Official Title of Study:

A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia

PROTOCOL(S) KAR-014

NCT Number: NCT05643170

Document Date (Date in which document was last revised): July 1, 2022

16.1.1 PROTOCOL AND AMENDMENTS

Protocol KAR-014, Version 1.0, 01 July 2022

Clarification Memorandum 20 October 2022

CLINICAL STUDY PROTOCOL

A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia

Protocol Number: KAR-014

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3b
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 99 High Street 26th Floor Boston, MA 02110 Tel: (857) 449-2244 Email: info@karunatx.com
Protocol Version:	v1.0
Protocol Date:	01 JUL 2022

[redacted]

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia

Protocol Number: KAR-014

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] MD
Karuna Therapeutics

[redacted]
Date (DD-MMM-YYYY)

[redacted] MD, MBA
Karuna Therapeutics

[redacted]
Date (DD-MMM-YYYY)

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia

Protocol Number: KAR-014

Confidentiality and GCP/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol. I will conduct the study as described in compliance with this protocol and relevant ICH guidelines, including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of the study drug, 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 IEC/IRB, I will not modify this protocol without obtaining prior approval from Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed e-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 parties assisting me with the study are adequately qualified and informed about the Karuna Therapeutics study drug 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 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. An 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 authorities or government agencies as required.

Name: _____ Signature: _____

Title: _____

Institution: _____ _____

Date (DD-MMM-YYYY)

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1. PROTOCOL SYNOPSIS

Title of Study:	A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia
Protocol Number:	KAR-014
Investigators/Study Sites:	Approximately 25 study sites in the United States (US)
Phase of Development:	Phase 3b
Rationale:	To collect long-term (up to 3-years) safety data in patients with schizophrenia requiring a change in antipsychotic medication because their current medication(s) is not well tolerated and/or clinical symptoms are not well controlled. Patients will be switched to receive KarXT based on the investigator's judgment to optimize treatment for each individual patient in a naturalistic trial.
Objective(s):	**Primary Objectives:** • Assess the long-term safety and tolerability of KarXT, • Assess effectiveness, persistence, and durability of effect of KarXT through the Investigator Assessment Questionnaire (IAQ) and Clinical Global Impression – Severity of Illness (CGI-S) scale in patients with a diagnosis of schizophrenia. **Secondary Objectives:** To further assess: • Effectiveness using the Clinical Global Impression - Global Improvement (CGI-I) at week 2 through week 24. • Long-term safety and tolerability of KarXT. • Evaluation of total scores from multiple economic patient scales and caregiver burden throughout the study.
Endpoint(s):	**Primary Endpoints:** • The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) leading to discontinuation.

	• The primary efficacy endpoints are persistence and durability of effect of KarXT via IAQ and CGI-S scores at clinical visits throughout the study. **Secondary Safety Endpoints:** • Incidence of serious TEAEs (TESAEs). • Incidence of TEAEs of special interest. **Secondary Efficacy Endpoints:** • CGI-I scores at week 2 through week 24. • MSQ throughout the study. **Other Endpoints:** Safety: • Incidence of spontaneously reported TEAEs of special interest. • Incidence of spontaneously reported anticholinergic and procholinergic symptoms. • Change from baseline in clinical laboratory assessments (with emphasis on monitoring metabolic syndrome; waist circumference, blood pressure, fasting [preferred] blood glucose, high-density lipoprotein [HDL] cholesterol, and triglyceride levels). • Change from baseline in physical examinations, vital signs, body weight, and body mass index (BMI). • Barnes Akathisia Rating Scale (BARS). • Abnormal Involuntary Movement Scale (AIMS). Other: • Adherence to KarXT at different timepoints. • Time to treatment discontinuation for any reason. • Accountable Health Communities Health-Related Social Needs (AHC HRSN) screening tool. • Zarit Caregiver Burden Interview (ZBI-22). • EQ-5D-3L questionnaire. • Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) (1. digit symbol substitution test, 2. trail making test part B, and 3. category fluency).

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	• Single nucleotide polymorphisms (SNPs) related to schizophrenia subtypes and drug metabolism.
Study Design:	This is a Phase 3b, 3-year, open-label, multi-center study in which patients with schizophrenia requiring a change in antipsychotic medication because their current medication(s) is not well tolerated and/or clinical symptoms are not well controlled will be switched to receive KarXT based on the investigator's judgment for need of treatment optimization for the individual patient. The study's objectives are to assess the effectiveness, long-term safety, tolerability, and durability of effect of KarXT in patients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia. A suitable number of patients with schizophrenia (age 18 to 65 years) will be screened to enroll approximately 380 patients. To be eligible, patients will have experienced symptoms during screening that require treatment with an antipsychotic medication, demonstrated a previous response to antipsychotic medication (other than clozapine), and require a change of medication regimen because current medication is not well-tolerated and/or clinical symptoms are not well-controlled as judged by the investigator. The patients can be adequately managed in outpatient settings (do not require hospitalization) across approximately 25 study sites in the United States via a decentralized, site-centric model. **Screening Phase:** The screening phase will be up to 21 days (up to 7 day screening extension is permitted with medical monitor approval). **Baseline Visit:** Patients who meet the screening criteria will participate in a study baseline visit. It is preferred that all baseline assessments are completed in one visit. **Treatment Phase:** In this open-label study, all patients will receive KarXT for up to 3 years. All patients will start on a lead in dose of KarXT 50/20 mg (50 mg xanomeline/20 mg trospium) twice daily (BID) for 7 days (Day 1 to Day 7). A telephone check-in will occur on Day 7 to determine if the patient will titrate to the KarXt 100/20 mg BID dose for the 2nd week (Day 8 to Day 14) or remain on the lead in dose (50/20 mg BID). At Clinic Visit 2 (end of week 2/Day 14), the dose may be titrated upwards to either KarXT 100/20 mg BID if the patient had remained

	on the 50/20 mg BID dose through Day14, or the dose will increase to KarXT 125/30 mg BID if the patient was on the 100/20 mg BID through Day 14. If the patient continues to experience adverse events (AEs) from the 50/20 mg BID dose of such severity that they are not able to titrate up at Day 14 (end of week 2), the patient must be discontinued. If the patient experiences AEs from the 100/20 mg BID dose and is not able to titrate up and/or, in the opinion of the investigator, a longer period on the 100/20 mg BID dose is necessary, patients may continue this dose. Thus, all patients will attempt 100/20 mg BID dosing for at least 1 week. All patients who are increased to KarXT 125/30 mg BID or 100/20 mg BID, depending on tolerability, will have the option to return to KarXT 100/20 mg BID or 50/20 mg BID throughout the study. Re-escalation to 125/30 mg BID or 100/20 mg BID or re-titration in cases in which the patient has been off KarXT for a longer period of time (at least 7 days) is allowed and will require a discussion between the investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated per investigator discretion. In summary, upward titration is expected to optimize efficacy; however, if efficacious and better tolerated, any of the available doses could be used for maintenance. Unscheduled (UNS) visits, which can be conducted in-clinic or by telemedicine, may occur between required clinic visits as deemed necessary by the investigator to facilitate patient retention and ensure compliance with study objectives. (See Schedule of Assessments Table 1). **End of Study (EoS) Safety Follow-up Visit:** An EoS safety follow-up visit will be performed for all patients who have been dosed with KarXT. The EoS visit will take place 7 to 28 days after the last dose of KarXT for patients who complete the treatment phase (End of Treatment [EoT]) and for patients who choose to discontinue from the study early (early termination [ET]), at the discretion of the investigator, per sponsor request, or if the sponsor terminates the study.(See Schedule of Assessments Table 1).
Entry criteria:	**Inclusion Criteria:** Individuals must meet all the following criteria to be included in the study: 1. Patient is aged 18 to 65 years, inclusive, at screening. 2. Patient can provide informed consent. a. A signed informed consent form (ICF) must be provided before any study assessments are performed.

[redacted]

	b. Patient must be fluent (oral and written) in the language of the ICF to consent. 3. Patient has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association, 2013) criteria and has been in the continuous care of the clinician or practice for at least 6 months prior to entering the study. 4. The patient is dissatisfied with the side effects or general tolerability of their current antipsychotic medication, and for this reason, desires to change medications. Or, the patient is dissatisfied with the overall effectiveness or benefit of their current antipsychotic medication, and for this reason, desires to change medications. 5. The patient has not required psychiatric hospitalization, acute crisis intervention, or other increase in their level of care due to symptom exacerbation within 4 weeks of screening, and in the opinion of the investigator, is psychiatrically stable to be managed in an outpatient setting. 6. The patient has a CGI-S score of ≤4 (moderately severe or less) at screening and baseline visits. 7. For at least 30 days prior to screening, the patient must have been prescribed and have taken an oral antipsychotic medication daily at a dose and frequency consistent with the drug label. 8. The patient is willing and able, and in the opinion of the investigator it is clinically appropriate, to discontinue all antipsychotic medications prior to the baseline visit or to taper their current antipsychotic medication(s) with cross-over administration for up to two weeks (14 days) of dosing with KarXT (unless the patient is on olanzapine or quetiapine, which require discontinuation before KarXT initiation). In summary: a. Patients may washout antipsychotic medication during the screening phase (21 to 28 days prior to baseline) at the discretion of the investigator. Thus, the patient would have discontinued all antipsychotic medication prior to baseline. b. Or patient may down taper or continue down taper (washout) antipsychotic medication through the initial 2 weeks of KarXT dosing (excluding olanzapine or

quetiapine, which require discontinuation before KarXT initiation).

c. All patients must be washed out (discontinued) of all antipsychotic medication other than KarXT by end of week 2 (Day 14).

9. Patient has an identified, reliable caregiver/informant that is willing (by informed consent) and able to respond to the ZBI-22 caregiver burden scale at specified visits. The caregiver/informant must be consistent throughout the duration of the study. If the patient has been the patient of the investigator for ≥6 months and, in the opinion of the investigator, the patient is self-sufficient, then a caregiver/informant may not be necessary.
10. At the time of the Baseline Visit, the patient will have been off lithium therapy for at least 2 weeks.
11. If taking a long-acting injectable (LAI) antipsychotic, the patient has not received a dose of the medication for at least 12 weeks (24 weeks for INVEGA TRINZA®) before the Baseline Visit.
12. Patient BMI must be ≥18.0 and ≤45.0 kg/m^2.
13. Patient resides in a stable living situation and is anticipated to remain in a stable living situation for the duration of the study, in the opinion of the investigator.
14. If a woman of childbearing potential (WOCBP) or a man whose sexual partner(s) is a WOCBP, the patient must be willing and able to adhere to the contraception guidelines as defined in Section 12.1 Appendix 1.

Exclusion Criteria:

If any of the following exclusion criteria apply, a patient may not participate in the study:

1. Any primary DSM-5 disorder diagnosis other than schizophrenia within 12 months before screening. Exclusionary disorders include, but are not limited to, bipolar I or II disorder and schizoaffective disorder. Symptoms of mild mood dysphoria or anxiety are allowed, as long as these symptoms are not the primary focus of treatment.
2. The patient 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 has a positive urine

[redacted]

	drug screen (UDS) for a substance other than cannabis at screening and baseline. a. A patient 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. Patients with a positive UDS for cannabis are permitted to enroll in the study provided that the patient's pattern of use is not indicative of a substance use disorder. 3. The patient has a history of or presence of a 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, is likely to jeopardize the safety of the patient or the validity of the study results. 4. Patient has human immunodeficiency virus (HIV) unless they are considered stable for 12 months prior to screening on highly active antiretroviral therapy (HAART) therapy (CD4 >500 and undetectable viral load); cirrhosis; biliary duct abnormalities; hepatobiliary carcinoma; and/or active hepatic viral infections based on either medical history or liver function test results. 5. Patient has a history of or is at high risk of urinary retention, gastric retention, or narrow-angle glaucoma. 6. Patient has a history of irritable bowel syndrome (with or without constipation) or constipation requiring treatment for more than 30 days within the last 6 months. 7. Patient is at risk for suicidal behavior during the study as determined by the investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS) as confirmed by the following: a. Patient answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or patient answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Non-suicidal self-injurious behavior is not exclusionary.

	8. Patient is at risk of violent or destructive behavior or serious harm to others, as determined by the investigator's clinical assessment. 9. Clinically significant abnormal finding on the physical examination, medical history, electrocardiogram (ECG), or clinical laboratory results at screening. (Aspartate aminotransferase (AST) or alanine transaminase (ALT) >2x upper limit of normal (ULN) or total bilirubin (Tbili) >2x ULN (unless due to suspected Gilbert's), hemoglobin <10 g.dL, white blood cell (WBC) <3 K, absolute neutrophil count (ANC) <1000, platelets <100 K, QTc >450 msec in males and >470 msec in females.) 10. Currently and within 2 weeks before the Baseline Visit, patients cannot be receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, Depakote), tricyclic antidepressants (e.g., imipramine, desipramine), centrally active anticholinergics (benztropine, trihexyphenidyl, diphenhydramine), or any other psychoactive medications other than daily antipsychotic maintenance therapy. a. As needed (PRN) anxiolytics and/or sleep aids are permitted (e.g., lorazepam, zolpidem). b. Selective serotonin reuptake inhibitors (SSRI's)/ serotonin and norepinephrine reuptake inhibitors (SNRIs) taken at stable dose for at least 4 weeks before screening and that are anticipated to be continued at the same dose throughout the study are permitted. c. Benztropine (Cogentin) or similar medications used for extrapyramidal symptoms (EPS) will need to be tapered down slowly as withdrawal symptoms are likely. The suggested approach is a maximum 50% reduction per week until a 0.25 mg dose is reached. d. PRN second generation antihistamines, e.g., fexofenadine, loratadine, and cetirizine (that do not readily cross the blood-brain barrier [BBB]), could be used after the first month of the study for temporary symptom management of allergies. 11. Patient has a history of treatment resistance to schizophrenia medications defined as: a. Failure to respond to 3 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.

	12. Patient is pregnant, lactating, or less than 3 months postpartum. 13. Patient has any other medical, psychiatric, or social condition that, in the opinion of the investigator, is likely to unfavorably alter the risk-benefit of patient participation, to interfere with protocol compliance, or to confound safety or efficacy assessments. 14. Patient has tested positive for coronavirus disease 2019 (COVID-19) within 2 weeks of screening and/or baseline or patients who have prolonged symptoms of past infection, long COVID, that, in the opinion of the investigator, may interfere with the interpretation of safety during the study. 15. Patient with extreme concerns relating to global pandemics, such as COVID-19, that precludes study participation. 16. Patient is currently or recently (within 4 weeks of screening) involuntary hospitalization or incarceration. 17. Patient participated in another clinical study in which they received an experimental or investigational drug agent within 30 days prior to screening.
Planned Sample Size:	Approximately 380 patients (age 18 to 65 years) are planned to be enrolled in this study.
Investigational Therapy:	• Lead in fixed dose KarXT 50/20 mg BID (50 mg xanomeline/20 mg trospium) oral (Day 1 to Day 7) that can be extended beyond week 1. • Fixed dose KarXT 100/20 mg BID (100 mg xanomeline/20 mg trospium) oral (Day 8 to Day 14) that can be extended throughout the study. • Fixed dose KarXT 125/30 mg BID (125 mg xanomeline/30 mg trospium) oral (Day 15 to 3 years) if tolerated or deemed appropriate beginning no earlier than Day 15. Throughout the study, the investigator will have the flexibility of managing (up or down-titrating) doses in accordance with their clinical judgement for best patient outcomes. If patients cannot tolerate KarXT 50/20 mg BID dose by the end of week 2 (Day 14) as to allow for up-titration to 100/20 mg BID, they must be early terminated from the study. Patients who cannot maintain 65% adherence to the study drug over any 8 week period throughout the study, unless there is

	hospitalization involved, will be discontinued from the study. The adherence assessments will be based on pill counts, patient recall, and caregiver report, if applicable.
Reference Therapy:	Not applicable.
Treatment Duration:	Treatment duration is approximately 3 years.
Safety Assessments:	• Adverse Events • Spontaneously reported TEAEs of special interest • Spontaneously reported anticholinergic and procholinergic symptoms • Clinical laboratory assessments (with an emphasis on monitoring metabolic syndrome; waist circumference, blood pressure, fasting (preferred) blood glucose, HDL cholesterol, and triglyceride levels) • Physical examinations, vital signs, body weight, and BMI • BARS • AIMS
Efficacy Assessments:	• CGI-S scores • IAQ • CGI-I scores • MSQ
Other Assessments:	• AHC HRSN screening tool to be completed by the patient, caregiver, or patient with help from caregiver • ZBI-22 • Adherence to KarXT at different timepoints • EQ-5D-3L questionnaire • B-CATS (1. digit symbol substitution test, 2. trail making test part B, and 3. category fluency) • SNPs related to schizophrenia subtypes and drug metabolism
Statistical Methods and Planned Analyses:	**Study Populations:** **Enrolled population:** All patients who give informed consent for KAR-014 will be included in the enrolled population.

[redacted]

	Safety population: All patients who receive at least 1 dose of KarXT in study KAR-014 will be included in the safety population and will be used in the safety analyses. **Modified intent-to-treat (mITT) population:** All patients who are enrolled and received KarXT through week 8, will be included in the mITT population and will be used in the efficacy and other analyses. 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 patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

Table 1: Schedule of Assessments

Screening and Baseline

DAY	-21 to -1	0
VISIT	Screening[1]	Baseline Visit 1[2]
TYPE OF VISIT	C	C
PROCEDURE		
Written informed consent[3]	X	
Collect demographic information (date of birth, age, sex, race, ethnicity)	X	
Patient eligibility verification process	X	
Medical, psychiatric, and medication history	X	
Urine pregnancy test (WOCBP only)[4]	X	X
Urine drugs of abuse and alcohol testing[5]	X	X
Review of inclusion/exclusion criteria	X	X
Height, body weight, BMI, waist circumference[6]	X	X
Complete Physical Examination[7]	X	
Targeted Physical Examination[8]		X
Spontaneous AEs[9]		X
Review of concomitant medications	X	X
Vital signs: BP and HR[10]	X	X
Resting ECG (12-lead)[11]	X	X
Blood samples for clinical laboratory tests[12]	X	X
Blood sample for viral serology[13]	X	
Blood sample for DNA testing		X

[redacted]

COVID-19 Rapid Test		X
C-SSRS[14]	X	X
CGI-S	X	X
IAQ		X
MSQ	X	
AHC HRSN[15]		X
EQ-5D-3L		X
AIMS		X
BARS		X
ZBI-22		X
Brief Cognitive Assessment Tool for Schizophrenia		X
KarXT dispensed[16]		X

Abbreviations: AE = adverse event; AHC HRSN = Accountable Health Communities Health-Related Social Needs; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BP = blood pressure; C= Clinic visit; CGI-I = Clinical Global Impression – Global Improvement; CGI-S = Clinical Global Impression–Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-3L = Euroqol-5D-3L; HBV= hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; IAQ= Investigator Assessment Questionnaire; MSQ = Medication Satisfaction Questionnaire; NIDA-5 = National Institute on Drug Abuse-5; PI = principal investigator; QTcF = QT interval corrected by Fridericia; WOCBP = women of childbearing potential; ZBI-22 = Zarit Caregiver Burden Interview.

1. Screening period of 21 days (up to 28 days). 7-day extension permitted with medical monitor approval.
2. Baseline visit may be up to 7 days. Preference is for baseline visit to be completed in one (1) day.
3. Informed Consent to be obtained from patient and patient's caregiver, if applicable. See inclusion criteria 9.
4. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of a positive urine pregnancy test result, a serum sample should be sent to the central laboratory for confirmation of the result.
5. A 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, except for cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
6. Height is recorded at screening only.
7. 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.

[redacted]

8. A targeted physical examination includes at a minimum body temperature, a check of general appearance, examination of organ systems that are relevant to the investigator based on review of the patient's reported AEs, review of systems, and concomitant medication use. These also include symptom-driven physical examinations, which will be performed as clinically indicated at any study visit.
9. AEs as reported by patients or observed by clinical staff and occurs after informed consent.
10. Vital signs measurements should be taken at scheduled in-clinic visits, which include systolic and diastolic BP and HR. Per PI discretion, orthostatic vital signs may be assessed, but are not mandatory.
11. ECG should be obtained before blood collection 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.
12. Refer to Section 8.2.12 (Table 2) 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.
13. All patients 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 patient tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.
14. C-SSRS past 12-months version will be utilized at screening.
15. AHC HRSN to be self-administered (preferred) or administered by site staff. Form of administration to be consistent throughout the study.
16. See Pharmacy Manual for dispensing details. All patients will start on a lead-in dose of KarXT 50/20 mg BID beginning on Day 1/week 0. At Baseline, dispense 2 week blister pack of KarXT 50/20 mg BID and 1 week blister pack of KarXT 100/20 mg BID. A telephone check-in at Day 7 (end of week 1) will determine if patients will titrate to the 100/20 mg BID dose beginning Day 8 through Day 14/end of week 2 or remain on the lead in dose 50/20 mg BID. At Visit 2 (Day 14), dosing will be titrated upwards to KarXT 100/20 mg BID or 125/30 mg BID (depending on previous week's dose) unless the patient is experiencing AEs or, in the opinion of the investigator, a longer period on 100/20 mg BID is necessary, they may continue that dose. If the patient is not able to titrate up from 50/20 mg BID to 100/20 mg BID at Day 14, the patient must be discontinued.

Week 0/Day 1 through Week 48/Day 336 (Year 1)

Day **All visit windows ± 2d unless otherwise indicated**	**1**	**7 (+/- 1d)**	**14 (+/-1d)**	**28**	**42**	**56**	**84**	**112**	**140**	**168**	**224**	**280**	**336**
End of WEEK	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48**
VISIT	**n/a**	**n/a**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
TYPE OF VISIT	**n/a**	**T**	**C**	**C**	**T**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
PROCEDURE													
Patient self-administration of KarXT BID[1]	X												
Determination of dose titration[2]		X	X	X									
Dispense KarXT[3]			X	X		X	X	X	X	X	X	X	X
Spontaneous AEs[4]		X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[5]		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[6]			X	X		X	X	X	X	X	X	X	X
Resting ECG (12-lead)[7]				X			X			X			X
Body weight, BMI, waist circumference			X	X		X	X	X	X	X	X	X	X
Complete physical exam[8]							X			X			X
AHC HRSN[9]										X			X
Blood samples for clinical laboratory tests[10]				X		X		X		X	X		X
Urine pregnancy test (WOCBP only)[11]			X	X		X	X	X	X	X	X	X	X
Urine drugs of abuse & alcohol[12]				X		X		X			X		X

[redacted]

C-SSRS[13]			X	X		X	X	X	X	X	X	X	X
CGI-I			X	X		X	X	X	X	X			
CGI-S			X	X		X	X	X	X	X	X	X	X
IAQ				X		X	X	X	X	X	X	X	X
MSQ						X		X		X			X
EQ-5D-3L							X			X			X
BARS				X		X	X			X			X
AIMS							X			X			X
ZBI-22[14]										X			X
Brief Cognitive Assessment Tool for Schizophrenia							X			X			X

Abbreviations: AE = adverse event; AHC HRSN = Accountable Health Communities Health-Related Social Needs; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BID = twice daily; BMI = body mass index; BP = blood pressure; C= Clinic visit; CGI-I = Clinical Global Impression – Global Improvement; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EQ-5D-3L = Euroqol-5D-3L; HR = heart rate; IAQ= Investigator Assessment Questionnaire; MSQ = Medication Satisfaction Questionnaire; NIDA-5 = National Institute on Drug Abuse-5; PI = principal investigator; QTcF = QT interval corrected by Fridericia; T = Telephone Call; WOCBP = women of childbearing potential; ZBI-22 = Zarit Caregiver Burden Interview.

1. The first dose of study drug is taken at home on the morning of Day 1. Patients will continue self-administration of KarXT BID throughout the treatment period of the study (at the appropriate dose level). Study drug should preferably be taken on an empty stomach, i.e., at least 1 hour before a meal or at least 2 hours after a meal.
2. See Pharmacy Manual for dispensing details. All patients will start on a lead-in dose of KarXT 50/20 mg BID beginning on Day 1/week 0. At Baseline, dispense 2 week blister pack of KarXT 50/20 mg BID and 1 week blister pack of KarXT 100/20 mg BID. A telephone check-in at Day 7 (end of week 1) will determine if patients will titrate to the 100/20 mg BID dose beginning Day 8 through Day 14/end of week 2 or remain on the lead in dose 50/20 mg BID. At Visit 2 (Day 14), dosing will be titrated upwards to KarXT 100/20 mg BID or 125/30 mg BID (depending on previous week's dose) unless the patient is experiencing AEs or, in the opinion of the investigator, a longer period on 100/20 mg BID is necessary, they may continue that dose. If the patient is not able to titrate up from 50/20 mg BID to 100/20 mg BID at Day 14, the patient must be discontinued.
3. At Visit 2 (Day 14/end of week 2), dispense a 2 week blister pack supply of KarXT. Beginning at Visit 3 (Day 28/end of week 4), dispense a 1 month bottle supply of KarXT at each clinic visit through week 24. Beginning at week 24, dispense a 2 month bottle supply of KarXT through week 152.
4. AEs as reported by patients or observed by clinical staff are to be collected after informed consent. For telephone call visits, spontaneous AEs may be collected by telemedicine.
5. Concomitant medications must be reviewed at every visit, including telephone visits (telemedicine).

6. Vital sign measurements should be taken at scheduled in-clinic visits, which include systolic and diastolic BP and HR. Per PI discretion, orthostatic vital signs may be assessed, but are not mandatory.
7. ECG should be obtained 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.
8. 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.
9. AHC HRSN to be self-administered (preferred) or administered by site staff. Form of administration to be consistent throughout the study.
10. Refer to Section 8.2.12 (Table 2) 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.
11. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of a positive urine pregnancy test result, a serum sample should be sent to the central laboratory for confirmation of the result.
12. A 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 exceptions of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
13. C-SSRS "since last visit" version will be conducted at all scheduled study clinic visits (other than screening). At an Unscheduled visit, the C-SSRS should be performed to monitor patients for suicidality.
14. ZBI-22 to be completed by a reliable caregiver/informant, if applicable.

Week 56/Day 392 through Week 152/Day 1064 (Year 2-3)

Day All visit windows ± 2d unless otherwise indicated	392	448	504	560	616	672	728	784	840	896	952	1008	1064
End of WEEK	**56**	**64**	**72**	**80**	**88**	**96**	**104**	**112**	**120**	**128**	**136**	**144**	**152**
VISIT	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
TYPE OF VISIT	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
PROCEDURE													
Dispense KarXT[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Spontaneous AEs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Resting ECG (12-lead)[5]			X			X			X			X	
Body weight, BMI, waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam[6]						X						X	
AHC HRSN[7]						X							
Blood samples for clinical laboratory tests[8]	X		X			X			X			X	
Urine pregnancy test (WOCBP only)[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drugs of abuse & ETOH [10]	X		X		X		X		X		X		X
C-SSRS[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X
IAQ	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

MSQ			X			X			X			X	
EQ-5D-3L			X			X			X			X	
BARS			X			X			X			X	
AIMS			X			X			X			X	
ZBI-22[12]			X			X			X			X	
Brief Cognitive Assessment Tool for Schizophrenia			X			X			X			X	

Abbreviations: AE = adverse event; AHC HRSN = Accountable Health Communities Health-Related Social Needs; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BID = twice daily; BMI = body mass index; BP = blood pressure; C= Clinic visit; CGI-I = Clinical Global Impression – Global Improvement; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EQ-5D-3L = Euroqol-5D-3L; HR = heart rate; IAQ= Investigator Assessment Questionnaire; MSQ = Medication Satisfaction Questionnaire; NIDA-5 = National Institute on Drug Abuse-5; PI = principal investigator; QTcF = QT interval corrected by Fridericia; T = Telephone Call; WOCBP = women of childbearing potential; ZBI-22 = Zarit Caregiver Burden Interview.

1. See Pharmacy Manual for dispensing details. All patients will start on a lead-in dose of KarXT 50/20 mg BID beginning on Day 1/week 0. At Baseline, dispense 2 week blister pack of KarXT 50/20 mg BID and 1 week blister pack of KarXT 100/20 mg BID. A telephone check-in at Day 7 (end of week 1) will determine if patients will titrate to the 100/20 mg BID dose beginning Day 8 through Day 14/end of week 2 or remain on the lead in dose 50/20 mg BID. At Visit 2 (Day 14), dosing will be titrated upwards to KarXT 100/20 mg BID or 125/30 mg BID (depending on previous week's dose) unless the patient is experiencing AEs or, in the opinion of the investigator, a longer period on 100/20 mg BID is necessary, they may continue that dose. If the patient is not able to titrate up from 50/20 mg BID to 100/20 BID at Day 14, the patient must be discontinued. At Visit 2 (Day 14/end of week 2), dispense a 2 week blister pack supply of KarXT. Beginning at Visit 3 (Day 28/end of week 4), dispense a 1 month bottle supply of KarXT at each clinic visit through week 24. Beginning at week 24, dispense a 2 month bottle supply of KarXT through week 152.
2. AEs as reported by patients or observed by clinical staff are to be collected after informed consent. For telephone call visits, spontaneous AEs may be collected by telemedicine.
3. Concomitant medications must be reviewed at every visit including telephone visits (telemedicine).
4. Vital sign measurements should be taken at scheduled in-clinic visits. Includes systolic and diastolic BP and HR. Per PI discretion, orthostatic vital signs may be assessed, but are not mandatory.
5. ECG should be obtained 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.
6. 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.
7. AHC HRSN to be self-administered (preferred) or administered by site staff. Form of administration to be consistent throughout the study.
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9. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of a positive urine pregnancy test result, a serum sample should be sent to the central laboratory for confirmation of the result.

[redacted]

10. A 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 exceptions of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
11. C-SSRS "since last visit" version will be conducted at all scheduled study clinic visits (other than screening). At an Unscheduled visit, the C-SSRS should be performed to monitor patients for suicidality.
12. ZBI-22 to be completed by a reliable caregiver/informant if applicable.

[redacted]

Week 156/Day 1092 (EoT) through Week 157/Day 1099 (EoS)/Early Termination (ET)/Unscheduled Visit (UNS)

Day All visit windows ± 2d unless otherwise indicated	1092	1099 (+7 to 28d)		
End of WEEK	**156**	**157-160**	**n/a**	**n/a**
VISIT	**26/EoT**	**27/EoS[1]**	**ET**	**UNS[2]**
TYPE OF VISIT	**C**	**C**	**C**	**C**
PROCEDURE				
Record final dose of KarXT[3]	X		X	
Spontaneous AEs[4]	X	X	X	X
Review of concomitant medications	X	X	X	X
Vital signs: BP and HR[5]	X	X	X	*X*
Resting ECG (12-lead)[6]	X		X	
Body weight, BMI, waist circumference	X	X	X	*X*
Complete physical exam[7]	X		X	
AHC HRSN[8]	X			
Blood samples for clinical laboratory tests[9]	X		X	
Urine pregnancy test (WOCBP only[10])	X		X	*X*
Urine drugs of abuse and alcohol testing[11]				*X*
C-SSRS[12]	X		X	*X*
BARS	X		X	
CGI-S	X		X	*X*
Brief Cognitive Assessment Tool for Schizophrenia	X			

[redacted]

IAQ	X		X	*X*
MSQ	X			
EQ-5D-3L	X			
AIMS	X		X	

Abbreviations: AE = adverse event; AHC HRSN = Accountable Health Communities Health-Related Social Needs; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BP = blood pressure; C= Clinic visit; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EoS = end of study; EoT = end of treatment; ET = early termination; EQ-5D-3L = Euroqol-5D-3L; HR = heart rate; MSQ = Medication Satisfaction Questionnaire; NIDA-5 = National Institute on Drug Abuse-5; PI = principal investigator; QTcF = QT interval corrected by Fridericia; UNS = unscheduled visit; WOCBP = women of childbearing potential.

1. EoS to be completed 7 to 28 days after last dose of KarXT (following EoT or ET Visits).
2. Unscheduled Visits (UNS) may be conducted as needed via telemedicine or in clinic to facilitate retention and ensure compliance with study objectives. Review of AEs and concomitant medications are required. Assessments (with an italic *X*) should be performed if an in clinic UNS visit occurs. All other assessments to be performed per PI discretion.
3. Patients will self-administer the morning dose of KarXT on Day 1092. Patients will self-report their last administered dose during the EoT visit (or ET visit). At the EoT/ET visit, patients will return all study drug. Patients may receive only 1 dose of KarXT on Day 1092/EoT.
4. AEs as reported by patients or observed by clinical staff and occurs after informed consent.
5. Vital signs measurements should be taken at scheduled in-clinic visits, which include systolic and diastolic BP and HR. Per PI discretion, orthostatic vital signs may be assessed, but are not mandatory.
6. ECG should be obtained 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.
7. 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.
8. AHC HRSN to be self-administered (preferred) or administered by site staff. Form of administration to be consistent throughout the study.
9. Refer to Section 8.2.12 (Table 2) 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.
10. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of a positive urine pregnancy test result, a serum sample should be sent to the central laboratory for confirmation of the result.
11. A 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 exceptions of cannabinoids or marijuana, a sample should be sent to the central laboratory for confirmation of the result.
12. C-SSRS “since last visit” version will be conducted at all scheduled study clinic visits (other than screening). At an Unscheduled visit, the C-SSRS should be performed to monitor patients for suicidality.

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TABLE OF CONTENTS

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LIST OF TABLES

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AHC HRSN	Accountable Health Communities Health-Related Social Needs
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APD	antipsychotic drug
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BBB	blood-brain barrier
B-CAT	Brief Cognitive Assessment Tool for Schizophrenia
BID	2 times a day
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression–Severity
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
D_2	dopamine receptor 2
DILI	drug induced liver injury
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
EoS	End of Study
EoT	End of Treatment
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
HPMC	hydroxypropyl methylcellulose
HR	heart rate
IAQ	Investigator Assessment Questionnaire
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
Karuna	Karuna Therapeutics
KarXT	combination of the muscarinic agonist xanomeline and the peripheral anticholinergic agent trospium
LAI	long-acting injectable
LFT	liver function test
M1, M4	muscarinic receptor subtypes
MCC	microcrystalline cellulose
mITT	modified intent-to-treat
MSQ	Medication Satisfaction Questionnaire
NF	National Formulary
OLE	open-label extension
PANSS	Positive and Negative Syndrome Scale

[redacted]

Abbreviation	Definition
PK	pharmacokinetic(s)
PRN	as needed
SAE	serious adverse event
SAP	statistical analysis plan
SNP	single nucleotide polymorphisms
SNRI	serotonin and norepinephrine reuptake inhibitors
SoA	schedule of assessments
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
Tbili	total bilirubin
TD	tardive dyskinesia
TDD	total daily dose
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UDS	urine drug screen
ULN	upper limit of normal
UNS	unscheduled visit
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WOCBP	women of childbearing potential
ZBI-22	Zarit Caregiver Burden Interview

3. INTRODUCTION

3.1. Study Rationale

Schizophrenia is a long-term mental disorder that requires chronic therapy. There is a significant unmet medical need in the treatment of patients with schizophrenia. Many patients with schizophrenia have an inadequate response to antipsychotic therapy and continue to be symptomatic, including positive symptoms, such as hallucinations, delusions, and other disabling psychotic symptoms, as well as negative and cognitive symptoms. Interventions to treat inadequate responders include dosing above the high end of the therapeutic range, switching to another first-line antipsychotic, combining the current antipsychotic with another class of psychotropic medication (e.g., mood stabilizer) in the hopes of augmenting the response to the current antipsychotic, or switching to clozapine if patients are treatment-resistant.

All antipsychotics currently approved for the treatment of schizophrenia have dopamine receptor (D_2) affinities that mediate antipsychotic activity. In the Phase 2 study (KAR-004), KarXT, a M_1/M_4 muscarinic agonist, demonstrated statistically significant results on the Positive and Negative Syndrome Scale (PANSS) positive subscale, the PANSS total score, and the PANSS negative subscale (Brannan et al., 2021). KarXT is a combination of the muscarinic agonist xanomeline and the peripheral anticholinergic agent trospium. Given that KarXT has no direct dopaminergic activity and differs from the D_2 antagonists risperidone, paliperidone, quetiapine (IR/XR), ziprasidone, and lurasidone and the D_2 partial agonist aripiprazole, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients with an inadequate response to risperidone, paliperidone, aripiprazole, or their long-acting injectables (LAIs); quetiapine (IR/XR); ziprasidone; or lurasidone.

The proposed study, KAR-014, is an open-label, multi-center, long-term study to evaluate the effectiveness, long-term safety, tolerability, and durability of effect of KarXT in patients with a Diagnostic and Statistical Manual–Fifth Edition (DSM-5; American Psychiatric Association, 2013) diagnosis of schizophrenia that require a change in their antipsychotic medication because their current medication(s) is not well tolerated and/or clinical symptoms are not well controlled.

3.2. Background

3.2.1. Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior that 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 (Patel et al., 2014). The prevalence of schizophrenia is between 0.6% and 1.9% in the United States (US) population (van Os and Kapur, 2009). Moreover, a claims analysis estimated that the annual prevalence of diagnosed schizophrenia in the US is 5.1 per 1000 lives (Wu et al., 2006). It is found equally in males and females, with males usually having an earlier onset of symptoms (Crismon et al., 2014).

The mainstay for treating schizophrenia is antipsychotic drugs (APDs) (Green et al., 2004). All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in

the brain. First generation APDs, particularly high D_2 potency therapies, such as haloperidol, were marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). They consequently have limited use today. The second-generation agents, including risperidone, paliperidone, aripiprazole, olanzapine, quetiapine (IR/XR), lurasidone, and lumateperone, tend to have lower levels of EPS or TD. They are currently the most commonly prescribed APD class; however, the second-generation drugs also have problematic side effects, including significant weight gain, metabolic disturbances, sedation, and akathisia (Huhn et al., 2019; Leucht et al., 2013; Lieberman et al., 2005). These side effects have contributed to poor medication adherence, resulting in frequent relapses and hospitalizations (Emsley et al., 2013; Kahn et al., 2015). Thus, there is a need for new 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 (Sellin et al., 2008; Wess et al., 2007). There are 5 subtypes of muscarinic receptors (M_1-M_5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to the agonism of M_1 and M_4 receptors in the central nervous system (CNS) (Mirza et al., 2003). However, compounds that agonize M_1 and M_4 receptors are often not specific enough to not also agonize M_2 and M_3 receptors outside of the CNS, 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, such as nausea, vomiting, diarrhea, sweating, and excess salivation.

3.2.2. KarXT

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but it preferentially stimulates M_1 and M_4 receptors. KarXT's potential therapeutic effects are thought to be mediated through its binding to M_1 and M_4 receptors in the CNS. A recent study reported that xanomeline is a potent M_4 muscarinic agonist in vivo as measured by various second messenger assays (Thorn et al., 2019). Xanomeline also rapidly enters the brain, achieving a brain-to-plasma ratio greater than 10, making it an attractive CNS drug candidate (Farde et al., 1996). 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 provided evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter, outpatient trial in AD (N = 343), 3 dose levels of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks. 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 placebo was found. In a completer analysis, cognitive improvement was also found, suggesting that longer treatment intervals may be necessary for cognitive enhancement (Bodick et al., 1997a; Bodick et al., 1997b). In a subsequent small, double-blind, placebo controlled inpatient trial in 20 treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to

placebo. Improvement in both negative symptoms and cognitive impairment was observed (Shekhar et al., 2008).

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

The procholinergic AEs associated with xanomeline appear to be mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting with peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist that binds to and antagonizes all five muscarinic receptor subtypes. Several studies in humans demonstrated that trospium does not appreciably cross the blood-brain barrier (BBB), which is consistent with the drug's quaternary ammonium structure (Scheife and Takeda, 2005).

Karuna Therapeutics (Karuna) hypothesized that adding trospium to xanomeline will mitigate peripheral procholinergic side effects, and thus, provide a strategy to allow xanomeline to be used to stimulate brain muscarinic receptors with a decreased side effect burden. Xanomeline is currently not approved or marketed in any country. Trospium has been approved for over 10 years by the Food and Drug Administration (FDA) and by European authorities to treat overactive bladder, and it is generally well tolerated (Staskin et al., 2010). The most frequently reported AEs for trospium are dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. The package insert for trospium chloride tablets for oral use can be found in the KarXT Investigator's Brochure (IB) for additional information.

KarXT significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after inpatient treatment for 5 weeks (Study KAR-004; Brannan et al., 2021). KarXT also showed an acceptable safety profile; the most common treatment-emergent adverse events (TEAEs) were constipation, nausea, dry mouth, dyspepsia, and vomiting (for completed clinical studies, see Section 3.2.3).

3.2.3. Clinical Studies

To date, across 19 completed clinical studies (conducted by Eli Lilly or Karuna) with durations up to 3 years of exposure, more than 840 subjects have been exposed to xanomeline tartrate (oral formulation; either alone, in combination with trospium, or as the combination drug KarXT). In completed studies, significant improvements in cognition and reduced psychotic symptoms were observed.

The clinical experience to date with KarXT includes 4 completed Phase 1 studies in healthy volunteers (KAR-001, KAR-002, KAR-003 and KAR-020) and 1 completed Phase 2 study (KAR-004) in adult patients with DSM-5 schizophrenia (Refer to KarXT IB for details). Multiple other Phase 1 and Phase 3 studies are ongoing.

[redacted]

3.3. Risk/Benefit Assessment

The risks and benefits of KarXT in humans are not fully known. The Phase 2 study, KAR-004, showed that KarXT monotherapy had statistically significant efficacy compared to placebo with an acceptable safety profile that appeared unique compared to available APDs. In this 5-week trial, treatment with KarXT was not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these AEs pose a significant risk with other APD treatments for schizophrenia, which can lead to discontinuation of treatment and to significant morbidity.

3.3.1. Known Potential Risks

The most common risks are procholinergic-related effects (e.g., nausea, vomiting, tremor, excess salivation, excess sweating, and diarrhea) and anticholinergic symptoms (e.g., dry mouth, blurred vision, dry eyes, constipation, urinary retention, etc.). The frequently observed AEs increased liver function test (LFT), tachycardia, fatigue, and chills have also been reported. In addition, patients treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium appears to decrease the peripheral cholinergic effect of xanomeline, creating a better tolerated therapy.

3.3.2. Known Potential Benefits

Patients who are inadequate responders to their current APD may benefit from switching from their current therapy to KarXT.

3.3.3. Assessment of Potential Risks and Benefits

KarXT represents a novel approach to the treatment of patients with schizophrenia that could provide an important and meaningful alternative to currently available therapies. The efficacy of KarXT, coupled with its apparently acceptable tolerability and AE profile, will potentially render significant benefits when used as an adjunctive therapy to currently prescribed APDs. Multiple study design elements are in place to minimize the risk to the study participants. The Sponsor believes the risk-benefit ratio is favorable, and continuous risk-benefit assessments will be conducted throughout the trial.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objectives of the study are to assess the long-term safety and tolerability of KarXT as well as its effectiveness, persistence, and durability of effect through the Investigator Assessment Questionnaire (IAQ) and Clinical Global Impression – Severity of Illness (CGI-S) scale in patients with a diagnosis of schizophrenia.

4.1.2. Secondary Objectives

The secondary objectives of the study are to further assess:

- Effectiveness using the Clinical Global Impression - Global Improvement (CGI-I) at week 2 through week 24.
- Long-term safety and tolerability of KarXT.
- Evaluation of total scores from multiple economic patient scales and caregiver burden throughout the study.

4.2. Study Endpoints

4.2.1. Primary Endpoints

- The primary safety endpoint is the incident of TEAEs leading to discontinuation.
- The primary efficacy endpoints are persistence and durability of effect of KarXT via IAQ and CGI-S scores at clinical visits throughout the study.

4.2.2. Secondary Safety Endpoints

The secondary safety endpoints are as follows:

- Incidence of serious TEAEs (TESAEs).
- Incidence of TEAEs of special interest.

4.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- CGI-I scores at week 2 through 24 weeks.
- MSQ throughout the study.

4.2.4. Other Safety Endpoints

The other safety endpoints are:

- Incidence of spontaneously reported TEAEs of special interest.

[redacted]

- Incidence of spontaneously reported anticholinergic and procholinergic symptoms.
- Change from baseline in clinical laboratory assessments (with emphasis on monitoring metabolic syndrome; waist circumference, blood pressure, fasting [preferred] blood glucose, high-density lipoprotein [HDL] cholesterol, and triglyceride levels).
- Change from baseline in physical examinations, vital signs, body weight and body mass index (BMI).
- Barnes Akathisia Rating Scale (BARS).
- Abnormal Involuntary Movement Scale (AIMS).

4.2.5. Other Endpoints

- Adherence to KarXT at different timepoints.
- Time to treatment discontinuation for any reason.
- Accountable Health Communities Health-Related Social Needs (AHC HRSN) screening tool.
- ZBI-22.
- EQ-5D-3L questionnaire.
- Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) (1. digit symbol substitution test, 2. trail making test part B, and 3. category fluency).
- Single nucleotide polymorphisms (SNPs) related to schizophrenia subtypes and drug metabolism.

5. STUDY DESIGN

5.1. Description of Overall Study Design

This is a Phase 3b, 3-year, open-label, multi-center study in which patients with schizophrenia requiring a change in antipsychotic medication because their current medication(s) is not well tolerated and/or clinical symptoms are not well controlled will be switched to receive KarXT based on the investigator's judgment for need of treatment optimization for the individual patient. The study's objectives are to assess the effectiveness, long-term safety, tolerability, and durability of effect of KarXT in patients with DSM-5 diagnosis of schizophrenia.

5.1.1. Screening

The study consists of a screening phase of up to 21 days (up to a 7 day screening extension is permitted with medical monitor approval). (See Table 1)

5.1.2. Baseline

Patients who meet the screening criteria will participate in a study baseline visit. It is preferred that all baseline assessments are completed in one (1) visit; however, they may be done over 7 days. (See Table 1)

5.1.3. Open-Label Treatment Phase

The open-label treatment phase is 3 years (156 weeks). (See Table 1)

5.1.3.1. Dosing with KarXT

The dosing of the study medication (KarXT) is described below. KarXT is expressed as mg xanomeline as the tartrate salt/mg trospium chloride.

- Week 1 (Days 1 to 7) – KarXT 50/20 mg, 2 times a day (BID).
- Week 2 (Days 8 to 14) – KarXT 100/20 mg, BID or remain on 50/20 mg, BID.
- Week 3 (Days 15 to 21) – KarXT 125/30 mg, BID or 100/20 mg, BID.
- Weeks 4 to 156 (Days 28 to 1092) – Flexible dosing based on tolerability and clinical response to KarXT 50/20 mg, KarXT 100/20 mg, and KarXT 125/30 mg doses, BID.

The dosing of KarXT is flexible; however, in the absence of tolerability issues, patients should have their dose increased if efficacy has not been observed (based on the clinical judgment of the investigator). The expectation is that most patients will respond to KarXT 100/20 mg, BID or KarXT 125/30 mg, BID.

Below is a more detailed breakdown of the early dosing and titration recommendations.

All patients will start on a lead in dose of KarXT 50/20 mg (50 mg xanomeline/20 mg trospium) BID for 7 days (Day 1 to Day 7). A telephone check-in will occur on Day 7 to determine if the patient will titrate to the KarXT 100/20 mg BID dose for the 2nd week (Day 8 to Day 14) or remain on the lead in dose (50/20 mg BID). At Clinic Visit 2 (end of week 2/Day 14), the dose may be titrated upwards to either KarXT 100/20 mg BID if the patient had remained on the

50/20 mg dose through Day14, or the dose will increase to KarXT 125/30 mg BID if the patient was on the 100/20 mg through Day 14. If the patient continues to experience AEs from the 50/20 mg BID dose of such severity that they are not able to titrate up at Day 14 (end of week 2), the patient must be discontinued. If the patient experiences AEs from the 100/20 mg BID dose and is not able to titrate up and/or, in the opinion of the investigator, a longer period on the 100/20 mg BID dose is necessary, patients may continue this dose. Thus, all patients will attempt 100/20 mg BID dosing for at least 1 week. All patients who are increased to KarXT 125/30 mg BID or 100/20 mg BID, depending on tolerability, will have the option to return to KarXT 100/20 mg BID or 50/20 mg BID throughout the study. Re-escalation to 125/30 mg BID or 100/20 mg BID or re-titration in cases in which the patient has been off KarXT for a longer period of time (at least 7 consecutive days) is allowed and will require a discussion between the investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated per investigator discretion.

Patients who cannot maintain 65% adherence to the study drug over any 8 week period throughout the study, unless there is hospitalization involved, will be discontinued from the study. The adherence assessments will be based on pill counts, patient recall, and caregiver report if applicable.

In summary, upward titration is expected to optimize efficacy; however, if efficacious and better tolerated, any of the available doses could be used for maintenance. Unscheduled (UNS) visits, which can be conducted in-clinic or by telemedicine, may occur between required clinic visits as deemed necessary by the investigator to facilitate patient retention and ensure compliance with study objectives. (See Table 1)

5.1.4. Safety Follow-up Visit

An End of Study (EoS) safety follow-up visit will be performed for all patients who have been dosed with KarXT. The EoS visit will take place 7 to 28 days after the last dose of KarXT for patients who complete the treatment phase (End of Treatment [EoT]), and for patients who choose to discontinue from the study early (early termination [ET]), at the discretion of the investigator, per sponsor request, or if the sponsor terminates the study. (See Table 1)

5.1.5. End of Study

A patient will have fulfilled all the requirements for the trial when the patient has completed all study visits, including the EoT visit (Visit 26) and the EoS visit (Visit 27), in accordance with the protocol (Table 1).

5.2. Safety and Efficacy

Safety will be assessed through spontaneous TEAEs, including TEAEs of special interest, TESAEs, and TEAEs leading to discontinuation of the study drug; cholinergic (pro- and anti-) symptoms; BARS; AIMS; body weight; BMI; orthostatic vital signs; clinical safety laboratory assessments (hematology, clinical chemistry, prolactin levels, coagulation, urinalysis, and drug screen); 12-lead electrocardiogram (ECG); physical examination; and Columbia-Suicide Severity Rating Scale (C-SSRS) will be evaluated throughout the study as scheduled.

Efficacy will be assessed through:

- Effectiveness using the CGI-I at week 2 through week 24 and persistence and durability of effect with IAQ and CGI-S scale throughout the study
- MSQ

5.3. Scientific Rationale for Study Design

Many patients with schizophrenia have an inadequate response to their antipsychotic therapy and either continue to be symptomatic, which includes positive symptoms, such as hallucinations and delusions, or they have to deal with unwanted side effects related to the D_2 receptor blockade, some of which could be permanent (e.g., TD). Given that KarXT has a different mechanism of action from D_2 antagonists (risperidone, paliperidone, quetiapine, ziprasidone, or lurasidone) or D_2 partial agonist (aripiprazole) and KarXT, as a monotherapy, has shown successful clinical data for both efficacy and safety from its Phase 2 study (KAR-004), KarXT therapy may provide efficacy with a side effect profile that could represent a more beneficial risk-benefit ratio than existing approved therapeutics for the treatment of schizophrenia symptoms and syndromes.

This current study aims to evaluate long-term safety, efficacy, persistence, and durability of effect in a close to real-world clinical setting; providing naturalistic, real-world evidence-like data to complement the ongoing registrational programs with KarXT in schizophrenia.

5.4. Justification for Dose

The Phase 2 study (KAR-004) was a 5 week inpatient trial that used flexible dosing of KarXT in subjects with acute psychosis. KarXT 100/20 mg BID or 125/30 mg BID significantly reduced the symptoms of schizophrenia. KarXT showed an acceptable safety profile; the most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. All reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject, and no deaths were reported. KarXT was generally well tolerated and found to be safe in this patient population (Brannan et al., 2021).

That is the reason why, in the current study, all patients will attempt 100/20 mg BID dosing for at least 1 week. All patients who are increased to KarXT 125/30 mg BID or 100/20 mg BID, depending on tolerability, will have the option to return to KarXT 100/20 mg BID or 50/20 mg BID throughout the study with the lowest dose allowed to accommodate cases of restarting the medication as well as ones where patients may be low metabolizers.

6. SELECTION OF AND WITHDRAWAL OF PATIENTS

6.1. Inclusion Criteria

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

1. Patient is aged 18 to 65 years, inclusive, at screening.
2. Patient can provide informed consent.
   a. A signed informed consent form (ICF) must be provided before any study assessments are performed.
   b. Patient must be fluent (oral and written) in the language of the ICF to consent.
3. Patient has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 criteria and has been in the continuous care of the clinician or practice for at least 6 months prior to entering the study.
4. The patient is dissatisfied with the side effects or general tolerability of their current antipsychotic medication, and for this reason, desires to change medications. Or, the patient is dissatisfied with the overall effectiveness or benefit of their current antipsychotic medication, and for this reason, desires to change medications.
5. The patient has not required psychiatric hospitalization, acute crisis intervention, or other increase in their level of care due to symptom exacerbation within 4 weeks of screening, and in the opinion of the investigator, is psychiatrically stable to be managed in an outpatient setting.
6. The patient has a CGI-S score of ≤4 at screening and baseline visits.
7. For at least 30 days prior to screening, the patient must have been prescribed and have taken an oral antipsychotic medication daily at a dose and frequency consistent with the drug label.
8. The patient is willing and able, and in the opinion of the investigator it is clinically appropriate, to discontinue all antipsychotic medications prior to the baseline visit or to taper their current antipsychotic medication(s) with cross-over administration for up to two weeks (14 days) of dosing with KarXT (unless the patient is on olanzapine or quetiapine, which require discontinuation before KarXT initiation)

   In summary:

   a. Patients may washout antipsychotic medication during the screening phase (21 to 28 days prior to baseline) at the discretion of the investigator. Thus, the patient would have discontinued all antipsychotic medication prior to baseline
   b. Or patient may down taper or continue down taper (washout) antipsychotic medication through the initial 2 weeks of KarXT dosing (excluding olanzapine or quetiapine).
   c. All patients must be washed out (discontinued) of all antipsychotic medication other than KarXT by end of week 2 (Day 14).

9. Patient has an identified, reliable caregiver/informant that is willing (by informed consent) and able to respond to the ZBI-22 caregiver burden scale at specified visits. The caregiver/informant must be consistent throughout the duration of the study. If the patient has been the patient of the investigator or the practice for ≥6 months and, in the opinion of the investigator, the patient is self-sufficient, then a caregiver/informant may not be necessary.
10. At the time of the Baseline Visit, the patient will have been off lithium therapy for at least 2 weeks.
11. If taking a LAI antipsychotic, the patient has not received a dose of the medication for at least 12 weeks (24 weeks for INVEGA TRINZA® [INVEGA TRINZA Package Insert, 2021]) before the Baseline Visit.
12. Patient BMI must be ≥18.0 and ≤45.0 kg/m^2.
13. Patient resides in a stable living situation and is anticipated to remain in a stable living situation for the duration of the study, in the opinion of the investigator.
14. If a woman of childbearing potential (WOCBP) or a man whose sexual partner(s) is a WOCBP, the patient must be willing and able to adhere to the contraception guidelines as defined in Section 12.1 Appendix 1.

6.2. Exclusion Criteria

If any of the following exclusion criteria apply, a patient may not participate in the study:

1. Any primary DSM-5 disorder diagnosis other than schizophrenia within 12 months before screening. Exclusionary disorders include, but are not limited to, bipolar I or II disorder and schizoaffective disorder. Symptoms of mild mood dysphoria or anxiety are allowed, as long as these symptoms are not the primary focus of treatment.
2. The patient 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 has a positive urine drug screen (UDS) for a substance other than cannabis at screening and baseline.
   a. A patient 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. Patients with a positive UDS for cannabis are permitted to enroll in the study provided that the patient's pattern of use is not indicative of a substance use disorder.
3. The patient has a history of or presence of a 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 patient or the validity of the study results.
4. Patient has human immunodeficiency virus (HIV) unless stable for 12 months prior to screening on highly active antiretroviral therapy (HAART) therapy (CD4 >500 and undetectable viral load); cirrhosis; biliary duct abnormalities; hepatobiliary carcinoma;

[redacted]

and/or active hepatic viral infections based on either medical history or liver function test results.

5. Patient has a history of or is at high risk of urinary retention, gastric retention, or narrow angle glaucoma.
6. Patient has a history of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
7. Patient is at risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
   a. Patient answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening, or patient answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Non-suicidal self-injurious behavior is not exclusionary.
8. Patient is at risk of violent or destructive behavior or serious harm to others, as determined by the investigator's clinical assessment.
9. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening. (Aspartate aminotransferase (AST) or alanine transaminase (ALT) >2x upper limit of normal (ULN) or total bilirubin (Tbili) >2x ULN (unless due to suspected Gilbert's), hemoglobin <10 g.dL, white blood cell (WBC) <3 K, absolute neutrophil count (ANC) <1000, platelets <100 K, QTc >450 msec in males and >470 msec in females.)
10. Currently and within 2 weeks before the Baseline Visit, patients cannot be receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, Depakote® [Depakote Package Insert, 2021]), tricyclic antidepressants (e.g., imipramine, desipramine), centrally active anticholinergics (benztropine, trihexyphenidyl, diphenhydramine), or any other psychoactive medications other than daily antipsychotic maintenance therapy.
    a. As needed (PRN) anxiolytics and/or sleep aids are permitted (e.g., lorazepam, zolpidem).
    b. Selective serotonin reuptake inhibitors (SSRI's)/serotonin and norepinephrine reuptake inhibitors (SNRIs) taken at stable dose for at least 4 weeks before screening and that are anticipated to be continued at the same dose throughout the study are permitted.
    c. Benztropine (Cogentin) or similar medications used for extrapyramidal symptoms (EPS) will need to be tapered down slowly as withdrawal symptoms are likely. The suggested approach is a maximum 50% reduction per week until a 0.25 mg dose is reached.
    d. PRN second generation antihistamines, e.g., fexofenadine, loratadine, and cetirizine (that do not readily cross the BBB), could be used after the first month of the study for temporary symptom management of allergies
11. Patient has a history of treatment resistance to schizophrenia medications defined as:
    a. Failure to respond to 3 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.

12. Patient is pregnant, lactating, or less than 3 months postpartum.
13. Patient has any other medical, psychiatric, or social condition that, in the opinion of the investigator, is likely to unfavorably alter the risk-benefit of patient participation, to interfere with protocol compliance, or to confound safety or efficacy assessments.
14. Patients has tested positive for coronavirus disease 2019 (COVID-19) within 2 weeks of screening and/or baseline or patients who have prolonged symptoms of past infection, long COVID, that, in the opinion of the investigator, may interfere with the interpretation of safety during the study
15. Patient with extreme concerns relating to global pandemics, such as COVID-19, that precludes study participation.
16. Patient is currently or recently (within 4 weeks of screening) involuntary hospitalization or incarceration.
17. Patient participated in another clinical study in which they received an experimental or investigational drug agent within 30 days prior to screening.

6.3. Patient Discontinuation Criteria

All patients are free to discontinue from participation in the study at any time and for any reason. The investigator must discontinue any patient from the study if the patient requests to stop participating in the study. The investigator, sponsor, or its designee may remove a patient from the study at any time and for any reason. In addition, patients may be discontinued if they:

- Experience an intolerable AE;
- Require a medication that is prohibited by the protocol;
- Do not follow guidelines specified in the protocol (i.e., is noncompliant with protocol procedures);
- Have any medically appropriate reason or significant protocol violation, in the opinion of the investigator;
- Have a clinically significant investigational treatment-related hypersensitivity reaction;
- Become pregnant;
- Meet an exclusion criterion (either newly developed or not previously recognized) such that risk-benefit is unfavorably affected, or he/she no longer meets criteria for the intended study population;
- Are lost to follow-up;
- Continued study participation poses an unfavorable risk-benefit to the patient, in the opinion of the investigator.

Discontinuation criteria related to adequately tolerating the investigational product are discussed in Section 5.1.3.1.

Should a patient discontinue early from the study, the reason(s) for study discontinuation will be documented on the electronic case report form (eCRF). All reasonable efforts will be made to have the patient complete the ET assessments (Table 1).

6.4. Patient Replacement

If patients discontinue the study, they will not be replaced.

6.5. Lost to Follow-Up

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

Reasonable efforts (3 documented phone calls and a certified letter) will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file. Patients with AEs ongoing at the EoS visit will be followed until the AE is resolved or the patient is considered to be in stable condition.

7. STUDY TREATMENT

7.1. Study Treatment Administration

7.1.1. Study Treatment Description

KarXT is formulated as hard hydroxypropyl methylcellulose (HPMC) oral capsules containing 2 distinct populations of drug beads. Each capsule contains xanomeline (as the tartrate salt) and trospium chloride in the stated dose strengths (Section 7.2.2). The main components of the drug beads are the active ingredients and microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

7.1.2. Dosing and Administration

The first dose of the study drug in this study will be taken at home on the morning of Day 1. The last dose will be taken at Visit 26 (week 156/Day 1092; the completion of the 3-year treatment period). The study drug should be taken daily BID, preferably on an empty stomach, i.e., at least 1 hour before a meal or at least 2 hours after a meal.

KarXT is expressed as mg xanomeline as the tartrate salt/mg trospium chloride. All patients will start on a lead in dose of KarXT 50/20 mg, BID Day 1 to Day 7.

- Week 1 (Days 1 to 7) – KarXT 50/20 mg, BID.
- Week 2 (Days 8 to 14) – KarXT 100/20 mg, BID or remain on 50/20 mg, BID.
- Week 3 (Days 15 to 21) – KarXT 125/30 mg, BID or 100/20 mg, BID.
- Weeks 4 to 156 (Days 28 to 1092) – Flexible dosing based on tolerability and clinical response KarXT 50/20 mg, KarXT 100/20 mg, and KarXT 125/30 mg doses, BID.

The dosing of KarXT is flexible after week 4 (Day 28); however, in the absence of tolerability issues, patients should have their dose increased if efficacy has not been observed (based on the clinical judgment of the investigator). The expectation is that most patients will respond to KarXT 100/20 mg or KarXT 125/30 mg, BID.

All investigational agents are to be stored according to requirements.

7.2. Preparation/Handling/Storage/Accountability

7.2.1. Acquisition and Accountability

The pharmacist or other designated individual will maintain records of the study treatment delivered to the study site, the inventory at the study site, the distribution to each patient, 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, ambient temperature log, and unique code numbers assigned to the product and study patients.

The administration of KarXT will be supervised by study site personnel (during in-clinic visits) and by an interactive response technology (IRT) system, 4G.

Investigators will maintain records that adequately document that patients were provided the correct study treatment. Study drugs will be dispensed in prepackaged blister card wallets and bottles. The wallets will contain 8 days of doses of KarXT capsules for BID administration. The bottles will contain 30 days of doses of KarXT capsules for BID administration. Patients will be advised to return all blister card wallets and bottles to the site staff at each in-clinic visit for drug accountability.

7.2.2. Formulation and Appearance

The formulations of all the drug products (KarXT 50/20 mg, 100/20 mg, and 125/30 mg xanomeline as the tartrate salt/trospium chloride) are provided below.

Note that xanomeline is formulated as the tartrate salt, but the tartrate moiety is not included in the nominal dose. Therefore, xanomeline doses reflect the dose of xanomeline, not the dose of xanomeline tartrate. Conversely, the nominal dose of trospium chloride reflects the combined weight of the trospium and the chloride. As an example, 50/20 mg KarXT contains 50 mg of xanomeline as the tartrate salt and 20 mg of trospium chloride.

Excipients in KarXT capsules are MCC (National Formulary [NF]); lactose monohydrate (NF); talc (United States Pharmacopeia [USP]); ascorbic acid (USP/NF); and Swedish orange, opaque, size 0, hard HPMC capsule shells.

- 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 HPMC 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, HPMC 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 HPMC hard capsule.

7.2.3. Packaging and Labeling

The packaging and labeling will be done by Catalent Pharma Solutions, located in Philadelphia, Pennsylvania. All packaging and labeling operations will comply with Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Blister pack wallets of KarXT capsules will be provided at Baseline and week 2 (Day 14), and they will be labeled. The label will include “KarXT (Xanomeline/Trospium Cl)”, 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.”). Bottles of KarXT capsules will be provided at week 4 (Day 14) through week 152 (Day 1064), and they will be labeled. The label will include “KarXT (Xanomeline/Trospium Cl)”, recommended storage conditions, the name and address of the manufacturer, and the Investigational Use Statement (“Caution: New Drug – Limited by Federal Law to Investigational Use.”).

7.2.4. Study Drug Storage

KarXT must be stored at controlled room temperature, 15°C to 25°C, in a secured location with no access to unauthorized personnel at the site. Patients should store study medication at room temperature.

7.3. Blinding

This is a single arm open-label study; therefore, blinding is not applicable.

7.4. Randomization

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

The Patient Number (14-XXX-XXX) in this trial will consist of a 2-digit study code (14), a 3-digit site identification, and a 3-digit patient number that will be assigned sequentially within each site, starting with 001.

7.5. Dose Modification

Patients will be dosed as described in Section 7.1.2 and in accordance with the schedule of assessments (SoA) (Table 1). KarXT doses were selected based on the results of previous clinical studies (see Section 3.2.3 and Section 5.4). Per the protocol, patients will be evaluated for dose adjustments at Day 7 (telephone visit) through Visit 25 and at unscheduled visits.

7.6. Study Treatment Adherence

Treatment adherence will be evaluated by on-site pill count/site drug accountability procedures. The number of pills dispensed and returned (for each dispensation visit) will be recorded on the appropriate electronic case report form (eCRF). Patients will be reminded to adhere to the BID medication schedule.

Patients who cannot maintain 65% adherence to the study drug over any 8 weeks period, unless there is hospitalization involved, will be discontinued from the study. The adherence assessments will be based on pill counts, patient recall, and caregiver report, if applicable.

7.7. Concomitant Therapy

Concomitant medications ongoing as of the Baseline visit will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the patient during the study, including those treatments initiated before the start of the study drug administration, must be recorded on the KAR-014 eCRF.

All patients participating in this study must not take any other antipsychotic medication beyond KarXT during the study, except for oral antipsychotics that may be down titrated during the first 2 weeks of KarXT. If there is a strong case to be made after first 6 months of treatment for augmentation or PRN therapy, it needs to be discussed with the Medical Monitor.

During the study (i.e., from Day 1 [day of 1st dose] until study completion), patients will refrain from the use of any other new concomitant medication(s) without the specific prior approval of

the investigator, unless its use is deemed necessary as in a medical emergency. Over the counter medications, such as acetaminophen, paracetamol, ibuprofen, aspirin etc., are permitted during the study.

Note: Please direct questions relating to prohibited medications to the Medical Monitor.

7.7.1. Concomitant Medications for Anxiety and/or Sleep Aid

Patients are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on a PRN basis. Patients may also use nonbenzodiazepine medications (e.g., zolpidem, zaleplon) as a sleep aid.

8. STUDY ASSESSMENTS AND PROCEDURES

The SoA (Table 1) outlines the efficacy and safety assessments to be performed throughout the study and their timing.

The first dose of the study drug in this study will be self-administered by the patient at home the morning of Day 1, which is one day following the in-clinic Baseline Visit. The last dose will be taken at week 156 (the end of the 3-year treatment period). The study drug should be taken daily BID, preferably on an empty stomach, i.e., at least 1 hour before a meal or 2 hours after a meal.

If completion of the visit is not possible on the scheduled day, the ± 2-day visit window (unless otherwise noted) may be used.

8.1. Efficacy Assessments and Diagnostic Scales

8.1.1. Clinical Global Impression–Severity (CGI-S)

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 modified CGI-S 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 (Guy, 1976).

This rating is based on 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 previous 7 days.

8.1.2. Clinical Global Impression – Improvement (CGI-I)

The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Clinicians are asked: *"Compared to the patient's condition at baseline, this patient's [average] condition has...?",* and they rate as: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse (Guy, 1976).

8.1.3. Investigator's Assessment Questionnaire (IAQ)

The IAQ was developed to be a simple, easily used tool that simultaneously evaluates all health concerns associated with antipsychotic use in patients with schizophrenia or schizoaffective disorder. Effectiveness of treatment is assessed by the IAQ total score (primary endpoint), which is defined as the sum of 10 out of 12 items (positive symptoms, negative symptoms, somnolence, weight gain, signs and symptoms of prolactin elevation, akathisia, EPS, cognition, energy, and mood); each item is rated on a 5-point Likert scale (1 = Much better, 2 = Slightly better, 3 = About the same, 4 = Slightly worse, and 5 = Much worse).

8.1.4. Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item questionnaire that evaluates satisfaction with antipsychotic medication in schizophrenia patients. Patient satisfaction with treatment can strongly influence health related behavior, pursuit and use of mental health services, treatment adherence, and long-term outcomes. Used for more than 20 years, the MSQ has different versions. The choice was made for utilizing the version with one single question rated on a 7-point scale; allowing for more nuanced responses to the question of overall how satisfied you are with your current antipsychotic therapy: 1 = Extremely dissatisfied, 2=Very dissatisfied, 3=Somewhat dissatisfied, 4=Neither satisfied nor dissatisfied, 5=Somewhat satisfied, 6 = Very satisfied, 7 = Extremely satisfied.

8.1.5. Brief Cognitive Assessment Tool for Schizophrenia (B-CATS)

B-CATS is a brief measure composed of 3 cognitive tests (digital symbol substitution test; trail making test, part B; and category fluency) that provides a global cognition score. It is highly correlated with the global scores from comprehensive neuropsychological batteries that take between 6 and 20 times as long to administer. The B-CATS has been developed specifically for use by clinicians, and the 3 tests have straightforward and easy instructions for administration and scoring.

- Digit symbol substitution: a sheet with a 9-item key pairing digit 1 through 9 with a unique symbol; below are rows of numbers with blank squares beneath. The subject pairs each number with its unique symbol. The score is the number of correct number-symbol pairs completed in 120 seconds.
- Trail making test, part B: a sheet with scattered circles containing letters or numbers. Subjects draw a ‘‘trail’’ from number to letter (1-A-2-B, etc.) to number 13 without lifting the pencil from the article. The score is the time to completion.
- Category fluency: subjects orally list as many animals, fruits, and vegetables as they can in 60 seconds per category. The administrator tracks responses, and the score is the number of unique and appropriate answers per category.

8.2. Safety Scales and Other Assessments

Safety assessments are to be performed at protocol-specified visits, as specified in the SoA (Table 1). Table 2 describes all the safety laboratory tests required for this study.

8.2.1. Barnes Akathisia Rating Scale (BARS)

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 (Barnes, 1989).

8.2.2. Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a rating scale used to measure involuntary movements known as TD, 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.

8.2.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study (Posner et al., 2011). The strength of this suicide classification system is its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS will be administered by a certified rater at the site and takes about 5 minutes to complete.

This study will use the "Since Last Visit" version during scheduled visits.

8.2.4. EQ-5D-3L

EQ-5D-3L is an instrument that evaluates the generic quality of life developed in Europe, and it is widely used. The EQ-5D-3L descriptive system is a preference-based Health Related Quality of Life (HRQL) measure with one question for each of the five dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

8.2.5. Accountable Health Communities Health-Related Social Needs (AHC HRSN)

Developed by Centers for Medicare & Medicaid Services (CMS) Center for Medicare and Medicaid Innovation (CMMI), the AHC HRSN screening tool is used to assess the health-related social needs of patients and their effect on total health care costs and health outcomes. For this study, it will be important to also note the insurance status of patients, so changes will be tracked over the 3-year duration of the study.

8.2.6. Zarit Caregiver Burden Interview (ZBI-22)

The Zarit Burden Interview, a popular caregiver self-report measure used by many aging agencies, originated as a 29-item questionnaire (Zarit, Reever & Bach-Peterson, 1980). The revised version contains 22 items (ZBI-22). Each item on the interview is a statement that the caregiver is asked to endorse using a 5-point scale. Response options range from 0 (never) to 4 (nearly always). For shorter administration, shorter versions, ranging from 1 to 18 items, have been developed. A study by Yu, Yap & Liew (2018) found that the 6-item version was the optimal short version as it provided similar diagnostic utility to the original 22-item version with the fewest items.

8.2.7. Demographics and Medical and Psychiatric History

Demographic data will be collected for all patients at the Screening visit of the KAR-014 study. The information to be captured includes the patient's date of birth (alternatively year of birth if the full date of birth is not allowed to be collected for legal reasons), age, sex at birth, race, and ethnicity, which will be obtained from the patient and recorded in the eCRF.

Medical and psychiatric history will be recorded at the Screening visit of the KAR-014 study. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including all baseline symptoms, ongoing illnesses, other chronic conditions, and surgical history at the Screening visit of KAR-014. The medical history will also include a

history of drug, substance, or alcohol abuse/dependence within 1 year before the Screening visit of KAR-014.

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 8.3. All clinical abnormalities not present at baseline or described in the past medical history that are subsequently identified as clinically noteworthy must be recorded as AEs.

8.2.8. Vital Signs

Vital signs (systolic and diastolic blood pressure [BP] and heart rate [HR] measurements) will be evaluated at the visits as indicated in the SoA (Table 1). All vital signs will be measured supine or sitting after 2 minutes. Blood pressure includes systolic and diastolic BP, and it is to be taken in the same arm for the duration of the study. Heart rate is measured in beats/minute.

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

8.2.9. Physical Examination

A complete physical examination (body temperature [orally collected, °C]; general appearance; head/eyes/ears/nose/throat; examination of thorax and abdomen; assessment of cardiac, musculoskeletal, and circulatory systems; palpations for lymphadenopathy; and limited neurological examination) will be performed at the visits specified in Table 1. Physical examinations will be performed by a physician.

8.2.10. Weight, Height, and Body Mass Index

Height (cm) and weight (kg) measurements will be obtained at the visits specified in the SoA (Table 1). BMI should be calculated at these visits. All findings should be recorded in the eCRF.

8.2.11. Electrocardiograms (ECG)

A 12-lead, resting ECG will be obtained at the visits indicated in the SoA (Table 1). During the ECG, ventricular rate (beats per minute [bpm]), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements will be obtained. ECGs at all scheduled visits will be performed before blood withdrawal for any safety laboratory tests or pharmacokinetic (PK) analysis.

All ECGs will be interpreted by experienced independent blinded reader(s) at a central reading facility.

8.2.12. Laboratory Assessments

Laboratory assessment samples (Table 2) are to be collected at designated visits as detailed in the SoA (Table 1). Fasting (preferred) blood laboratory samples will be analyzed at a central laboratory. Patients should be asked to present at the baseline visit in a fasting state (no eating or drinking except water for 8 to 12 hours). The state the patient presents at baseline should be maintained for all laboratory assessments throughout the course of the study.

Table 2: Laboratory Assessments

Hematology	**Serum Chemistry**	**Urinalysis (Dipstick)**
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 UDS
HbA1c (glycated Hb test)		
Prolactin		
COVID 19 Rapid[a]		
Coagulation	**Serology**[b]	
PT Activated PTT Fibrinogen	HBV HCV HIV	
Pregnancy test: A urine pregnancy test for WOCBP should be performed per the SoA (Table 1). 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; COVID-19 = covid disease 2019; GGT = gamma-glutamyl transpeptidase; Hb = hemoglobin; HCG = human chorionic gonadotropin; Hct = hematocrit; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular

volume; PCR = polymerase chain reaction; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; UDS = urine drug screen; WBC = white blood cell.
a COVID-19 Rapid test to be performed locally at Baseline. If positive, PCR to be performed by central laboratory.
b 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 patients tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.

Approximately 7 to 30 mL of venous blood will be withdrawn for the tests listed above at scheduled time points as per the SoA (Table 1).

A minimum urine volume of 10 mL will be collected for urinalysis and a urine drug screen at scheduled time points as per the SoA (Table 1).

Blood and abnormal urine samples will be analyzed at a central laboratory facility for microscopic analyses.

All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patient's eCRF and 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 until repeat test results return to normal, stabilize, or are no longer clinically significant.

8.2.13. Other Laboratory Assessments

A urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed at designated visits as detailed in the SoA (Table 1).

Urine alcohol testing will be performed for alcohol content.

8.2.14. Blood Sampling for Pharmacogenetics

A blood sample may be collected at baseline for exploratory pharmacogenetic analysis if the patient provides consent for the procedure. Approximately 9 mL of blood may be collected for subsequent DNA extraction. The samples will be stored at a central laboratory facility where DNA will be extracted and retained. The collection, storage, shipping, processing of the blood samples, and the analytical methods to be used will be detailed in the laboratory manual.

The genetic variants to be analyzed may include SNPs and any other variants as deemed necessary by the Sponsor.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Definition of Adverse Events (AEs)

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at Screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions present at Screening will be documented in the medical history eCRF. Clinically significant changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on 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 patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history. In addition, all COVID-19 related events should be reported as AEs.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and concurrent illness during and at the safety follow-up visit, and these will be recorded on the appropriate page of the eCRF. AEs will be elicited by asking the patient a nonleading question, for example, *"Have you experienced any new or changed symptoms since we last asked?"*

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.

Specific guidelines for classifying AEs by intensity and relationship to study drug are provided in Table 3 and Table 4.

Table 3: Classification of Adverse Events by Intensity

MILD	An event that is easily tolerated by the patient, causes minimal discomfort, and does not interfere 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 4: Classification of Adverse Events by Relationship to Study Drug

UNRELATED	This category applies to adverse events (AEs) that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY	This category applies to 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 the study drug when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from the administration of the test drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (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 AEs for which a connection with the test drug appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from the administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug.
PROBABLY	This category applies to AEs that the investigator believes with a high degree of certainty are related to the test drug. An AE may be considered probably related when it meets 3 of the following criteria: (1) it follows a reasonable temporal

	sequence from the administration of the drug; (2) it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases upon cessation or reduction in dose (note that sometimes an AE does not disappear upon discontinuation of the drug yet drug-relatedness clearly exists; for example, 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 AEs that the investigator believes are incontrovertibly related to the test drug. An AE may be assigned an attribution of "definitely related when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from the administration of the drug; (2) it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases upon cessation or reduction in dose and recurs with re-exposure to the drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

8.3.2. Adverse Events of Special Interest (AESIs)

AESIs will be monitored, and they include orthostasis and LFT elevations (inclusive of drug induced liver injury [DILI]; Section 8.3.6).

AESIs should be recorded as AEs and reported as SAEs when appropriate.

Orthostasis will be defined as the patient being symptomatic with at least one of the following differences in orthostatic vitals between sitting position and standing after 2 minutes:

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

Changes of the orthostatic vitals alone will not be considered an AESI without the patient being symptomatic. If the patient is asymptomatic with the above differences in orthostatic vitals, the event will be captured as an AE.

Since BP and HR will be taken at each visit, orthostatic evaluation will be conducted when indicated and per the clinical judgement of the investigator with at least one such assessment within the first 2 months of drug initiation and at least one assessment every 6 months thereafter.

8.3.3. Definition of Serious Adverse Events (SAEs)

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

- Results in death.
- Is life-threatening.
- Results in inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective treatment of a pre-existing, non-worsening condition is

[redacted]

not; however, considered an SAE; the details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based on appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to consider both the investigator's and the Sponsor's assessments. 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.

8.3.4. Serious Adverse Event Reporting

SAEs and AESIs will be classified as treatment-emergent as appropriate. SAEs and AESI reported by patients or observed by clinical staff after the patient has signed the ICF must be reported to the pharmacovigilance group of the Sponsor. Any such SAE or AESI due to any cause, whether related to the study drug or not, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. SAEs must be reported directly through the electronic data capture (EDC)/eSource system, but as a backup (in case the EDC/eSource system is not available), sites can use the email address **Safety@catalystcr.com**.

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

The events must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions, 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 the investigator considers the event to be related to the investigational drug or not.

Appropriate remedial measures should be taken to treat the SAE, and the treatment procedure should be recorded. The investigator must report all additional follow-up evaluations to the pharmacovigilance group **within 24 hours** of becoming aware of the additional information or as soon as it 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 safety follow-up visit or upon discontinuation of the patient'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 the study drug or procedures.

8.3.5. Pregnancy and Pregnancy Reporting

WOCBP must have a negative pregnancy test at Screening and Baseline prior to receiving the first dose of study treatment for this study (KAR-014).

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

If the female patient or the female partner of the male patient 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 informed consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner with a specialist. The specialist will discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

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

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, and the event will be considered an SAE.

The investigator should also be notified of pregnancy that occurs during the study but is not confirmed until after completion of the study. In the event that a patient 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.

8.3.6. Drug-Induced Liver Injury (DILI)

The sponsor has incorporated the following for monitoring of the DILI:

- An increase of serum ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, alkaline phosphatase [ALP], and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).
- Close observation should be initiated with ALT or AST ≥3 × ULN.
- Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the trial drug has been discontinued and the patient is asymptomatic.

[redacted]

- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio, direct bilirubin).
- Consider gastroenterology or hepatology consultations.

Discontinuation of treatment should be considered if:

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

Gamma-glutamyl transpeptidase elevations alone should not prompt drug discontinuation.

Hepatic adjudication of cases should include an evaluation for alternative causes, such as viral, autoimmune, alcohol, hepatobiliary disorders, nonalcoholic steatohepatitis, concomitant medications, etc.

Follow-up is expected until resolution of elevated liver enzyme cases.

8.3.7. Trial Discontinuation Criteria Other than Pregnancy

8.3.7.1. Individual Stopping Criteria

Based on Common Terminology Criteria for Adverse Events (CTCAE, 2017) v5.0, the study drug will be discontinued in any patient who has a ≥ Grade 4 AE. Discontinuation or dose reduction for Grade 3 AEs will be at the discretion of the investigator.

8.3.7.2. Trial Stopping Rules

The safety and tolerability aspects of KarXT will be overseen by the medical monitors and the study team of the Sponsor and the Contract Research Organization (CRO). They will be responsible for safeguarding the interests of clinical study patients. The study team is expected to recommend to the sponsor whether to:

- Continue the clinical study without modification; or

- Continue the clinical study with modification (listing the specific modifications recommended); or
- Terminate the study.

8.3.8. Suspected Unexpected Serious Adverse Reactions (SUSARs)

AEs that meet all 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 (i.e., the event is not consistent with the safety information in the KarXT IB, or package insert of generic trospium).
- At least a reasonable possibility that there is a causal relationship between the event and the study treatment.

The investigator will assess whether or not an event is causally related to study treatment. The Sponsor (or their designee CRO) 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)/ Institutional Review Board (IRBs) (where required) within 7 days after the Sponsor (or their designee) 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 their designee) first has knowledge of them.

The Sponsor (or their designee) 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.

8.3.9. Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with the study drug. Overdose should be managed with symptomatic and supportive care. For the purpose of this study, an overdose is defined as any intentional or unintentional consumption of investigation medicinal product that exceeds the maximum TDD (total daily dose) specified in the protocol (250/60 mg TDD).

8.3.10. Warnings and Precautions

Risk of Urinary Retention

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

Angioedema

[redacted]

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, an active ingredient in KarXT. In one case, angioedema occurred after the first dose of trospium chloride as SANCTURA® (SANCTURE Package Insert, 2012). Angioedema associated with upper airway swelling may be life-threatening. If the involvement of the tongue, hypopharynx, or larynx occurs, KarXT should be promptly discontinued and appropriate therapy and/or measures necessary to ensure an open patent airway should be promptly provided.

Decreased Gastrointestinal Motility

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

Controlled Narrow-angle Glaucoma

In patients being treated for narrow-angle glaucoma, trospium chloride should be used only 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. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how trospium chloride affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Patients 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 patients with moderate renal impairment.

Elevation of Liver Enzymes

Elevated liver enzymes have been reported in previous studies of xanomeline as a monotherapy in AD patients. Elevations in hepatic enzymes have not been seen in Phase 1 studies with KarXT in healthy volunteers. The LFT elevations in the Phase 2 schizophrenia study (KAR-004) with KarXT were quite limited when compared to the effects of xanomeline alone in the elderly AD population. Moreover, even in the AD patients who experienced hepatic enzyme elevations, the elevations were reversible even with continued xanomeline treatment in patients who provided sufficient follow-up data. Importantly, there were no Hy's law cases or elevations in total bilirubin to > 2 × upper limit of the reference range for either xanomeline or KarXT.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

No statistical hypothesis testing will be performed for this study.

9.2. Sample Size Determination

The primary objectives of this study are to assess the long-term safety and tolerability of KarXT as well as its effectiveness, persistence, and durability of effect through the IAQ and CGI-S scale in patients with a diagnosis of schizophrenia. Approximately 380 patients are planned to be enrolled in this study. The goal is to have at least 100 patients remain in the study after 2 years, which equates to an approximate 60% yearly retention rate, which would be higher than the average of 50% (including LAIs) adherence observed for patients living with schizophrenia. Thus, achieving the retention goal of this naturalistic study will position KarXT above the overall average for adherence amongst available therapies.

9.3. Populations for Analyses

Table 5: Populations for Analyses Descriptions

Population	Description
Enrolled	All patients who have given informed consent for KAR-014 will be included in the enrolled population.
Safety	All patients who receive at least 1 dose of KarXT in study KAR-014 will be included in the safety population and will be used in the safety analyses.
Modified Intent-to-Treat (mITT)	All patients who are enrolled and received KarXT through week 8, will be included in the mITT population and will be used in the efficacy and other analyses.

9.4. Statistical Analyses

9.4.1. General Approach

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 patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purposes of analysis. No statistical hypothesis testing will be performed. For endpoints defined as change from baseline, the baseline is defined as the last measurement prior to the first dose of the study medication unless otherwise specified. Further methods pertaining to the summary and analyses of the efficacy and safety data are presented in the following sections and will be described in more detail in the Statistical Analysis Plan (SAP).

9.4.2. Safety Analysis

Safety endpoints will be summarized for all patients in the safety population. The presentation of safety data will be based on the treatment received in KAR-014.

The primary safety endpoint of the study is the incidence of TEAEs leading to discontinuation. Secondary safety endpoints are the incidence of TESAEs and the incidence of TEAEs of special interest.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities version 23.0 or higher. The incidence of TEAEs (events with onset dates on or after the start of the study drug in KAR-014) will be summarized by system organ class and preferred term. All AEs will be listed by patient, along with information regarding onset, duration, severity, relationship to study drug, action taken with the study drug, treatment of the event, and outcome. The incidence and severity of AEs, TEAEs leading to discontinuation, TEAEs, TEAEs of special interest, and TESAEs will be presented by defined study populations.

Vital signs, clinical laboratory data, prolactin levels, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change-from-baseline values, as well as numbers of patients with values outside the limits of the normal range at each time point by treatment group. Similar descriptive summaries will be provided for BARS, AIMS, height, body weight, and BMI.

Additional details pertaining to the summary of safety data will be provided in the SAP.

9.4.3. Efficacy Analysis

Efficacy analysis will be conducted for all patients in the modified intent-to-treat (mITT) population.

The primary efficacy endpoints will be measured by IAQ and CGI-S, secondary efficacy endpoints will be assessed by CGI-I and MSQ, and a cognition endpoint will be assessed by B-CATS.

Other endpoints of the study include functional and observed outcomes (EQ-5D-3L and ZBI-22), adherence to KarXT at different timepoints, AHC HRSN, and SNPs related to schizophrenia subtypes and drug metabolism.

Descriptive statistics will be used for observed values and change from baseline (as applicable) of efficacy endpoints. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum, and maximum. For categorical parameters, the number and percentage of patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

9.4.4. Planned Interim Analysis

No interim analysis is planned for this study.

9.5. Handling of Missing Data

Safety and efficacy analyses will be based on the observed case data. No missing data will be imputed.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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.

10.1.2. Independent Ethics Committee/Institutional Review Board

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

10.1.3. Informed Consent Process

For each study patient, informed consent will be obtained before any protocol-related activities. As part of this procedure, the investigator 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 patient should be informed that they may discontinue from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The investigator 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 a patient to participate. Revisions to the ICF 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 ICFs, the patients must be re-consented for continued participation in the study.

10.1.4. Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 10.1.5.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on 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 patient 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 include only coded identifiers such that directly identifying personal information is not transmitted. The primary method of data

transmittal is via the secure, internet-based EDC system maintained by the CRO. Access to the EDC system is available only to authorized users via the study's secured 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 EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

10.1.5. 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 patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.

Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

10.1.6. Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation 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 patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and a form satisfactory to the Sponsor.

10.1.7. Monitoring

The study will be monitored according to the KAR-014 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, on-site, remote, and virtual (telephone) or a combination, and contacts will be made at appropriate times during the study. The investigator will assure that adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical

monitors must have direct access to source documentation to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

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, will provide appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

10.1.8. 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 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.

10.1.9. 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 patients are required to give informed consent before participation in the study.

10.1.10. Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on the 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.

10.1.11. Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed in the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be patient to the terms of the clinical study agreement, which will be agreed upon 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 study

described in this protocol, patient 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 outlined in the clinical study agreement.

10.2. Protocol Amendment and Protocol Deviation

10.2.1. 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 patients or the conduct of the study will be classified as administrative amendments and will be submitted to the IEC/IRB for informational use only. The CRO will ensure that acknowledgment is received and filed. Amendments that are classified as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and, except for urgent safety measures, will not be implemented at sites until such approvals are received.

10.2.2. 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 and evaluated on an ongoing basis. Deviations considered major will be identified as such during the Medical Monitor's periodic review.
- Minor deviations are those which do not affect the scientific soundness of the research study or the rights or safety of patient. One example is a visit outside a visit window by a day or 2.
- Major deviations are those that do affect the scientific soundness of the research study or the rights or safety of patients.

Major protocol deviations will be tabulated by type of deviation.

11. LIST OF REFERENCES

ABILIFY® (aripiprazole) (2020). Package Insert, Highlights of Prescribing Information. Otsuka American Pharmaceutical, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021436s044s045,021713s035s036,021729s027s028,021866s029s030lbl.pdf

ABILIFY MAINTENA® (aripiprazole) (2020). Package Insert, Highlights of Prescribing Information. Otsuka American Pharmaceutical, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202971s013lbl.pdf

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.) https://doi.org/10.1176/appi.books.9780890425596.

ARISTADA® (aripiprazole lauroxil) (2020). Package Insert, Highlights of Prescribing Information. Alkermes, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207533s017,209830s005lbl.pdf

Barnes, T.R. (1989). A rating scale for drug-induced akathisia. Br J Psychiatry *154,* 672-676.

Bodick, N.C., Offen, W.W., Levey, A.I., Cutler, N.R., Gauthier, S.G., Satlin, A., Shannon, H.E., Tollefson, G.D., Rasmussen, K., Bymaster, F.P., *et al.* (1997a). Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. Arch Neurol *54,* 465-473.

Bodick, N.C., Offen, W.W., Shannon, H.E., Satterwhite, J., Lucas, R., van Lier, R., and Paul, S.M. (1997b). The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. Alzheimer Dis Assoc Disord *11 Suppl 4,* S16-22.

Brannan, S.K., Sawchak, S., Miller, A.C., Lieberman, J.A., Paul, S.M., and Breier, A. (2021). Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia. N Engl J Med *384,* 717-726.

Crismon, L., Argo, T.R., and Buckley, P.F. (2014). Schizophrenia, 9th edn (New York, New York: McGraw-Hill).

CTCAE (2017). Common Terminology Criteria for Adverse Events; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

Depakote (divalproex sodium) (2021). Package Insert, Highlights of Prescribing Information. AbbVie Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018723s065lbl.pdf

Emsley, R., Chiliza, B., Asmal, L., and Harvey, B.H. (2013). The nature of relapse in schizophrenia. BMC Psychiatry *13,* 50.

Farde, L., Suhara, T., Halldin, C., Nyback, H., Nakashima, Y., Swahn, C.G., Karlsson, P., Ginovart, N., Bymaster, F.P., Shannon, H.E., *et al.* (1996). PET study of the M1-agonists [11C]xanomeline and [11C]butylthio-TZTP in monkey and man. Dementia *7,* 187-195.

GEODON® (ziprasidone) (2022). Package Insert, Highlights of Prescribing Information. Pfizer Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020825s063lbl.pdf

Green, M.F., Kern, R.S., and Heaton, R.K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr Res *72,* 41-51.

Guy, W. (1976). EDCEU Assessment Manual for Psychopharmacology – Revised., E. US Department of Health, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, ed. (DHEW Publication No ADM 76 338.), pp. 534-537.

HMA (2020). Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Backers, L., Rothe, P., Cipriani, A., *et al.* (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet *394,* 939-951.

INVEGA® (paliperidone) (2021). Package Insert, Highlights of Prescribing Information. Janssen Pharmaceuticals, Inc.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021999Orig1s039lbl.pdf

INVEGA SUSTENNA® (paliperidone palmitate) (2021). Package Insert, Highlights of Prescribing Information. Janssen Pharmaceuticals, Inc.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022264Orig1s033lbl.pdf

INVEGA TRINZA® (paliperidone palmitate) (2021). Package Insert, Highlights of Prescribing Information. Janssen Pharmaceuticals, Inc.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207946Orig1s011lbl.pdf

Kahn, R.S., Sommer, I.E., Murray, R.M., Meyer-Lindenberg, A., Weinberger, D.R., Cannon, T.D., O'Donovan, M., Correll, C.U., Kane, J.M., van Os, J., *et al.* (2015). Schizophrenia. Nat Rev Dis Primers *1,* 15067.

LATUDA (lurasidone hydrochloride) (2019). Package Insert, Highlights of Prescribing Information. Sunovion Pharmaceuticals Inc.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/200603s035lbl.pdf

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., *et al.* (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet *382,* 951-962.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., *et al.* (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med *353,* 1209-1223.

Mirza, N.R., Peters, D., and Sparks, R.G. (2003). Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. CNS Drug Rev *9,* 159-186.

Patel, K.R., Cherian, J., Gohil, K., and Atkinson, D. (2014). Schizophrenia: overview and treatment options. P T *39,* 638-645.

PERSERIS™ (risperidone) (2019). Package Insert, Highlights of Prescribing Information. Indivior Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210655s004lbl.pdf

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., *et al.* (2011). The Columbia-Suicide Severity Rating

RISPERDAL CONSTA® ((risperidone) (2021). Package Insert, Highlights of Prescribing Information. Janssen Pharmaceuticals, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020272Orig1s083,020588Orig1s071,021444Orig1s057,021346Orig1s061lbl.pdf#page=60

Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry *168,* 1266-1277.

SANCTURA® (trospium chloride) (2012). Package Insert, Highlights of Prescribing Information. Allergan, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021595s009lbl.pdf

Scheife, R., and Takeda, M. (2005). Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clin Ther *27,* 144-153.

Sellin, A.K., Shad, M., and Tamminga, C. (2008). Muscarinic agonists for the treatment of cognition in schizophrenia. CNS Spectr *13,* 985-996.

SEROQUEL® (quetiapine) (2022). Package Insert, Highlights of Prescribing Information. AstraZeneca. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020639s072lbl.pdf

SEROQUEL XR® (quetiapine) (2022). Package Insert, Highlights of Prescribing Information. AstraZeneca. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022047s046lbl.pdf

Shekhar, A., Potter, W.Z., Lightfoot, J., Lienemann, J., Dube, S., Mallinckrodt, C., Bymaster, F.P., McKinzie, D.L., and Felder, C.C. (2008). Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. Am J Psychiatry 165, 1033-1039.

Staskin, D., Kay, G., Tannenbaum, C., Goldman, H.B., Bhashi, K., Ling, J., and Oefelein, M.G. (2010). Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. Int J Clin Pract *64,* 1294-1300.

Thorn, C.A., Moon, J., Bourbonais, C.A., Harms, J., Edgerton, J.R., Stark, E., Steyn, S.J., Butter, C.R., Lazzaro, J.T., O'Connor, R.E., *et al.* (2019). Striatal, Hippocampal, and Cortical Networks Are Differentially Responsive to the M4- and M1-Muscarinic Acetylcholine Receptor Mediated Effects of Xanomeline. ACS Chem Neurosci *10,* 1753-1764.

van Os, J., and Kapur, S. (2009). Schizophrenia. Lancet *374,* 635-645.

Wess, J., Eglen, R.M., and Gautam, D. (2007). Muscarinic acetylcholine receptors: mutant mice provide new insights for drug development. Nat Rev Drug Discov *6,* 721-733.

Wu, E.Q., Shi, L., Birnbaum, H., Hudson, T., and Kessler, R. (2006). Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. Psychol Med *36,* 1535-1540.

Yu J, Yap P, Liew TM. (2019) The optimal short version of the Zarit Burden Interview for dementia caregivers: diagnostic utility and externally validated cutoffs. Aging Ment Health. *23(6):*706-710.

[redacted]

Zarit, S.H., Reever, K.E. and Bach-Peterson, J. (1980) Relatives of the impaired elderly: correlates of feelings of burden. The gerontologist, *20*(6), pp.649-655.

12. APPENDICES

12.1. Appendix 1

Contraception Guidelines

Female patients 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 on Day 1 and continuing until 30 days after the last dose of study drug. If oral contraceptives are used, the patient 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 (HMA, 2020). Female patients 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 patient's follicle-stimulating hormone (FSH) level which must be elevated and consistent with postmenopausal levels (ie, >40 IU/L); otherwise, these patients must agree to use contraceptives listed below. Female patients who are surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) will not need to undergo the FSH level test.

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)

All patients will be strongly advised that they (or the female partners of male patients) should not become pregnant while on study treatment or for 30 days after the last dose. A female patient 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. Male patients should refrain from sperm donation for 30 days after the last dose of study drug.

[redacted]

12.2. Appendix 2

Background Antipsychotic Dosing Regimen

Antipsychotic drugs	Trade name	Dosing Recommendations
Paliperidone	INVEGA® (Schizophrenia)	Recommended Dose: 3to 12 mg/day Maximum Dose: 12 mg/day
	INVEGA SUSTENNA®	Dose range is 117 mg, 156 mg, or 234 mg (IM injection every month)
	INVEGA TRINZA®	Dose range is 410 mg, 546 mg, or 819 mg (IM injection every 3 months) Invega Trinza® Doses for Adult Patients Adequately Treated with Invega Sustenna® Invega Sustenna of 117 mg the Invega Trinza = 410 mg Invega Sustenna of 156 mg the Invega Trinza = 546 mg Invega Sustenna of 234 mg the Invega Trinza = 819 mg
Risperidone	Risperidone (oral)	Target dose Schizophrenia: 4 to 6 mg / day Effective Dose Range Schizophrenia: 4 to 16 mg /day
	RISPERDAL CONSTA®	Dose range is 25 mg, 37.5 mg, or 50 mg (IM injection every 2 weeks)
	PERSERIS™	Dose range is 90 to 120 mg monthly (SQ injection) 90 mg (0.6 mL) equivalent to 3 mg oral risperidone 120 mg (0.8 mL) equivalent to 4 mg oral risperidone
Aripiprazole	Aripiprazole (oral)	Dose range: 10 mg to 30 mg / day
	ABILIFY MAINTENA® (Aripiprazole monohydrate)	300 mg, 400 mg every month (IM injection)
	ARISTADA®(Aripiprazole lauroxil)	441 mg, 662 mg, or 882 mg every month (IM injection) 882 mg every 6 weeks

[redacted]

		1064 mg every 2 months
Quetiapine IR	SEROQUEL® (oral) (Schizophrenia; Adults)	Dose range: 300 to 750 mg/day
Quetiapine XR	SEROQUEL XR® (oral) (Schizophrenia; Adults)	Dose range: 400 to 800 mg/day
Ziprasidone	GEODON® (oral) (Schizophrenia; Adults)	Dose range: 40 to 160 mg/day
Lurasidone	LATUDA (oral) (Schizophrenia)	Dose range: 40 to 160 mg/day

Abbreviations: IM = intramuscular; SQ = subcutaneous

[redacted]

KARUNA THERAPEUTICS™
99 High Street | Floor 26 | Boston, MA 02110

October 20, 2022

Advarra IRB
6100 Merriweather Dr.
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Columbia, MD 21044

RE: Karuna Therapeutics KAR-014 [Pro00065534]
A Multi-center, Open-label Study to Assess the Effectiveness, Long-term Safety, Tolerability, and Durability of Effect of KarXT in Patients With DSM-5 Diagnosis of Schizophrenia

Please accept this KAR-014 Protocol Clarification Memorandum to document the below noted protocol clarifications that will be incorporated in a forthcoming amendment.

- Remove the Brief Cognitive Assessment tool for Schizophrenia (B-CATS) and replace with Brief Assessment of Cognition in Schizophrenia Symbol Coding (BACS SC) test.
  - The B-CATS consists of three (3) parts; 1. digit symbol substitution test, 2. trail making test, and 3. category fluency
  - Karuna decided to proceed with the BACS SC for cognition endpoint. This reduces patient and site burden by two (2) tests

- Remove NIDA-5 UDS (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and replace with 12 Panel UDS (AMP (amphetamines), BAR (barbituates) BUP (Buprenorphine), BZO (Benzodiazepines), COC (cocaine), mAMp (Methamphetamine), MDMA (molly), MTD (methodone), OPI (opiates), OXY (oxycodone), PCP (Phencyclidine), THC (marijuana)). The 5 panel UDS was not able to be sourced through the central laboratory.

- Clarify that all patients who titrate from 50/20mg BID to 100/20mg BID are not required to remain on 100/20mg BID for 'at least 1 week'. Further details on dose titration are specified in the protocol.

- Clarify that C-SSRS is to be performed at Unscheduled 'in clinic' visits to monitor patients for suicidality. C-SSRS is not performed if via telemedicine.

- Revise Laboratory Assessments Table 2
  - Urinalysis (Dipstick) section; add bilirubin
  - Full and microscopic urinalysis section; remove parasites

Karuna is committing to revising the protocol to incorporate these revisions and clarifications within 60 days.

Regards,

[redacted]

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