

Changed the secondary efficacy endpoint for CGI-S Score:

- CGI-S score at Week 52

6.2.3.2 Pharmacokinetic Endpoint

Updated Endpoint to add more specific language
Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009.

7.1 Description of Overall Study Design and Plan

Updated Language to define "de novo" and extend screening period:

This is a Phase 3, multicenter, 52 week, outpatient, open-label study to evaluate the long term safety, tolerability, and efficacy of KarXT in de novo subjects, defined as not previously participated in a study of KarXT, who meet DSM-5 criteria for schizophrenia. The study consists of a screening phase of up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval), a baseline phase of up to 5 days, a 52-week open-label treatment phase, and a 7-day safety follow-up/end of study (EOS) visit following the last dose of KarXT for subjects who complete the treatment phase and those who prematurely discontinue from the study.

Screening Phase:

A suitable number of subjects will be screened to enroll approximately 400 subjects (aged 18 to 65 years) with schizophrenia who are psychiatrically stable and can be adequately managed in an outpatient setting across approximately 40 study sites in the United States. The screening phase will last up to 14 days (up to a 7-day screening extension is permitted with medical monitor approval) and will end upon the start of the study baseline phase.

Table 1

Moved early termination subjects to Day 364/Visit 29 from Day 371/Visit 30

7.2 Discussion of Study Design

Updated Language to define "de novo":
The KarXT clinical development program includes this open-label study to evaluate the long-term safety, tolerability, and efficacy data for KarXT in de novo subjects, defined as not previously participated in a study of KarXT, who meet the DSM-5 criteria for schizophrenia.

8.1 Inclusion Criteria

Updated language to direct reader to contraception guidelines section:
15. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1.

8.2 Exclusion Criteria

Added new exclusion criteria

19. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 3 months before screening.

9.1.1 Identity of Study Treatments

Added new statement
Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor (see also Section 9.4).

9.2.4 Visit 3/Day 8 Dosing

Removed specific visit language

In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, dispense a single 100/20 maintenance blister card wallet.

9.2.5 Visit 3/Day 8 Dosing

Removed specific visit language

In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, dispense a single 100/20 maintenance blister card wallet.

9.2.7 Visits 9 to 29 (Days 84 to 364) Dosing

Changed day of PK draw

For Days 84, 168, and 280, a single PK sample will be collected and the dose of KarXT and time of most recent dosing should be recorded.

9.4 Dosage Modification

Changed evaluation for dose adjustments to start at Visit 3, not Visit 4

Subjects will self-administer KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.1.1).

9.6.1 Prior and Concomitant Medications

Removed Language

During the study (ie, from the time of enrollment at the screening visit until study completion (EOS), subjects should refrain from the use of any new concomitant medications without the approval of the investigator.

10. Study Procedures

Removed and updated language

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Section 11, Section12, Section 13, and Section 14 for additional details regarding safety, efficacy, PK, [redacted] assessments, respectively.

COVID-19 testing will be completed in accordance with clinical site standard operating procedures. If a subject tests positive for COVID-19 during the study, they may be quarantined as needed and any scheduled visits should be rescheduled or conducted by telemedicine at the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as outlined in Section 11.7.4.

Table 2. Schedule of Assessments

Updated footnotes for clarification

Moved the Early Termination visit from Day 371/Visit 30 to Day 364/Visit 29

Moved a PK sample collection from Day 364/Visit 29 to Day 280/Visit 40

[redacted].

Added blood sample for Viral serology at screening

10.2 Study Procedures

Removed language

PK assessments are described in Section 13.

11.3 Complete/Targeted Physical Examination

Added language

Physical examinations will be performed by a physician or qualified designee.

11.5 Electrocardiograms

Updated language

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

Table 3 Laboratory Assessments

Removed Albumin from Serum Chemistry

[redacted]

HbA1c added (glycated Hb test)

Added viral serology and associated footnotes

11.6 Laboratory Assessments

Corrected language

- Alcohol testing will be performed using a breathalyzer or urine alcohol test.

11.7.8 Pregnancy

Added language for clarity

WOCBP must have a negative pregnancy test at Baseline Visit B (Day 0).

13.1.1 Blood Samples

On Days 8, 14, 84, 168, and 364280, a single sample will be collected during the subject's regularly scheduled study visit (see Table 2). On Day 8 the PK sample should be drawn within 1 to 2 hours post-dose whenever possible.

Approximately 4 mL of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

Note: A single PK sample may be drawn if a relevant/significant AE is reported or if there is a dose adjustment. For ET that is related to an AE, collection of PK blood sample at the ET visit is recommended.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Bioanalysis of Trospium and Xanomeline

Administrative update to language

The plasma concentration of trospium and xanomeline in PK samples will be measured using a validated bioanalytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

[redacted]

15.5 Pharmacokinetic Analysis

Updated language to add more specific details

The PK evaluation will rely on an existing population PK model for KarXT in subjects with schizophrenia. The plasma concentrations of xanomeline and trospium measured in this study will be overlaid onto distributions of concentrations predicted by the population PK model developed from KAR-007 and KAR-009 data. Percentages of measured concentrations in the current study that lie within, above, and below the 90% prediction interval of concentrations predicted by the model will be calculated.

Details of the PK analysis will be described in the SAP.

APPENDIX 1. CONTRACEPTION GUIDELINES

Updated language for clarity

Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception (eg, hormonal or double barrier method of birth control, or intrauterine device) beginning >30 days before receiving study drug on Day 1 and continuing until 30 days after the End of Study (EOS) Visit. If oral contraceptives are used, the subject must have been on a stable dose for >/= 6 months.

A woman is considered to be WOCBP following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy [22]. Female subjects who are postmenopausal, which is defined as 12 consecutive months with no menses without an alternative medical cause, must have been postmenopausal for >1 year if they wish to not use contraceptives. Postmenopausal status must be confirmed by a test of the subject's follicle stimulating hormone (FSH) level which must be elevated and consistent with postmenopausal levels (ie, >40 IU/L); otherwise, these subjects must agree to use contraceptives listed below. Female subjects who are surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) will not need to undergo the FSH level test.

Deleted reference:

Reference: [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-

About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed April 8, 2020.

APPENDIX 3. ALTERNATIVE PROCEDURES DURING COVID-19 PANDEMIC-RELATED PHYSICAL DISTANCING

Deleted Appendix 3 – removed the alternative procedure schedule in event of required physical distancing