Official Title of Study:

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Adjunctive KarXT in Subjects with Inadequately Controlled Symptoms of Schizophrenia

NCT Number: NCT05145413

Document Date (Date in which document was last revised): 30 Jul 2024

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Adjunctive KarXT in Subjects with Inadequately Controlled Symptoms of Schizophrenia

Protocol Number: KAR-012

IND Number:	127471
EudraCT Number:	2022-001665-12
EU CT Number	2024-510770-25-00
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics, A Bristol Myers Squibb Company 99 High Street 26th Floor Boston, MA 02110 Tel: (857) 449-2244 Email: info@karunatx.com
Protocol Version:	6.0
Protocol Issue Date:	30-Jul-2024

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of adjunctive KarXT in subjects with inadequately controlled symptoms of schizophrenia

Protocol Number: KAR-012

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, including European Union No. 536/2014.

Sponsor Signatory

[redacted]

Karuna Therapeutics, A Bristol Myers Squibb Company

[redacted]

Date: 30-Jul-2024 (v6.0)

INVESTIGATOR SIGNATURE PAGE

Protocol Title:
A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of adjunctive KarXT in subjects with inadequately controlled symptoms of schizophrenia

Protocol Number: KAR-012

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), and regulatory authorities, as applicable, all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by IEC, IRB, and regulatory authorities, I will not modify this protocol without obtaining prior approval from Karuna Therapeutics and of the IEC, IRB, and regulatory authorities. I will submit the protocol amendments and/or any consent form modifications to Karuna Therapeutics and the IEC, IRB, and regulatory authorities, 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 the applicable 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: _____ Date: DD-MMM-YYYY

Institution: _____

1. PROTOCOL SYNOPSIS

Title of Study:	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of adjunctive KarXT in subjects with inadequately controlled symptoms of schizophrenia
Protocol Number:	KAR-012
Investigators/Study Sites:	Approximately 135 sites
Phase of Development:	Phase 3
Rationale:	KarXT combines the muscarinic agonist xanomeline with the peripheral anticholinergic agent trospium to mitigate some of the procholinergic adverse events (AEs) observed in earlier studies of xanomeline as monotherapy. KarXT significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after inpatient treatment for 5 weeks. KarXT also showed an acceptable safety profile, with the most common treatment-emergent adverse events (TEAEs) being constipation, nausea, dry mouth, dyspepsia, and vomiting. Risperidone, paliperidone, aripiprazole or their long-acting injectable [LAI] formulations, ziprasidone, lurasidone, and cariprazine are widely prescribed for the long-term treatment of schizophrenia. Many patients with schizophrenia have an inadequate response to these antipsychotic therapies and continue to be symptomatic, including persistent positive symptoms such as hallucinations and delusions, despite the antipsychotic treatment. Given that KarXT has a different mechanism of action from the dopamine antagonists (D_2) (risperidone, paliperidone, ziprasidone, or lurasidone), D_2 partial agonist (aripiprazole), and D_2 and D_3 partial agonist (cariprazine), adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their LAI formulations, ziprasidone, lurasidone, or cariprazine. As such, adjunctive KarXT might fulfill an important unmet need for schizophrenic patients.
Objective(s):	**Primary Objective:** • To evaluate the efficacy of adjunctive KarXT compared with placebo in the treatment of subjects with inadequately controlled symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total score **Key Secondary Objective:** • To evaluate the efficacy of adjunctive KarXT compared with placebo on the Personal and Social Performance Scale (PSP)

	Additional Secondary Objectives: • To evaluate the efficacy of adjunctive KarXT compared with placebo on Clinical Global Impression Severity (CGI-S), PANSS Marder Positive symptom factor (PANSS M-Pos), PANSS Marder Negative symptom factor (PANSS M-Neg), PANSS responder rate, and Preference of Medication (POM) • To evaluate the safety and tolerability of adjunctive KarXT compared with placebo [redacted]
Efficacy Endpoints:	**Primary efficacy endpoint:** • Change from Baseline in PANSS total score at Week 6 **Key Secondary efficacy endpoint:** • Change from Baseline in PSP at Week 6 **Additional Secondary efficacy endpoints:** • Change from Baseline in CGI-S at Week 6 • Change from Baseline in PANSS M-Pos Symptom Factor score at Week 6 • Change from Baseline in PANSS M-Neg symptom factor score at Week 6 • Categorical response defined as the proportion of subjects achieving a ≥ 30% improvement in PANSS total score at Week 6 • POM at Week 6 [redacted]

Safety Endpoints:	• To evaluate the safety and tolerability of adjunctive KarXT compared with placebo when added to risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine for the treatment of schizophrenia – Spontaneously reported AEs, including TEAEs, serious adverse events (SAEs), and TEAEs leading to study drug withdrawal – Spontaneously reported procholinergic symptoms (e.g., tremor, bradycardia, nausea, vomiting, and diarrhea) and anticholinergic symptoms (e.g., dry mouth, blurred vision, dry eyes, constipation, urinary retention, etc.) – Adverse events of special interest (AESIs) such as orthostasis, syncope, and elevated liver function tests (LFTs) requiring drug-induced liver injury monitoring – Simpson-Angus Scale – Barnes Akathisia Rating Scale – Abnormal Involuntary Movement Scale – Body weight and body mass index (BMI) – Vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate – Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, prolactin levels, and urinalysis – 12-lead electrocardiogram (ECG) – Physical examination – Suicidal ideation assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)
[redacted]	
Study Design:	This study will be conducted as a Phase 3, 6-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study in subjects with schizophrenia with an inadequate response to their current atypical antipsychotic treatment (aripiprazole, risperidone, or paliperidone or their LAI formulations, ziprasidone, lurasidone, or cariprazine). The study will randomize approximately 360 subjects with schizophrenia to adjunctive KarXT or placebo (1:1). The randomization will be stratified by background oral antipsychotic drugs (APDs) vs LAI formulations and country. The effect of adjunctive KarXT on atypical antipsychotics is unknown.

[redacted] An independent Data Monitoring Committee (DMC) will review accumulated unblinded data [redacted]. The DMC structure, roles and responsibilities, procedures, and other operational details will be detailed in the DMC charter. The Statistical Analysis Plan will describe the planned [redacted] in detail.

Subjects will be outpatients, 18 to 65 years old (inclusive) at the time of randomization (Visit 3), with a primary diagnosis of schizophrenia who have been on a stable regimen of aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine for at least 8 weeks at the same dose prior to Day 1 (Visit 3) and continue to experience ongoing positive symptoms despite therapy. The study periods include an [redacted] Screening Period, [redacted], a 6-week double-blind Treatment Period, and a Safety Follow-up (SFU) Visit (end of Week 7) for subjects who do not roll over into the long-term open-label study KAR-013.

The Schedule of Events is shown in Table 1. [redacted]

Screening Period

Subjects meeting prescreening criteria will enter a Screening Period [redacted] to determine eligibility for randomization into the Treatment Period. The subjects will continue to take the same APD they were taking before they came into the study. [redacted]

During Screening, the site will confirm that the subject is meeting randomization criteria including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine at Screening. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1).

Subjects are required to remain on the same appropriate approved APD; the dose of the background APD should not be changed during the study (including during the Screening Period).

Double-blind Treatment Period (6 weeks)

Subjects successfully completing the Screening Period will start double-blind treatment of either adjunctive KarXT or adjunctive placebo. All subjects will continue their currently prescribed atypical antipsychotic (oral aripiprazole or LAI aripiprazole; oral risperidone or LAI risperidone; oral paliperidone or

	LAI paliperidone, ziprasidone, lurasidone, or cariprazine), at the same dose or regimen schedule as prior to entry into the study. Subjects who are randomized will begin receiving KarXT or matching placebo 2 times per day (BID) [redacted]. Study visits will be completed at the end of Weeks 1, 2, 3, 4, and 6. Study visits should be in-person at the study site. For each Study Visit the visit window is ± 3 days. Dosing of blinded study medication is as follows. KarXT is expressed as mg xanomeline as the tartrate salt/mg trospium chloride. • Week 1 – KarXT 50/20 or matched placebo, BID • Week 2 – KarXT 75/20 or matched placebo, BID • Week 3 – Flexible dosing based on tolerability and clinical response between KarXT 75/20 and KarXT 100/20 or matched placebo, BID • Weeks 4 to 6 – Flexible dosing based on tolerability and clinical response between KarXT 75/20 , KarXT 100/20 , and KarXT 125/30 or matched placebo, BID [redacted] <u>Safety Follow-up Visit</u> A SFU Visit will occur at the end of Week 7 (Day 49 ± 3) for all those subjects who do not roll over into the long-term open-label study KAR-013.

	[redacted]
Inclusion/exclusion criteria:	Inclusion Criteria Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years (inclusive) at the time of randomization (Visit 3) 2. Subject is capable of providing signed Informed Consent Form (ICF) before any study assessments will be performed. Subject must be fluent in the language of the ICF to consent 3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the Diagnostic Statistical Manual 5 (DSM-5) criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2 4. Subject is currently being treated with stable dosing of monotherapy risperidone, paliperidone, aripiprazole, or their LAI formulations, ziprasidone, lurasidone, or cariprazine and has been taking this treatment with the same dosing regimen for at least 8 weeks at the time of Day 1 (Visit 3) (supported by documentation) 5. The subject has an inadequate response to above antipsychotics that was dosed appropriately (within the label), as defined per inclusion criteria 8 and 9 6. The subject has not required psychiatric hospitalization, incarceration in prison, acute crisis intervention, or other increase in the level of care due to symptom exacerbation within 8 weeks of Screening and is psychiatrically stable in the opinion of the Investigator 7. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1) 8. PANSS total score ≥ 70 at Screening (Visit 1) and randomization (Day 1, Visit 3)

	9. CGI-S scale with a score ≥ 4 (moderate) at Screening (Visit 1) and randomization (Day1, Visit 3) 10. PANSS Marder Positive symptom factor ≥ 4 on 2 (or more) items (PANSS items, delusions, hallucinations, grandiosity, suspiciousness and persecution, stereotyped thinking, somatic concern, unusual thought content or lack of judgment and insight), at Screening (Visit 1) and randomization (Day 1, Visit 3) 11. Subjects with ≤ 20-point decrease in PANSS total score between Visit 1 and Visit 3 12. Subject is willing and able to visit the clinic in an outpatient setting for the study duration, follow instructions, and comply with the protocol requirements 13. BMI must be within 18 to 40 kg/m^2 (inclusive of both values) 14. Subject resides in a stable living situation, in the opinion of the Investigator 15. Subject has identified a reliable informant/caregiver willing and able to assist with study activities as needed throughout the subject's participation in the study. The informant does not have to be someone responsible for the subject's physical or psychiatric well-being. The informant needs to be physically present at the Screening Visit 1 and can complete the remaining study visits assessments via phone (as needed and as per local regulations). In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial. Individuals who can serve as an informant for a subject include: a. Family member, relative, or partner b. Friend, clubhouse staff member (clubhouse model of psychosocial rehabilitation), or day center co-member c. Social worker, caseworker, residential facility staff, nurse, or other home care staff d. Person who interacts with the subject regularly e. If the subject is well known to the site staff, a site staff member may serve as the informant. Site staff serving as an informant should not have other study responsibilities (i.e., rating scales) delegated to them for that respective subject 16. Women of childbearing potential (WOCBP), or men whose sexual partners are WOCBP, must be able and willing to use at least 1 highly effective method of contraception during the study and for at least 1 menstrual cycle (e.g., 30 days) after the last dose of study drug. Sperm donation is not allowed for 30 days after the final dose of the study drug. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, or bilateral

oophorectomy). For the definition and list of highly effective methods of contraception, [redacted]

Exclusion criteria

Subjects will be excluded from the study if 1 or more of the following criteria at Screening or Baseline are applicable:

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before Screening (confirmed using MINI version 7.0.2 at Screening)
2. The subject has a history of moderate to severe substance use disorder (other than nicotine) within the past 12 months
    a. A Screening subject with mild substance use disorder within the 12 months before Screening must be discussed with the Medical Monitor before being allowed into the study
    b. Subjects who test positive for cannabis at Screening may be permitted to enroll in consultation with the Medical Monitor if the subject's pattern of use is not indicative of a moderate to severe substance use disorder
3. Subject has a history of treatment-resistant schizophrenia defined as:
    a. Failure to minimally respond to 2 adequate courses of APD pharmacotherapy

    Note: Failure to minimally respond is defined as persistence of symptoms of moderate severity in 2 or more psychotic symptom domains or persistence of severe symptoms in 1 or more psychotic symptom domains despite adequate dose and duration (6 weeks or longer) of APD treatment
4. History of symptom instability
    a. > 3 psychiatric hospitalizations over the last 12 months or 2 over the last 6 months
5. Current APD is other than aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine
6. Subjects who are diagnosed with schizophreniform disorder or are experiencing their first treated episode of schizophrenia
7. Significant or severe medical conditions including pulmonary, cardiovascular, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, could jeopardize the safety of the subject or the validity of the study results. Subjects with any of the following laboratory values at Screening (Visit 1) are excluded:
    a. eGFR < 60 mL/min
    b. Alanine transaminase or aspartate transaminase (AST) > 1.5 x upper limit of normal (ULN)

c. Total bilirubin > 1.5 x ULN (Subjects with Gilbert's syndrome can be included as long as direct bilirubin is ≤ 1.5 x ULN)

8. Subjects with human immunodeficiency virus, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections as indicated by medical history, serologies, or LFT results
9. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma as evaluated by the Investigator
10. History of irritable bowel syndrome (with or without constipation) or any serious constipation requiring treatment within the last 6 months
11. Risk of suicidal behavior during the study as determined by the Investigator's clinical assessment and/or C-SSRS as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before Screening or,
    b. Answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before Screening
12. Clinically significant abnormal finding on the physical examination, medical history, ECG (QTcF of > 450 msec in males and > 470 msec in females), or clinical laboratory results at Screening
13. Urine toxicology screen is positive for phencyclidine, amphetamines, opiates, cocaine, or alcohol (clinically significant alcohol use in the opinion of the Investigator)
14. Subject is currently taking, or plans to take while in the study, any prohibited concomitant medication as outlined in [redacted]
15. Pregnant, lactating, or less than 3 months postpartum
16. If, in the opinion of the Investigator and/or Sponsor/Medical Monitor, subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the Investigator and/or Sponsor/Medical Monitor, may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements
17. Positive test for SARS-CoV-2 (COVID-19) within 2 weeks before or at Screening
18. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that would obscure ratings or be expected to disrupt adherence to trial procedures
19. Unable to taper and discontinue a concomitant medication that would preclude participation in the double-blind adjunctive treatment (e.g., cannot stop anticholinergic)
20. Subjects with prior exposure to KarXT

	21. Subjects who experienced any adverse effects due to xanomeline or trospium 22. Subjects who received investigational product as part of a clinical trial within 3 months of Screening 23. Risk of violent or destructive behavior as per Investigator's judgment that would interfere with subject's participation 24. Current involuntary hospitalization or incarceration or on parole/probation, unless approved by the Medical Monitor 25. For all male subjects only, any one of the following: a. History of bladder stones b. History of recurrent urinary tract infections c. Serum prostate-specific antigen > 10 ng/mL d. An International Prostate Symptom Score (IPSS) of 5 (almost always) on either item 1, 3, 5, or 6 e. A sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 Note: IPSS will be required only for male subjects ≥ 45 years of age.
Planned Sample Size:	Approximately 360 subjects will be randomized.
Investigational Therapy:	KarXT is expressed as mg xanomeline as the tartrate salt/mg trospium chloride. 1. KarXT 50/20 BID oral 2. KarXT 75/20 BID oral 3. KarXT 100/20 BID oral 4. KarXT 125/30 BID oral
Reference Therapy:	Not applicable.
Duration:	The duration of the study can be up to 89 days. This includes an [redacted] Screening Period, [redacted], 6-week Treatment Period, and an SFU Visit (end of Week 7) for subjects who do not roll over into the long-term open-label study KAR-013.
Statistical Methods and Planned Analyses:	**General considerations:** All statistical analyses will use SAS® version 9.4 or higher. Summary tables will be organized by treatment group. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), coefficient of variation, median, 95% confidence interval, minimum, and maximum values unless otherwise noted. For categorical variables, frequencies and percentages will be provided.

Sample size:

Approximately 360 subjects will be randomized. The randomization will be stratified by background oral antipsychotic drugs versus LAI formulations and country.

The sample size of up to 360 subjects is based on the assumption of a treatment difference of 5 points on the primary efficacy endpoint (change from Baseline to Week 6 in the PANSS total score), a SD of 13 points, and a 20% drop out rate. A total of 180 subjects per arm will provide a 90% power to detect a significant difference between treatment groups, using a 2-sided alpha of 0.05. [redacted]

Analysis populations:

The intent-to-treat (ITT) population will include all subjects who are randomized into the study.

The modified ITT (mITT) population will include all subjects in the ITT population who received at least 1 dose of study medication, have a Baseline PANSS assessment, and at least 1 post-Baseline PANSS assessment.

The safety population will include all subjects who received at least 1 dose of study medication.

[redacted]

Efficacy analyses:

All efficacy analyses will be performed using the mITT population.

Primary Efficacy Endpoint

The primary efficacy endpoint in the study is the PANSS total score. For the primary efficacy endpoint, the difference between adjunctive KarXT and adjunctive placebo at Week 6 will be estimated using a Mixed Model for Repeated Measurements (MMRM). The model will include the change from Baseline PANSS total scores at Weeks 1, 2, 3, 4, and 6 as the response. The treatment difference at Week 6 will be estimated using contrasts. The MMRM will include the treatment group (adjunctive KarXT or adjunctive placebo), visit, and the interaction between the treatment group and visit as

fixed factors. Age, sex at birth, Baseline PANSS total score, and the randomization stratification factors of background oral APDs versus LAI formulations and country will be used as covariates in the model.

Key Secondary Endpoint

The key secondary endpoint, change from Baseline to Week 6 in PSP, will be analyzed in a manner similar to the primary endpoint. [redacted]

Additional Secondary Efficacy Endpoints

The analysis methods for the additional secondary efficacy endpoints will be detailed in the Statistical Analysis Plan (SAP).

Safety analyses:

The incidence and severity of TEAEs, AESIs, and SAEs will be presented by treatment group. Observed and change from Baseline summaries will be produced for vital signs, clinical laboratory assessments, ECG parameters, and physical examinations. Additional details pertaining to the summary of safety data will be provided in the SAP.

[redacted]

Table 1. Schedule of Events

PROCEDURE	SCREENING PERIOD[a]		TREATMENT PERIOD						SFU[t]	UNS Visits[u]
WEEK	-4	-1	0 Day 1	1	2	3	4	6 ET/EOT	7	
VISIT Window (Days)	1	2	3	4 ± 3	5 ± 3	6 ± 3	7 ± 3	8 ± 3	9 ± 3	
Informed Consent (subject)	X									
Informed Consent (informant)[b]	X									
Collect demographic information	X									
Pregnancy test[c] (WOCBP only)	X	X	X	X	X	X	X	X		
Urine test for drugs of abuse and alcohol testing[d]	X	X	X	X	X	X	X	X		-
Review of inclusion/exclusion criteria	X	X	X							
Subject eligibility verification process	X		X							
Medical, psychiatric, and medication history	X									
MINI version 7.0.2[e]	X									
Complete physical examination[f]	X							X		
[redacted]										
Spontaneous AEs[g]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Height (Screening only), body weight, BMI	X		X					X		
Vital signs[h]: (HR & BP)	X	X	X	X	X	X	X	X		X
Resting 12-lead ECG[i]	X		X			X		X		
Urine analysis[j]	X		X			X		X		
Blood samples for safety laboratory tests	X		X			X		X		
HbA1c[k]	X							X		
Serum prolactin	X		X			X		X		
Viral serology tests[l]	X									
COVID-19 testing[v]	X		X			X		X		
[redacted]										
Randomization			X							
PANSS[n]	X	X	X	X	X	X	X	X		

PROCEDURE	SCREENING PERIOD[a]		TREATMENT PERIOD						SFU[t]	UNS Visits[u]
WEEK	-4	-1	0 Day 1	1	2	3	4	6 ET/EOT	7	
VISIT Window (Days)	1	2	3	4 ± 3	5 ± 3	6 ± 3	7 ± 3	8 ± 3	9 ± 3	
PSP			X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X		
POM								X		
[redacted]										
C-SSRS[p]	X		X	X	X	X	X	X	X	X
SAS	X		X	X	X	X	X	X		
BARS	X		X	X	X	X	X	X		
AIMS	X		X	X	X	X	X	X		
IPSS questionnaire[q]	X		X				X	X	X	
Dispense study drug			X	X	X[r]	X[r]	X[r]			
Collect study drug				X	X	X	X	X		
[redacted]										

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Rating Scale for Akathisia; BMI = body mass index; BID = 2 times per day; BP = blood pressure; [redacted]; CGI-S = Clinical Global Impression–Severity scale; COVID-19 = SARS-CoV-2; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = End-of-Treatment; ET = early termination; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; IPSS = International Prostate Symptom Score; MINI = Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies; PANSS = Positive and Negative Syndrome Scale; PCR = polymerase chain reaction; [redacted] POM = preference of medication; PSP = Personal and Social Performance Scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; SFU = Safety Follow-up; SOE = Schedule of Events; UNS = unscheduled; WOCBP = women of childbearing potential.

a. The Screening Period is [redacted].
b. The informant can provide consent in person or remotely in accordance with local regulations and site processes and prior to any study procedures being conducted at the Screening Visit (Visit 1). The informant needs to be physically present at the Baseline Visit but can complete the remaining study visits assessments via phone (as needed and as per local regulations). In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial, and will sign the informant consent in person.
c. A serum pregnancy test for WOCBP should be done at Visit 1, and urine pregnancy tests should be done at other visits. A serum pregnancy should be done to confirm any positive urine pregnancy test.
d. A urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, cocaine, and alcohol) will be performed at scheduled visits as noted in the SOE.

e. [redacted].
f. A complete physical examination includes body temperature (orally collected, °C), general appearance, head/eyes/ears/nose/throat, an examination of thorax and abdomen, assessment of cardiovascular, pulmonary, and musculoskeletal systems, palpations for lymphadenopathy, and limited neurological examination.
g. AEs as reported by subjects or observed by clinical staff after they have signed the Informed Consent Form
h. Vital signs taken at supine and standing approximately after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in beats/minute.
i. ECGs at all scheduled visits will be performed before blood sample collection for any safety laboratory tests and/or [redacted] analysis. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained.
j. Urine analysis should be performed as noted in the SOE and Table 4.
k. HbA1c should be performed on Visit 1 (Screening) and end of Week 6 (Visit 8; Day 42 ± 3). See Table 4 for details.
l. All subjects must have the following viral serology tests: anti-HCV antibody, HBV surface antigen, HIV-1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via PCR should be performed to confirm or rule out active infection.
[redacted].
n. [redacted]
p. C-SSRS first time use lifetime, other times use "Since Last Visit" version.
q. IPSS questionnaire completion should be performed at the specified timepoints for male subjects ≥ 45 years of age only.
[redacted]
t. A SFU Visit will be performed 1 week after EOT (Week 7; Day 49 ± 3 days) except for subjects that roll over into the KAR-013 study (open-label safety study).
u. Other assessments as needed.
v. Optional COVID-19 testing (antigen or PCR) may be performed at any visit based on the Investigator's discretion. If a subject tests positive for COVID-19 during the study, they may be quarantined, and any scheduled visits should be rescheduled at the discretion of the Investigator. If the subject requires hospitalization, an SAE should be reported, and the subject should be followed up. In the United States, mandatory timepoints are done by the central laboratory and optional are done locally.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BID	2 times per day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
[redacted]	[redacted]
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
CNS	central nervous system
COVID-19	SARS-CoV-2
CRO	clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
D_2	dopamine receptor 2
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	End-of-Treatment
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HIPAA	Health Insurance Portability Accountability Act
HIV	human immunodeficiency virus
[redacted]	[redacted]
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
KarXT	combination of the muscarinic agonist xanomeline and the peripheral anticholinergic agent trospium
LAI	long-acting injectable
LFT	liver function test
[redacted]	
M1, M4	muscarinic agonist receptors
[redacted]	[redacted]
MI	multiple imputation
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	Mixed Model for Repeated Measurements
[redacted]	
PANSS	Positive and Negative Syndrome Scale
PANSS M-Neg	PANSS Marder Negative
PANSS M-Pos	PANSS Marder Positive
[redacted]	[redacted]
POM	preference of medication

Abbreviation	Definition
PR	time elapsing between the beginning of the P wave and the beginning of the next QRS complex
PRN	as needed
PSA	prostate-specific antigen
PSP	Personal and Social Performance
QRS	combination of Q wave, R wave, and S wave in ECG
QT	time from Q wave to the end of the T wave
QTcF	QT interval corrected with Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SD	standard deviation
SFU	Safety Follow-up
SOE	Schedule of Events
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WOCBP	women of childbearing potential

2. INTRODUCTION

2.1. 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 have included dosing above the high end of the therapeutic range, switching to another first-line antipsychotic, combining 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 treatment-resistant.

All antipsychotics currently approved for the treatment of schizophrenia have dopamine (D_2) receptor affinities that mediate antipsychotic activity. In the Phase 2 study (KAR-004), KarXT, a M1/M4 muscarinic agonist, demonstrated statistically significant results on the Positive and Negative Syndrome Scale (PANSS) positive subscale as well as on the PANSS total score and PANSS-negative subscale (Brannan 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, ziprasidone, lurasidone, or the D_2 partial agonist aripiprazole, and D_2 and D_3 partial agonist cariprazine, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their long-acting injectable (LAI) formulations, ziprasidone, lurasidone, or cariprazine.

The proposed study is a registration-quality trial to assess the safety and efficacy of adjunctive KarXT as a treatment for subjects with schizophrenia who have had an inadequate response to their current antipsychotic (aripiprazole, risperidone, paliperidone, ziprasidone, lurasidone, or cariprazine) at a therapeutic dose and appropriate duration.

2.2. BACKGROUND

2.2.1. Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability (Patel 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 has estimated that the annual prevalence of diagnosed schizophrenia in the US is 5.1 per 1000 lives (Wu 2006). It is found equally in males and females, with males usually having an earlier onset of symptoms (Crismon 2014).

The mainstay for treating schizophrenia is antipsychotic drugs (APDs) (Green 2004). All currently available APDs 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, and they consequently have limited use today. The second-generation agents that include risperidone, paliperidone, aripiprazole, olanzapine, quetiapine, lurasidone, and lumateperone tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia (Lieberman 2005, Leucht 2013, Huhn 2019). These side effects have contributed to poor medication adherence resulting in frequent relapses and hospitalizations (Emsley 2013, Kahn 2015). Thus, there is a need for medications for schizophrenia that act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence, including both animal and human studies (Wess 2007, Sellin 2008). There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to the agonism of M1 and M4 receptors in the central nervous system (CNS) (Mirza 2003). However, compounds that agonize M1 and M4 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.

2.2.2. 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 preferentially stimulates M1 and M4 receptors, and binding to M1 and M4 receptors in the CNS is thought to be responsible for the drug's potential therapeutic effects. A recent study reports that xanomeline is a potent M_4 muscarinic agonist in vivo, measured by various second messenger assays (Thorn 2019). Xanomeline also rapidly enters the brain, achieving a brain-to-plasma ratio greater than 10, making it an attractive CNS drug candidate (Farde 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 have 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 1997, Bodick 1997). 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 2008).

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

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 5 muscarinic receptor subtypes. Several studies in humans have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure (Scheife and Takeda 2005).

Karuna hypothesized that adding trospium to xanomeline would 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 is generally well tolerated (Staskin 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.

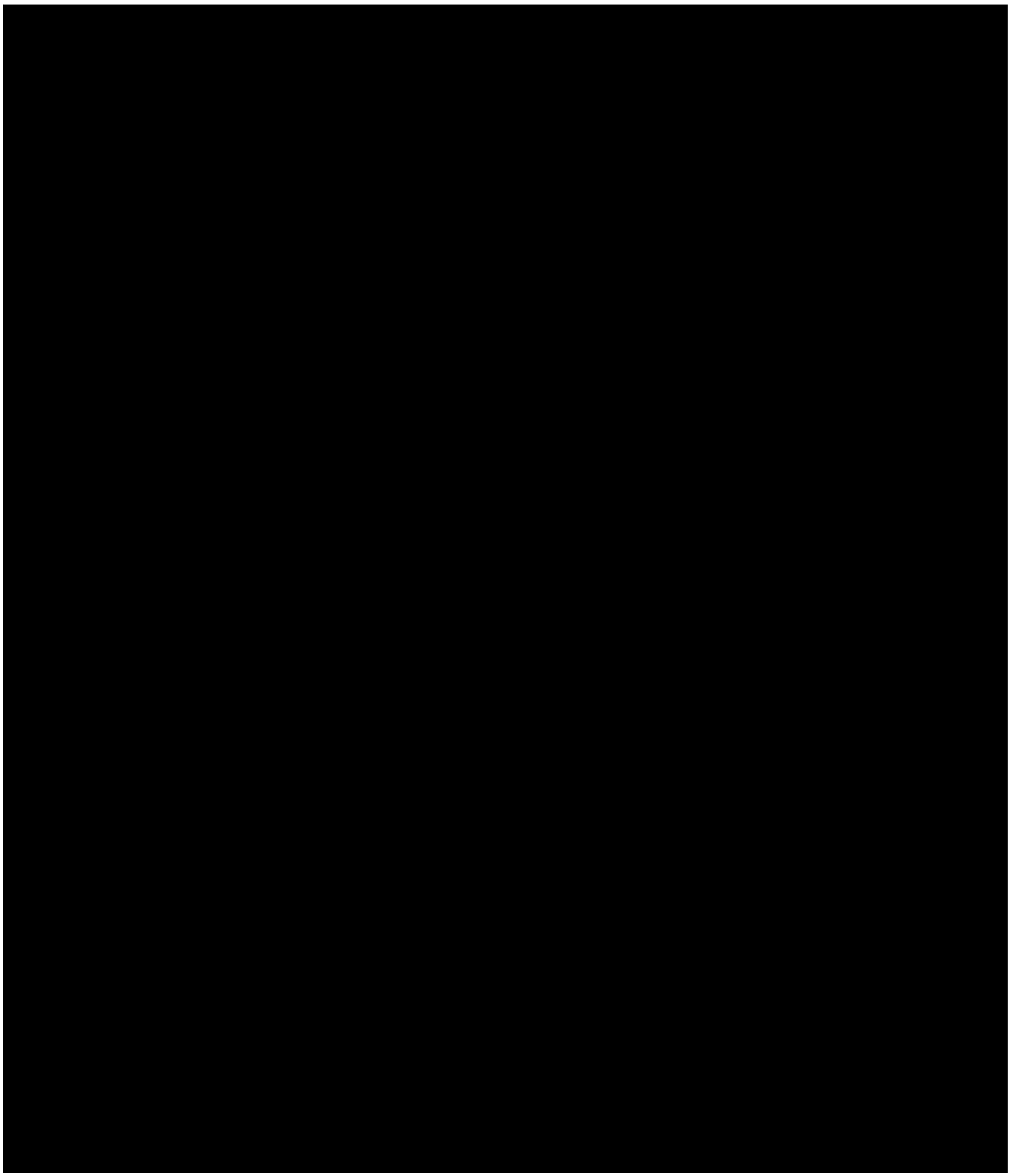
KarXT significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after inpatient treatment for 5 weeks (KAR-004) (Brannan 2021). KarXT also showed an acceptable safety profile, with the most common treatment-emergent adverse events (TEAEs) being constipation, nausea, dry mouth, dyspepsia, and vomiting (for completed clinical studies, see Section 2.2.4).

2.2.3. Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT IB.

No evidence of mutagenicity or treatment effects on reproduction, fertility, or fetal parameters has been demonstrated in animals following the administration of xanomeline. There are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Based on animal data, trospium chloride is predicted to have a low probability of increased risk of

adverse development outcomes, above background risk. Adverse development findings were not observed to correlate with dose in rats or in rabbits. No increased risk above background was observed in rats and rabbits treated at an exposure approximately equivalent to the maximal recommended human dose of 40 mg. Trospium chloride should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus.



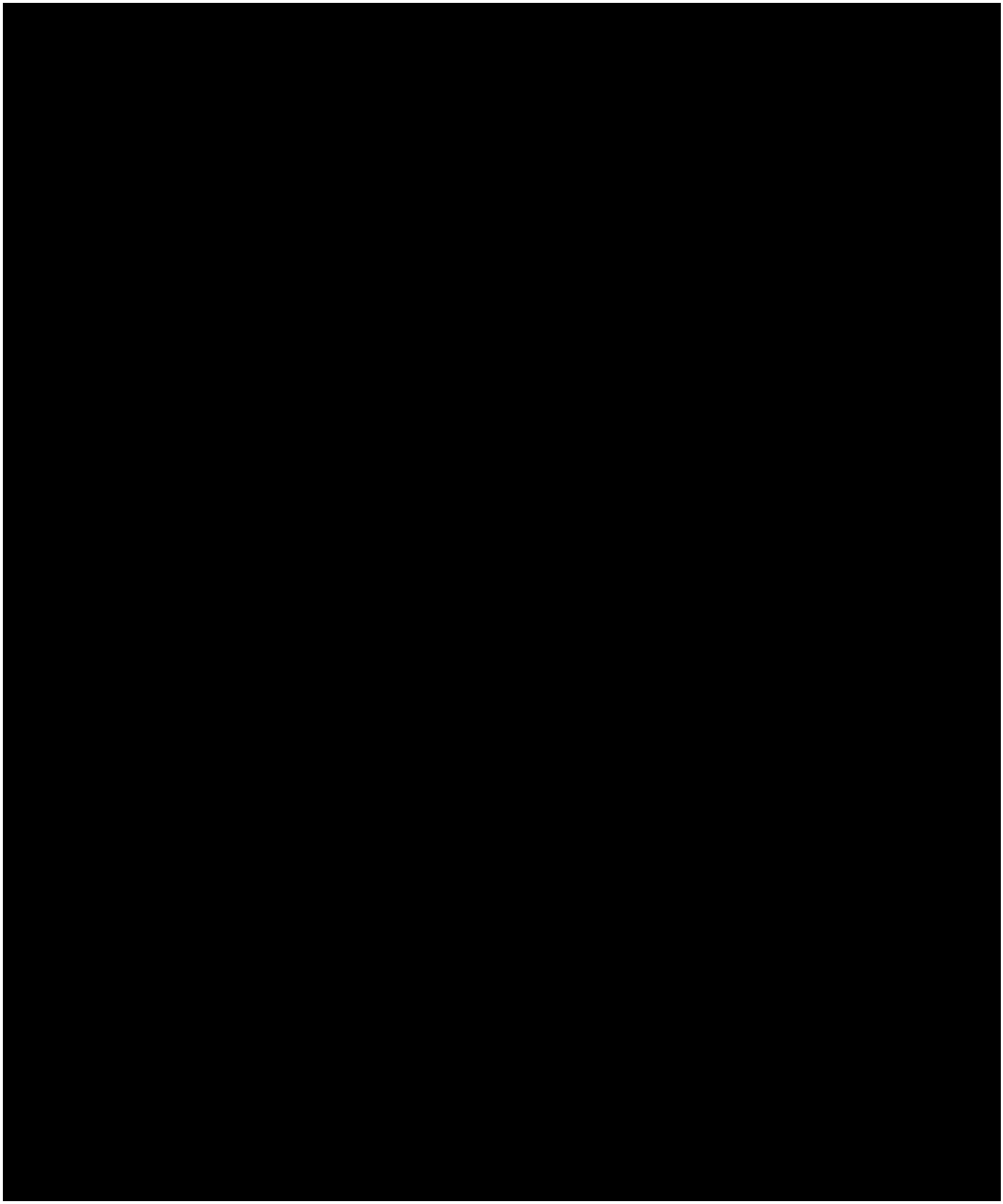
[redacted]

2.2.4. Clinical Studies

To date, in 32 completed clinical studies conducted by Eli Lilly or Karuna Therapeutics approximately 1632 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 multiple completed Phase 1 studies in healthy volunteers [redacted] findings described below), 1 completed Phase 2 study (KAR-004 findings described below), and multiple completed Phase 3 studies (KAR-007 and KAR-009 findings described below) in adult subjects with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) schizophrenia. Multiple other Phase 1 and Phase 3

studies are ongoing. Refer to the KarXT IB for details on all completed and ongoing KarXT studies.



[redacted]

2.2.4.4. KAR-004

Study KAR-004 was a Phase 2 randomized, double-blind study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia hospitalized with acute psychosis. The primary objective was to evaluate the efficacy of KarXT 125/30 BID vs placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a Treatment Period of 5 weeks. [redacted]

KarXT demonstrated statistically significant and clinically meaningful mean reductions in total PANSS scores at 5 weeks compared to placebo ($p < 0.0001$) in the modified intent-to-treat (mITT) population (Brannan 2021). [redacted]

[redacted]

[redacted]

2.2.4.5. KAR-007

KAR-007 was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, inpatient clinical study in adults who were acutely psychotic with a DSM-5 diagnosis of schizophrenia. This study was conducted at 21 sites in the US. Total study duration was ≤ 8 weeks, including a 7-day Screening phase (≤ 7-day extension of the Screening phase was allowed, if necessary), a 5-week Treatment Period, and a 7-day follow-up period (only for subjects who did not roll over to the KAR-008 study). This Phase 3 study largely confirms the findings of the previous Phase 2 study (KAR-004).

A total of 252 subjects were enrolled and randomized to receive either KarXT (N = 126) or placebo (N = 126). [redacted]

The trial met the pre-specified primary endpoint and all secondary endpoints with KarXT, showing statistically superior efficacy compared with placebo (Kaul 2024a). [redacted]

[redacted]

Overall, administration of KarXT for 5 weeks resulted in consistent, significant reductions in both positive and negative symptoms of schizophrenia and CGI-S. In addition, the safety and tolerability of KarXT was consistent with that of the previous placebo-controlled trial (KAR-004) and notably, free of many common side effects associated with currently approved antipsychotic drugs. [redacted]. This indicates how well this patient population tolerates KarXT. These results confirm and extend the antipsychotic benefit of xanomeline observed in past studies and the well-tolerated nature of KarXT. KarXT may represent a new mechanism and a completely new drug class for the treatment of schizophrenia.

2.2.4.6. KAR-009

KAR-009 was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, inpatient clinical study in adults who were acutely psychotic with a DSM-5 diagnosis of schizophrenia. This study was conducted at 30 sites (18 sites in the US and 12 sites in Ukraine). Total study duration was ≤ 8 weeks, including a 7-day Screening phase (≤ 7-day extension of the Screening phase was allowed, if necessary), a 5-week Treatment Period, and a 7-day follow-up period (only for subjects who did not roll over to the KAR-008 study). This Phase 3 study largely confirms the findings of the previous Phase 2 study (KAR-004) and the parallel Phase 3 study (KAR-007). [redacted]

A total of 256 subjects were enrolled and randomized to receive either KarXT (N = 125) or placebo (N = 131). [redacted]

The trial met the pre-specified primary endpoint (Kaul 2024b). For the primary endpoint of mean change from baseline change from baseline in PANSS total score at Week 5 (Visit 10 [Day 35]), KarXT was superior to placebo with an least squares mean difference of -8.4 points (-20.6 versus -12.2 points; $p < 0.0001$), with a Cohen-d effect size of 0.60. The placebo changes were greater in this study as compared to those of previous study KAR-004, but were similar to KAR-007 and more in line with what has been seen in most antipsychotic trials.

Overall, administration of KarXT for 5 weeks resulted in consistent, significant reductions in symptoms of schizophrenia and CGI-S compared with placebo. In addition, the safety and tolerability of KarXT was consistent with the previous placebo-controlled trial (KAR-004) and

the parallel Phase 3 trial (KAR-007) and notably, free of many common side effects associated with currently approved antipsychotic drugs. [redacted] These results confirm and extend the antipsychotic benefit of xanomeline observed in past studies and the well-tolerated nature of KarXT. KarXT may represent a new mechanism and a completely new drug class for the treatment of schizophrenia.

2.3. 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 and had an acceptable safety profile that appeared unique compared with 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 and can lead to discontinuation of treatment and to significant morbidity.

2.3.1. Known Potential Risks

The most common risks with KarXT are procholinergic- and anticholinergic-related effects. The frequently observed AEs with the use of KarXT from other clinical trials include nausea, dry mouth, vomiting, salivary hypersecretion, diarrhea, hyperhidrosis, vision blurred, constipation, dysuria, dyspepsia, gastroesophageal reflux disease (GERD), somnolence, urinary retention, increased liver function tests (LFTs), tachycardia, fatigue, chills, headache, abdominal pain, and sensation of foreign body. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline, creating a better tolerated therapy.

2.3.2. Known Potential Benefits

Subjects assigned to active study drug may benefit from improvement in the positive symptoms of schizophrenia.

2.3.3. 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 current 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 subjects. The Sponsor believes the risk-benefit ratio is favorable, and continuous risk-benefit assessments will be conducted throughout the trial.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. STUDY OBJECTIVES

3.1.1. Primary Objective

To evaluate the efficacy of adjunctive KarXT compared with placebo in the treatment of subjects inadequately controlled symptoms of schizophrenia as measured by PANSS total score

3.1.2. Key Secondary Objective

To evaluate the efficacy of adjunctive KarXT compared with placebo on the Personal and Social Performance Scale (PSP)

3.1.3. Additional Secondary Objectives

Additional secondary objectives are as follows:

- To evaluate the efficacy of adjunctive KarXT compared with placebo on CGI-S, PANSS Marder Positive symptom factor (PANSS M-Pos), PANSS Marder Negative symptom factor (PANSS M-Neg), PANSS responder rate, and Preference of Medication (POM)
- To evaluate the safety and tolerability of adjunctive KarXT compared with placebo

[redacted]

3.2. STUDY ENDPOINTS

3.2.1. Primary Efficacy Endpoint

Change from Baseline in PANSS total score at Week 6

3.2.2. Key Secondary Efficacy Endpoint

Change from Baseline in PSP at Week 6

3.2.3. Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints are as follows:

- Change from Baseline in CGI-S at Week 6
- Change from Baseline in PANSS M-Pos Symptom Factor score at Week 6
- Change from Baseline in PANSS M-Neg symptom factor score at Week 6
- Categorical response defined as the proportion of subjects achieving a ≥ 30% improvement in PANSS total score at Week 6

- POM at Week 6

[redacted]

3.2.5. Safety Endpoints

The safety endpoints are as follows:

- To evaluate the safety and tolerability of adjunctive KarXT compared with placebo when added to risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine for the treatment of schizophrenia
  - Spontaneously reported AEs, including TEAEs, SAEs, and TEAEs leading to study drug withdrawal
  - Spontaneously reported procholinergic symptoms (e.g., tremor, bradycardia, nausea, vomiting, and diarrhea) and anticholinergic symptoms (e.g., dry mouth, blurred vision, dry eyes, constipation, urinary retention, etc.)
  - Adverse events of special interest (AESIs) such as orthostasis, syncope, and elevated LFTs requiring drug-induced liver injury (DILI) monitoring
  - Simpson-Angus Scale (SAS)
  - Barnes Akathisia Rating Scale (BARS)
  - Abnormal Involuntary Movement Scale (AIMS)
  - Body weight, body mass index (BMI)
  - Vital signs (supine and standing after 2 minutes): blood pressure (BP) (systolic and diastolic) and heart rate (HR)
  - Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, prolactin levels, and urinalysis
  - 12-lead electrocardiogram (ECG)
  - Physical examination
  - Suicidal ideation assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)

[redacted]

4. STUDY DESIGN

4.1. DESCRIPTION OF OVERALL STUDY DESIGN

This study will be conducted as a Phase 3, 6-week, randomized, double-blind, placebo-controlled, multicenter, outpatient study in subjects with schizophrenia with an inadequate response to their current atypical antipsychotic treatment (aripiprazole, risperidone, paliperidone or their LAI formulations, ziprasidone, lurasidone, or cariprazine).

The study will randomize approximately 360 subjects with schizophrenia to adjunctive KarXT or placebo (1:1). The randomization will be stratified by background oral APDs vs LAI formulations and country. The effect of adjunctive KarXT on atypical antipsychotics is unknown.

[redacted]

Subjects will be outpatients, 18 to 65 years old (inclusive) at the time of randomization (Visit 3), with a primary diagnosis of schizophrenia who have been on a stable regimen of aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine for at least 8 weeks at the same dose prior to Day 1 (Visit 3) and continue to experience ongoing positive symptoms despite therapy. The study periods include [redacted] Screening Period, [redacted], a 6-week double-blind Treatment Period, and a Safety Follow-up (SFU) Visit (end of Week 7) for subjects who do not roll over into KAR-013. The total duration of the study can be up to 89 days.

[redacted]

Screening Period

Subjects meeting prescreening criteria will enter a Screening Period [redacted] to determine eligibility for randomization into the 6-week double-blind Treatment Period. The subjects will continue to take the same antipsychotic they were taking before they came into the study. The recommended background dosing of aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine are provided in APPENDIX 1.

The subjects will continue to take the same antipsychotic they were taking before they came into the study. [redacted]. During Screening, the site will confirm that the subject is meeting randomization criteria, including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine at Screening. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1).

Subjects are required to remain on the same appropriate approved APD; the dose of the background APD should not be changed during the study (including the Screening Period).

Double-blind Treatment Period (6 weeks)

Subjects successfully completing the Screening Period will start double-blind treatment of either adjunctive KarXT or adjunctive placebo. All subjects will continue their currently prescribed atypical antipsychotic (oral aripiprazole or LAI aripiprazole; oral risperidone or LAI risperidone; oral paliperidone or LAI paliperidone, ziprasidone, lurasidone, or cariprazine) at the same dose or regimen schedule as prior to entry into the study.

The dosing of blinded study medication is as follows. KarXT is expressed as mg xanomeline as the tartrate salt/mg trospium chloride.

- Week 1 – KarXT 50/20 or matched placebo, BID
- Week 2 – KarXT 75/20 or matched placebo, BID
- Week 3 – Flexible dosing based on individual tolerability and clinical response. Subjects will receive KarXT 75/20, or KarXT 100/20, or matched placebo, BID
- Weeks 4 to 6 – Flexible dosing based on individual tolerability and clinical response. Subjects will receive KarXT 75/20, or KarXT 100/20, or KarXT 125/30, or matched placebo, BID

[redacted]

[redacted]

Subjects who are randomized will begin receiving KarXT or placebo BID. All visits will occur in-person.

Early termination (ET) and withdrawal subjects should follow all the procedures mentioned under the End-of-Treatment (EOT) visit (see Schedule of Events [SOE], Table 1).

All randomized subjects will have structured diagnostic interview sessions and questionnaires administered throughout the Treatment Period (see SOE, Table 1). Changes from Baseline in diagnostic measures will be analyzed.

Efficacy assessments (PANSS scores, CGI-S scores, and other efficacy endpoints as defined in Section 3.2) will be assessed at scheduled visits. Refer to Section 7.5 for more details.

Safety will be assessed through spontaneous AEs including TEAEs, TEAEs leading to study drug withdrawal, AESIs, procholinergic and anticholinergic symptoms, SAS, BARS, AIMS, body weight, BMI, vital signs, ECG, International Prostate Symptom Score (IPSS) questionnaire, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), prolactin levels, physical examination, and C-SSRS throughout the study as scheduled. Section 7.6 provides complete details on these safety assessments.

[redacted].

Safety Follow-up Visit:

A SFU Visit at the end of Week 7 (Visit 9) will occur for all subjects, except for subjects that roll over into the KAR-013 study (open-label safety study).

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study uses a group sequential design used to determine the efficacy of an adjunctive treatment.

Duration of Study

Schizophrenia is a long-term mental disorder that requires chronic therapy. A 6-week treatment duration is considered an acceptable treatment duration to observe clinically significant response (i.e., a primary endpoint can be achieved). The 6-week duration is consistent with registrational trials in both depression and schizophrenia studies and fulfills European Medicines Agency requirements for adjunctive schizophrenia trials.

Background antipsychotic

The study will allow 6 different monotherapy background antipsychotics. Aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine are widely prescribed for the long-term treatment of schizophrenia. Many patients with schizophrenia have an inadequate response to antipsychotic therapy and continue to be

symptomatic, including positive symptoms such as hallucinations and delusions. Given that KarXT has a different mechanism of action from D_2 antagonists (risperidone, paliperidone, ziprasidone, or lurasidone), D_2 partial agonist (aripiprazole), and D_2 and D_3 partial agonist (cariprazine), adjunctive KarXT therapy may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine taken as oral medications. As such, adjunctive KarXT might fulfill a critical unmet need for schizophrenic patients.

[redacted]

4.4. DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to review accumulated data [redacted]. The DMC charter will describe the procedures related to the committee operations in greater detail.

[redacted]

4.6. END OF STUDY

A subject will have fulfilled all the requirements for the trial when the subject has completed all study visits, including the EOT visit (Visit 8) and the SFU Visit 1 week after the EOT visit (Visit 9). Subjects who entered into the KAR-013 study (open-label safety study) will not have a SFU Visit in this study.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

Section 4.1 provides information regarding the number of subjects planned to be randomized.

5.1. INCLUSION CRITERIA

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

1. Subject is aged 18 to 65 years (inclusive) at the time of randomization (Visit 3)
2. Subject is capable of providing signed Informed Consent Form (ICF) before any study assessments will be performed. Subject must be fluent in the language of the ICF to consent
3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2
4. Subject is currently being treated with stable dosing of monotherapy risperidone, paliperidone, aripiprazole, or their LAI formulations, ziprasidone, lurasidone, or cariprazine and has been taking this treatment with the same dosing regimen for at least 8 weeks at the time of Day 1 (Visit 3) (supported by documentation)
5. The subject has an inadequate response to above antipsychotics that was dosed appropriately (within the label) as defined per inclusion criteria 8 and 9
6. The subject has not required psychiatric hospitalization, incarceration in prison, acute crisis intervention, or other increase in the level of care due to symptom exacerbation within 8 weeks of Screening and is psychiatrically stable in the opinion of the Investigator
7. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1)
8. PANSS total score ≥ 70 at Screening (Visit 1) and randomization (Day 1, Visit 3)
9. CGI-S scale with a score ≥ 4 (moderate) at Screening (Visit 1) and randomization (Day 1, Visit 3)
10. PANSS Marder Positive symptom factor ≥ 4 on 2 (or more) items (PANSS items, delusions, hallucinations, grandiosity, suspiciousness and persecution, stereotyped thinking, somatic concern, unusual thought content or lack of judgment and insight), at Screening (Visit 1) and randomization (Day 1, Visit 3)
11. Subjects with ≤ 20-point decrease in PANSS total score between Visit 1 and Visit 3
12. Subject is willing and able to visit the clinic in an outpatient setting for the study duration, follow instructions, and comply with the protocol requirements
13. BMI must be within 18 to 40 kg/m^2 (inclusive of both values)
14. Subject resides in a stable living situation, in the opinion of the Investigator
15. Subject has identified a reliable informant/caregiver willing and able to assist with study activities as needed throughout the subject's participation in the study. The informant

does not have to be someone responsible for the subject's physical or psychiatric well-being. The informant needs to be physically present at the Screening Visit 1and can complete the remaining study visits assessments via phone (as needed and as per local regulations). In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial. Individuals who can serve as an informant for a subject include:

   a. Family member, relative, or partner
   b. Friend, clubhouse staff member (clubhouse model of psychosocial rehabilitation), or day center co-member
   c. Social worker, caseworker, residential facility staff, nurse, or other home care staff
   d. Person who interacts with the subject regularly
   e. If the subject is well known to the site staff, a site staff member may serve as the informant. Site staff serving as an informant should not have other study responsibilities (i.e., rating scales) delegated to them for that respective subject

16. Women of childbearing potential (WOCBP), or men whose sexual partners are WOCBP, must be able and willing to use at least 1 highly effective method of contraception during the study and for at least 1 menstrual cycle (e.g., 30 days) after the last dose of study drug. Sperm donation is not allowed for 30 days after the final dose of the study drug. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). For the definition and list of highly effective methods of contraception, see [redacted]

5.2. EXCLUSION CRITERIA

Subjects will be excluded from the study if 1 or more of the following criteria at Screening or Baseline are applicable*:*

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before Screening (confirmed using MINI version 7.0.2 at Screening)
2. The subject has a history of moderate to severe substance use disorder (other than nicotine) within the past 12 months
   a. A Screening subject with mild substance use disorder within the 12 months before Screening must be discussed with the Medical Monitor before being allowed into the study
   b. Subjects who test positive for cannabis at Screening may be permitted to enroll in consultation with the Medical Monitor if the subject's pattern of use is not indicative of a moderate to severe substance use disorder
3. Subject has a history of treatment-resistant schizophrenia defined as:
   a. Failure to minimally respond to 2 adequate courses of APD pharmacotherapy

Note: Failure to minimally respond is defined as persistence of symptoms of moderate severity in 2 or more psychotic symptom domains or persistence of severe symptoms in 1 or more psychotic symptom domains despite adequate dose and duration (6 weeks or longer) of APD treatment.

4. History of symptom instability
    a. > 3 psychiatric hospitalizations over the last 12 months or 2 over the last 6 months
5. Current APD is other than aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine
6. Subjects who are diagnosed with schizophreniform disorder or are experiencing their first treated episode of schizophrenia
7. Significant or severe medical conditions including pulmonary, cardiovascular, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, could jeopardize the safety of the subject or the validity of the study results. This includes subjects with the following laboratory values at Screening (Visit 1):
    a. eGFR < 60 mL/min
    b. Alanine transaminase (ALT) or aspartate transaminase (AST) > 1.5 × upper limit of normal (ULN)
    c. Total bilirubin > 1.5 × ULN (Subjects with Gilbert's syndrome can be included as long as direct bilirubin is ≤ 1.5 × ULN)
8. Subjects with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections as indicated by medical history, serologies, or LFT results
9. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma as evaluated by the Investigator
10. History of irritable bowel syndrome (with or without constipation) or any serious constipation requiring treatment within the last 6 months
11. Risk of suicidal behavior during the study as determined by the Investigator's clinical assessment and/or C-SSRS as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before Screening or,
    b. Answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before Screening
12. Clinically significant abnormal finding on the physical examination, medical history, ECG (QTcF of > 450 msec in males and > 470 msec in females), or clinical laboratory results at Screening
13. Urine toxicology screen is positive for phencyclidine, amphetamines, opiates, cocaine, or alcohol (clinically significant alcohol use in the opinion of the Investigator)

14. Subject is currently taking, or plans to take while in the study, any prohibited concomitant medication as outlined in [redacted]
15. Pregnant, lactating, or less than 3 months postpartum
16. If, in the opinion of the Investigator and/or Sponsor/Medical Monitor, subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the Investigator and/or Sponsor/Medical Monitor, may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements
17. Positive test for SARS-CoV-2 (COVID-19) within 2 weeks before or at Screening
18. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that would obscure ratings or be expected to disrupt adherence to trial procedures
19. Unable to taper and discontinue a concomitant medication that would preclude participation in the double-blind adjunctive treatment (e.g., cannot stop anticholinergic)
20. Subjects with prior exposure to KarXT
21. Subjects who experienced any adverse effects due to xanomeline or trospium
22. Subjects who received investigational product as part of a clinical trial within 3 months of Screening
23. Risk of violent or destructive behavior as per Investigator's judgment that would interfere with subject's participation
24. Current involuntary hospitalization or incarceration or on parole/probation, unless approved by the Medical Monitor
25. For all male subjects only, any one of the following:
    a. History of bladder stones
    b. History of recurrent urinary tract infections
    c. Serum prostate-specific antigen (PSA) > 10 ng/mL
    d. An IPSS of 5 (almost always) on either item 1, 3, 5, or 6
    e. A sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9

    Note: IPSS will be required only for male subjects ≥ 45 years of age.

5.3. SCREEN FAILURE AND RESCREENING

Individuals who sign the ICF to participate in the study and then do not subsequently meet all inclusion/exclusion criteria are not enrolled in the study and are categorized as Screen Failure. Subjects may be rescreened one time on a case-by-case basis upon approval of the Medical Monitor. Any subject who is considered for rescreen should sign a new ICF.

5.4. STUDY TERMINATION

The availability of any new adverse safety information related to KarXT may result in stopping the study. An Investigator, Sponsor, or Independent Ethics Committee (IEC)/Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects

will be notified immediately and assured that appropriate treatment and follow-up will be available. If an Investigator terminates the subject's participation in the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the Investigators, the IEC/IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

5.5. SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

If a subject discontinues the study treatment and/or is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF).

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

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

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

- Unacceptable toxicity or AE
- Subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request. The reason for subject withdrawal will be noted on the eCRF
- On the basis of the Investigator's clinical judgment
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- General or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria (e.g., the subject needs a medication prohibited by the protocol)
- Subject fails to adhere to the protocol requirements (e.g., drug non-compliance [if a study subject is off study drug for > 5 days in a row])
- Violation of entry criteria, i.e., subjects who are enrolled but are later discovered to not meet entry criteria
- Development of suicidal or assaultive behavior
- Clinically significant alcohol use or illegal drug use in the opinion of the Investigator or Sponsor.
- Pregnancy, as indicated in Section 5.6, any study subject who becomes pregnant while participating in the study will be unblinded to study treatment randomization. If found to

be on active treatment assignment, the subject will be followed until the pregnancy reaches term

- Sponsor's decision to discontinue the study

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations (Visits 8/ET and 9/SFU) as indicated in the SOE (Table 1). The aim is to record data in the same way as for subjects who completed the study.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the study drug become known, making further treatment of subjects impossible. In this event, the Investigator(s) will be informed of the reason for study termination.

5.6. PREGNANCY

Subjects with a positive urine pregnancy test must immediately stop taking study medication until the results of the confirmatory serum pregnancy test are available. If a pregnancy is verified, the subject will be permanently discontinued from the study drug. Upon discontinuation from the study drug, only procedures that would not expose the pregnant female subject to undue risk will be performed at the ET Visit and the SFU Visit. See Section 7.7.6 for further reporting and monitoring details.

The effects of KarXT on the developing human fetus are unknown, with the potential for teratogenic or abortifacient effects (Section 2.2.3).

5.7. LOST TO FOLLOW-UP

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

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

6. STUDY TREATMENT ADMINISTRATION

[redacted]

6.2. DOSING AND ADMINISTRATION

[redacted]

- Week 1: Subjects will receive KarXT 50/20 xanomeline/trospium chloride BID or matching placebo BID during Week 1
- Week 2: Subjects will receive KarXT 75/20 xanomeline/trospium chloride BID or matching placebo BID during Week 2
- Week 3: At the beginning of Week 3, the KarXT dose should be increased to 100/20 BID or matching placebo BID if the KarXT 75/20 BID dose is tolerated
- Weeks 4 to 6: Flexible dosing based on tolerability and clinical response between KarXT 75/20, KarXT 100/20, and KarXT 125/30 (mg xanomeline as the tartrate salt/mg trospium chloride or matched placebo), BID.

[redacted]

All investigational agents are to be stored according to requirements.

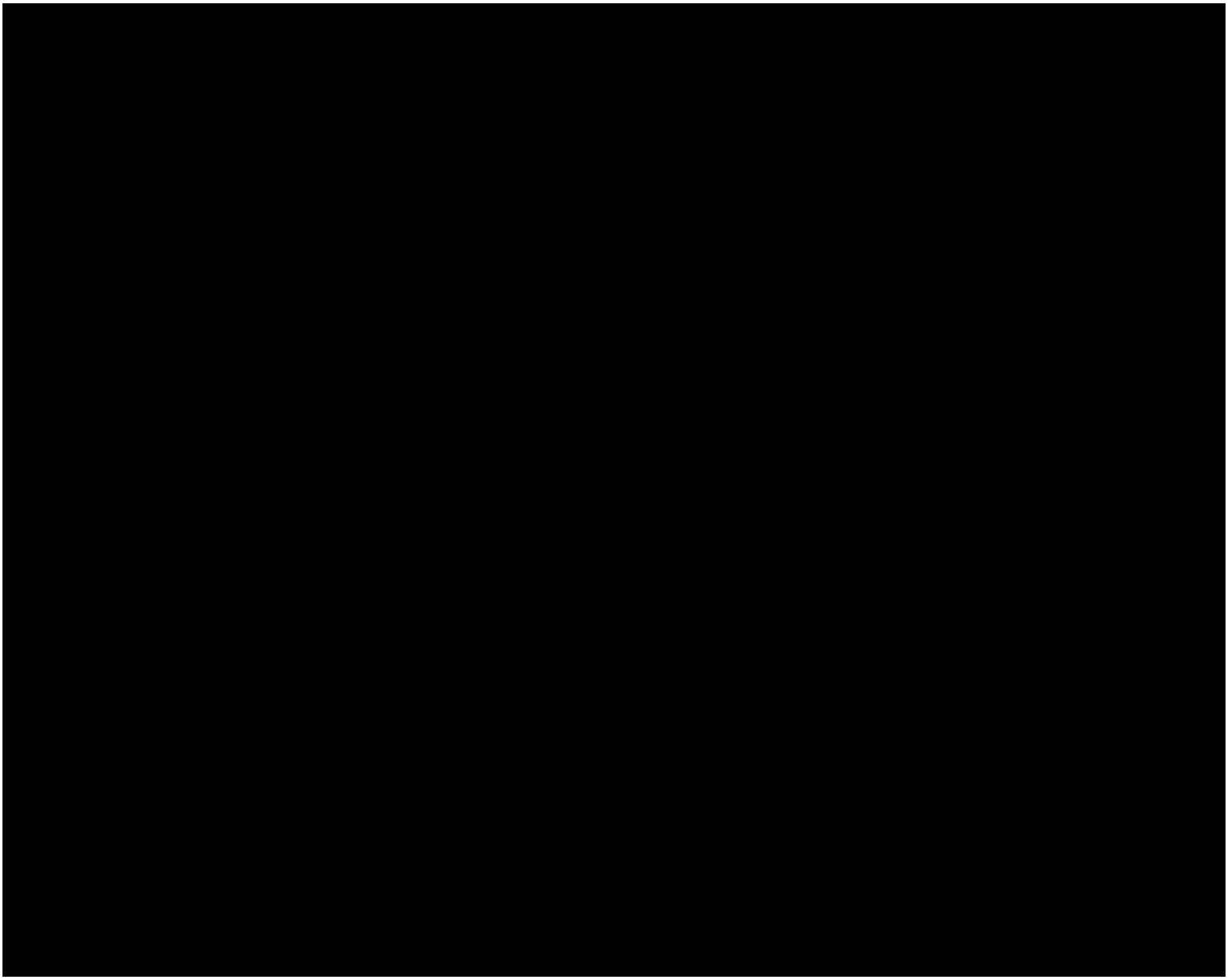
6.3. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.3.1. Acquisition and Accountability

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, the amount of study drug returned by each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers,

expiration dates, ambient temperature log, and unique code numbers assigned to the product and study subjects.

Investigators will maintain records that adequately document that the subjects were provided the correct study treatment. Study drugs will be dispensed in prepackaged blister card wallets. The wallet will contain 10 days of doses of KarXT capsule based on the Investigator-confirmed dose or placebo for BID administration. Subjects will be advised to return the blister card wallets to the site staff at each in-clinic visit for drug accountability.



6.3.3. Packaging and Labeling

All packaging and labeling operations will comply with Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Blister pack wallets of KarXT or placebo capsules will be provided at each visit and will be labeled, “KarXT (Xanomeline/Trospium Cl) or Placebo”, recommended storage conditions, and other information according to labeling requirements specific to countries participating in the KAR-012 study. Further details on the investigational product label will be provided in the Pharmacy Manual.

6.3.4. Study Drug Storage

KarXT and placebo 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. Subjects should store study medication at room temperature.

6.4. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.4.1. Randomization

At Screening, during the ICF process, the electronic data capture (EDC) system will assign a unique subject identification number to the subject known as the Subject Number. This number will be associated with the subject throughout the study.

On Day 1 (Visit 3), all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups. The randomization will be stratified by background oral APDs vs LAI formulations and country. Subjects will be assigned a randomization number through the interactive web response system (IWRS), in accordance with the randomization code generated by a third-party unblinded statistician. Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the first subject discontinued the study.

6.4.2. Blinding

An IWRS will allocate treatment based on a pre-specified randomization list generated by a third-party unblinded statistician. For all dose strengths, the study drug and blister packaging will be identical in size, shape, color, and appearance (see Section 6.3.3). No study site personnel, subjects, informants, Sponsor personnel, or Sponsor designees (e.g., Sponsor’s Medical Monitor) will be unblinded to treatment assignment during the study unless unblinding is required. Active study drug and placebo will be supplied as identical matching capsules.

If an Investigator becomes unblinded to a given subject’s treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject to not be discontinued. Approval from the Sponsor/Medical Monitor must be obtained in such instances.

A third-party unblinded statistician will generate and maintain the security of the randomization code. In the event that emergency unblinding is required for a given subject because of AEs or concerns for the subject’s safety or well-being, the Investigator may break the randomization code for just that subject via the IWRS, by which system the unblinding will be captured. The site is expected to consult the study Medical Monitor before breaking the study blind unless it is in the subject’s best interest if the blind is broken immediately. The unblinding and its cause will

also be documented in the eCRF. Unblinding according to the protocol will occur only after database lock.

If an AE is thought to be related to the study drug and poses a safety risk, the Investigator must decide whether to stop investigational treatment and/or treat the subject. Subject withdrawal should be avoided, if possible. If discontinuation of treatment occurs, every attempt should be made to restart the study drug if medically appropriate, whatever the duration of discontinuation.

Note that in most circumstances, it is not necessary to unblind a subject, even if an SAE has occurred. The appropriate course of action is to stop the investigational drug and treat the signs and symptoms resulting from the AE.

[redacted]

6.5. DOSE MODIFICATION

Subjects will be dosed as described in Section 4.1 and in accordance with the SOE (Table 1). KarXT doses were selected based on the results of previous clinical studies (see Section 2.2.4). Per the protocol, subjects will be evaluated for dose adjustments at Visits 3 to 7 and at unscheduled visits.

6.6. STUDY TREATMENT COMPLIANCE

Treatment compliance will be evaluated by on-site pill count. Number of pills dispensed and returned (for each dispensation visit) will be recorded on the appropriate eCRF.

6.7. CONCOMITANT THERAPY

Subjects will be asked to report all prior medications they were taking up to 6 months before the study, up to the time of the first dose of study medication on Day 1. All prior medications will be recorded on the eCRF. In addition, the subjects will identify all of the medications that they are currently taking.

All medications and other treatments taken by the subject during the study, including treatments initiated before the start of the study, must be recorded on the eCRF. Refer to [redacted] for guidance on allowed and prohibited medications.

During the study (i.e., from the time of Screening visit until study completion), the use of any other concomitant medication(s) other than specified in [redacted] is prohibited without the prior approval of the Investigator unless its use is deemed necessary as in a medical emergency. Over-the-counter medications such as acetaminophen, paracetamol, and ibuprofen are permitted during the study.

After signed ICF is obtained from the subjects, the subjects will need to be washed out of excluded APDs for 8 weeks prior to Visit 3/Day 1.

Subjects need to be on stable dosing of monotherapy aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine that they have been taking under the same dosing regimen for at least 8 weeks prior to Visit 3/Day 1. Subjects who are taking LAI formulations but occasionally supplement with oral antipsychotics as needed (PRN) must wash out of the PRN oral antipsychotic for at least one week prior to Visit 3. Subjects must remain on the same APD during the study; the dose should not be changed during the study.

Please direct questions relating to prohibited and concomitant medications to the Medical Monitor.

7. STUDY ASSESSMENTS AND PROCEDURES

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

[redacted]

If completion of the visit is not possible on the scheduled day, the ± 3-day visit window may be used.

7.1. SCREENING VISITS

The Screening Period is [redacted]

During Screening, the site will confirm that the subject is meeting randomization criteria, including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine at Screening. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1).

7.1.1. Visit 1/[redacted]

Study candidates will be screened to assess eligibility for enrollment into the study. A Screening log will be maintained for all consented study candidates. The study candidate's initials, date screened, and reason(s) for Screening failure must be recorded on the Screening log.

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

- Subjects will sign the ICF on their first visit before any study-related procedures are performed, including Screening evaluations.
- Informed Consent will also be obtained from the informant prior to any protocol-related activities. Informant consent can be done in person or remotely in accordance with local regulations and site processes and prior to any study procedures being conducted at the Screening visit. The informant will continue to interact with the subject throughout the ARISE trials to have firsthand knowledge about the subject's behavior. In Bulgaria, the informant needs to be physically present at the Baseline visit (Visit 3) and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial, and will sign the informant consent in person.
- Collect demographic information

- A serum pregnancy test for WOCBP should be done at Visit 1, and urine pregnancy tests should be done at other visits. A serum pregnancy test should be done to confirm any positive urine pregnancy test
- Urine drug and alcohol screen
- Urine analysis
- Review inclusion/exclusion criteria to ensure eligibility
- Subject eligibility verification process: independent diagnostic verification procedure and identity check using appropriate software/database. Verify eligibility
- Review medical and psychiatric history. Medical histories should include baseline symptoms, ongoing illnesses, other chronic conditions, surgical history, review of current and recently used (past 6 months) medications, as well as any other important information that may affect the eligibility of the subject
- Perform the MINI, version 7.0.2, a psychiatric evaluation to confirm the DSM-5 criteria for schizophrenia and does not meet psychiatric exclusionary criteria
  - [redacted]
- Perform a complete physical examination that includes body temperature (orally collected, °C), general appearance, head/eyes/ears/nose/throat, an examination of thorax and abdomen, assessment of cardiovascular, pulmonary, and musculoskeletal systems, palpations for lymphadenopathy, and limited neurological examination

[redacted]

- For male subjects only: collect blood sample for PSA analysis.
- Record spontaneous AEs as reported by subjects or observed by clinical staff after the subject signs the ICF
- Record concomitant medications
- Record height (cm), weight (kg) and determine BMI
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in beats/minute (bpm)
- Perform 12-lead ECGs as scheduled before blood sample collection for any safety laboratory tests and [redacted] analysis. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained
- Collect blood samples for routine hematology, coagulation, prolactin, and serum chemistry
- Collect blood sample for hemoglobin A1c (HbA1c) analysis
- All subjects must have the following viral serology tests: anti-hepatitis C virus (HCV) antibody, hepatitis B virus surface antigen, HIV-1 antibody, and HIV-2 antibody. If the

subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction (PCR) should be tested to confirm or rule out active infection

- Perform COVID-19 testing
- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, and IPSS (for male subjects ≥ 45 years of age only) assessments. Study candidates must have a PANSS total score ≥ 70, CGI-S scale of positive symptoms with a score ≥ 4 (moderate), and PANSS M-Pos Symptom Factor ≥ 4 on 2 (or more) items to continue to the study. [redacted]
- For the IPSS, study candidates must have < 5 (almost always) on items 1, 3, 5, and 6, and a sum of scores on IPSS items 1, 3, 5, and 6 of < 9 to be eligible for the study
- [redacted]

7.1.2. Visit 2/ [redacted] Screening [redacted]

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Review inclusion/exclusion criteria to ensure eligibility
- Urine drug and alcohol screen
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Complete the PANSS and CGI-S assessments. [redacted]
- During this visit the site will review and confirm that the subject has detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine (test conducted at first Screening visit)
- [redacted]
- [redacted]

7.2. DOUBLE-BLIND TREATMENT VISITS (VISITS 3-8)

7.2.1. Visit 3/Day 1 Randomization and Dosing; Dose is KarXT 50/20

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Urine drug and alcohol screen
- Urine analysis

- Review inclusion/exclusion criteria to ensure eligibility
- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, IPSS (for male subjects ≥ 45 years of age only), and PSP assessments. [redacted]
- [redacted]
- Study candidates must have a PANSS total score ≥ 70, PANSS M-Pos Symptom Factor ≥ 4 on 2 (or more) items to continue to the study. [redacted]
- For the IPSS, study candidates must have < 5 (almost always) on items 1, 3, 5, and 6, and a sum of scores on IPSS Items 1, 3, 5, and 6 of < 9 to be eligible for the study
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Record weight (kg) and determine BMI
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Perform 12-lead ECGs as scheduled before blood sample collection for any safety laboratory tests and [redacted] analysis
- Collect blood samples for routine hematology, coagulation, prolactin, and serum chemistry testing
- [redacted]
- Perform COVID-19 testing
- [redacted]
- Complete randomization of eligible subject via IWRS. The IWRS will assign the randomization number
- [redacted]
- All subjects will start with a lead-in dose of KarXT 50/20 BID or its matching placebo
- Dispense study drug by giving the subject 1 wallet

7.2.2. Visit 4/Day 7 ± 3 and Dose Escalation to KarXT 75/20

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Urine drug and alcohol screen
- Record spontaneous AEs as reported by subjects or observed by clinical staff

- Record changes in concomitant medications
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, and PSP assessments. [redacted]
- [redacted]
- All subjects will have the dose increased to KarXT 75/20 BID or its matching placebo
- Dispense study drug by giving the subject 1 wallet
- Collect the used study drug wallets from the subjects

7.2.3. Visit 5/Day 14 ± 3 and Dose Escalation to KarXT 100/20

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Urine drug and alcohol screen
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- [redacted]
- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, and PSP assessments. [redacted]
- [redacted]
- Dispense study drug by giving the subject 1 wallet
- Collect the used study drug wallets from the subjects

7.2.4. Visit 6/Day 21 ± 3 and Dose Escalation to KarXT 125/30 (End of Week 3)

- Perform a urine pregnancy test for females of childbearing potential (if positive, perform a serum pregnancy test)

- Urine drug and alcohol screen
- Urine analysis
- Record changes in concomitant medications
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Perform 12-lead ECGs as scheduled before blood sample collection for any safety laboratory tests and [redacted] analysis
- Collect blood samples for routine hematology, coagulation, prolactin, and serum chemistry testing.
- [redacted]
- Perform COVID-19 testing
- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, and PSP assessments. [redacted]

[redacted]

- Dispense study drug by giving the subject 1 wallet
- Collect the used study drug wallets from the subjects

7.2.5. Visit 7/Day 28 ± 3 and KarXT Dose Modifications

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Urine drug and alcohol screen
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- [redacted]
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm

- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, IPSS (for male subjects ≥ 45 years of age only), and PSP assessments. [redacted]

[redacted]

- Dispense study drug by giving the subject 2 wallets
- Collect the used study drug wallets from the subjects

7.2.6. Visit 8/Day 42 ± 3/End of Week 6/End-of-Treatment Visit or Early Termination

- Perform a urine pregnancy test for WOCBP (if positive, perform a serum pregnancy test)
- Urine drug and alcohol screen
- Urine analysis
- Perform a complete physical examination that includes body temperature (orally collected, °C), general appearance, head/eyes/ears/nose/throat, an examination of thorax and abdomen, assessment of cardiovascular, pulmonary, and musculoskeletal systems, palpations for lymphadenopathy, and limited neurological examination
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Record weight (kg), and determine BMI
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Perform 12-lead ECGs as scheduled before blood sample collection for any safety laboratory tests and [redacted] analysis
- Collect blood samples for routine hematology, coagulation, prolactin, and serum chemistry testing
- Collect blood sample for HbA1c analysis
- [redacted]
- Perform COVID -19 testing
- [redacted]

- Complete the PANSS, CGI-S, C-SSRS, SAS, BARS, AIMS, PSP, IPSS (for male subjects ≥ 45 years of age only), and POM assessments. [redacted]
- [redacted]
- Collect the used study drug wallets from the subjects

7.3. VISIT 9/DAY 49 ± 3/SFU VISIT

- All subjects who do not elect to participate in the KAR-013 study will be followed for 7 days after the last dose of KarXT or matching placebo on Day 42 ± 3
- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Complete the C-SSRS and IPSS (for male subjects ≥ 45 years of age only) assessments
- The site will verify that all tasks have been completed for the last visit
- Follow-up any ongoing TEAEs until resolved based on the Investigator's judgment

7.4. UNSCHEDULED VISITS

The Investigator may at his/her discretion (and in consultation with Medical Monitor) arrange for an Unscheduled Visit and conduct any protocol specific assessment that is deemed necessary. At a minimum, the following assessments will be conducted at an Unscheduled Visit:

- Record spontaneous AEs as reported by subjects or observed by clinical staff
- Record changes in concomitant medications
- Perform vital signs measurements at supine and standing after 2 minutes (at the site). BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in bpm
- Complete the C-SSRS assessment

[redacted]

7.5. EFFICACY ASSESSMENTS AND DIAGNOSTIC SCALE

7.5.1. Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy (Kay 1989). The PANSS rating form contains 7 positive symptom items, 7 negative symptom items, and 16 general psychopathology symptom items. Subjects are rated from 1 to 7 on each symptom

item. The positive symptoms in schizophrenia are the excess or distortion of normal function, such as hallucinations, delusions, or grandiosity. The negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. The PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210. The disease severity increases with the higher PANSS score. The PANSS assessment includes the Marder Factor.

[redacted]

7.5.2. PANSS Marder Positive Symptom Factor

The PANSS M-Pos Symptom Factor score is based on the following items on the PANSS scale:

- P1 Delusions
- P3 Hallucinations
- P5 Grandiosity
- P6 Suspiciousness and persecution
- N7 Stereotyped thinking
- G1 Somatic concern
- G9 Unusual thought content
- G12 Lack of judgment and insight

7.5.3. PANSS Marder Negative Symptom Factor

The PANSS M-Neg Symptom Factor score is based on the following items on the PANSS scale:

- N1 Blunted affect
- N2 Emotional withdrawal
- N3 Poor rapport
- N4 Passive social withdrawal
- N6 Lack of spontaneity of conversation
- G7 Motor retardation
- G16 Active social avoidance

7.5.4. Personal Social Performance scale

The PSP scale assesses functioning using a structured clinical interview across 4 dimensions: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors. The PSP provides a score between 1 and 100 using a 6-point severity scale for each domain. Higher scores represent better personal and social functioning (Nafees 2012).

7.5.5. Clinical Global Impression–Severity

The CGI-S is a rating scale completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The 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.

7.5.6. Preference of Medication

The POM is a two-item questionnaire assessing the subject's and informant's preference, respectively, for the current antipsychotic as compared with the most recent pre-study antipsychotic (Tandon 2006, Taylor 2008). The POM is scored on the following scale: 1 = 'much better, I prefer this medication,' 2 = 'slightly better,' 3 = 'about the same,' 4 = 'slightly worse,' and 5 = 'much worse, I much prefer my previous medication.'

7.5.7. Mini International Neuropsychiatric Interview Version 7.0.2

The MINI is a short structured diagnostic interview developed for DSM-5 psychiatric disorders. It takes about 15 minutes to administer and was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical studies and epidemiology.

[redacted]

7.6. Safety Scales and Other Assessments

Safety assessments (spontaneous AEs, AESIs, TEAEs, TEAEs leading to study drug withdrawal, procholinergic and anticholinergic symptoms, SAS, BARS, AIMS, body weight, BMI, vital signs, ECG, IPSS questionnaire, clinical laboratory assessments [hematology, clinical chemistry, coagulation, urine analysis and drug screen], serum prolactin, physical examination, and C-SSRS) are to be performed at protocol-specified visits, as specified in the SOE (Table 1). Table 4 describes all the safety laboratory tests required for this study.

7.6.1. Simpson-Angus Scale

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

7.6.2. Barnes Akathisia Rating Scale

The BARS is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements, and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity (Barnes 1989).

7.6.3. Abnormal Involuntary Movement Scale

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

7.6.4. Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study (Posner 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 trained rater at the site and takes about 5 minutes to complete.

This study will use 2 versions of the C-SSRS. The "Lifetime" version will be completed at the Screening visit, while for all subsequent visits, the "Since Last Visit" version will be used.

7.6.5. Demographics, and Medical and Psychiatric History

Demographic data will be collected for all subjects at Screening. The information to be captured includes the 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 subject and recorded in the eCRF.

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

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 7.7. All clinical abnormalities not present at Screening or described in the past medical history and subsequently identified as clinically noteworthy must be recorded as AEs.

7.6.6. Vital Signs

Vital signs (systolic and diastolic BP and HR measurements) will be evaluated at the visits as indicated in the SOE (Table 1). All vital signs will be measured supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR 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.

7.6.7. Physical Examination

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat, examination of thorax and abdomen, assessment of cardiovascular, pulmonary, and musculoskeletal 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.

7.6.8. Weight, Height, Body Mass Index

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

7.6.9. Electrocardiograms

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

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

At Screening, the central ECG reader will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal ECG will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. An ECG can be repeated during the Screening Period in the instance clinically significant abnormalities are identified, and if the Investigator deems it appropriate. The ECG should be repeated prior to a screen failure determination being made.

7.6.10. International Prostate Symptom Score

The IPSS is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the subject to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 (not at all) to 5 (almost always). The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic) (Barry 1992).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency

5	Weak Stream
6	Straining
7	Nocturia

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

During the Screening period (Visit 1) male subjects ≥ 45 years of age will be excluded from the study if they have an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9.

If a subject has an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 during the Treatment Period, the subject should be referred to an urologist. The study Investigator should take the urologist's input into consideration when determining whether the subject should be discontinued from the study.

7.6.11. Laboratory Assessments

Laboratory assessment samples (Table 4) are to be collected at designated visits as detailed in the SOE (Table 1). Laboratory Assessments may be repeated if results are clinically significant. During the Screening Period, if the Investigator deems it appropriate to repeat safety laboratory testing, this should be completed prior to a screen failure determination being made. Blood laboratory samples will be analyzed at a central laboratory.

Table 4. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis**
Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	Albumin ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose HDL Hemoglobin A1c (Visits 1 and 8) LDH LDL PSA Total bilirubin Direct bilirubin Total cholesterol Triglycerides Total protein	pH Protein Glucose Ketones Indicators of blood and WBCs Specific gravity Urobilinogen FSH[a]
Prolactin		
Blood sample for background antipsychotic		
Coagulation	**Serology[b]**	**COVID-19[c]**
PT PT/INR Activated PTT Fibrinogen	HBV HCV HIV	PCR
Pregnancy test: A serum pregnancy test will be performed on all women of childbearing potential at Screening, and a urine pregnancy test (urine HCG) will be performed at other scheduled visits at the site. If a urine pregnancy test is positive, a serum sample should be sent to a central laboratory for confirmation of the result.		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; COVID-19 = SARS-CoV-2; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; Hb = hemoglobin; HBV = Hepatitis B; HCG = human chorionic gonadotropin; Hct = hematocrit; HCV = Hepatitis C; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

[a] FSH test for post menopausal females at the Screening Visit 1 only.

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

[c] In the US, mandatory timepoints are done by central laboratory and optional are done locally.

[redacted]

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 or designee, and be filed with both the subject'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 up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All study subjects will be closely monitored for DILI toxicity, detailed in Section 7.7.7, during the study.

7.6.12. Other Laboratory Assessments

A urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, cocaine, and alcohol [clinically significant alcohol use in the opinion of the Investigator]) will be performed at scheduled visits as noted in the SOE (Table 1).

7.6.13. Change in Prolactin

Blood samples to assess the change in prolactin levels will be collected at Screening (Visit 1), end of Baseline (Visit 3), end of Week 3 (Visit 6), and end of Week 6 (Visit 8; EOT or ET)

[redacted]

7.7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.7.1. Definition of Adverse Events

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 (except those related to the indication under study) 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. In addition, all novel coronavirus (COVID-19) related events should be reported as AEs.

Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the Investigator and/or study staff will elicit AEs and intercurrent illness during and at all visits, and these will be recorded on the appropriate page of the eCRF. AEs will be elicited by asking the subject a nonleading question, for example, "*Have you experienced any new or changed symptoms since we last asked*?"

7.7.2. Classification of Adverse Events

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

The period of observation for collection of AEs extends from the Screening (Visit 1) time to SFU (Visit 9) or ET. If the AE persists, then follow-up of the AE is required until the event resolves or stabilizes at a level acceptable to the Investigator, even if it persists beyond the discontinuation of therapy.

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 given in Table 5 and Table 6.

Table 5: Classification of Adverse Events by Intensity

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

Table 6: 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY	This category applies to 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY	This category applies to 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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (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 subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (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.

7.7.3. Adverse Events of Special Interest

AESIs will include symptomatic orthostasis (Section 7.7.3.1), syncope (Section 7.7.3.2), and elevated LFTs requiring DILI monitoring (Section 7.7.3.3).

The Investigator will assess and record any additional information on the AESI in detail which must be submitted **within 24 hours** of awareness of the event.

As follow-up information becomes available, the site should update the AESI **within 24 hours** of awareness of the new information. All relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summaries, post-mortem results, etc.) and all other updated information should be entered in the EDC. The Investigator should follow the subject until the AESI resolves or until the condition becomes chronic in nature, stabilizes, or returns to baseline values (if a baseline value is available).

7.7.3.1. Symptomatic Orthostasis

Orthostasis will be defined as the subject is **symptomatic** and has at least one of the following changes in vital signs from the sitting to standing measurements:

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

Changes of the orthostatic vital signs alone will not be considered an AESI without the subject being symptomatic. See APPENDIX 3 for guidance on orthostatic hypotension AEs.

7.7.3.2. Syncope

Syncope is defined as a sudden, transient loss of consciousness. Syncope is due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery (Task Force for the Diagnosis Management of Syncope 2009).

7.7.3.3. Elevated Liver Function Test Requiring Drug-Induced Liver Injury Monitoring

An AESI should be reported any time the subject exhibits:

- ALT and/or AST > 3 × ULN reference range

All LFT AESIs should also be recorded as an AE and subsequently follow the DILI monitoring criteria as explained in Section 7.7.7.

7.7.4. Definition of Serious Adverse Events

A 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 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 subject 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 take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

7.7.5. Serious Adverse Event Reporting

SAEs/AESIs reported by subjects or observed by clinical staff after subject has signed the ICF must be reported to the Sponsor's pharmacovigilance group. Any such SAE/AESI due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. SAEs will be reported directly through the EDC, but as a backup (in case the EDC is not available), sites can use the Sponsor's pharmacovigilance group email address: **worldwide.safety@bms.com** or Fax to: +1 609 818-3804.

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

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 Sponsor's 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 SFU Visit or upon discontinuation of the subject's participation in the study is to be followed up until it 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.

7.7.6. Pregnancy and Pregnancy Reporting

WOCBP must have a negative pregnancy test at Screening and end of Baseline (Day 1).

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

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

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

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow-up with the subject until 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. This event is considered an SAE.

Upon discontinuation from the study drug, only procedures that would not expose the subject to undue risk will be performed at the ET Visit and the SFU Visit. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

7.7.7. Drug-Induced Liver Injury

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

- An increase of 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, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash)
- Close observation should be initiated with ALT or AST ≥ 3 × ULN as follows:

  - 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 subject is asymptomatic
  - 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 ≥ 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%)
- 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 will continue to the resolution of elevated liver enzymes
- Gamma-glutamyl transpeptidase elevations alone should not prompt drug discontinuation

7.7.8. Trial Discontinuation Criteria Other than DILI and Pregnancy

7.7.8.1. Individual Stopping Criteria

Based on Common Terminology Criteria for Adverse Events (CTCAE 2017) v5.0, the study drug will be discontinued in any subject who experiences a life-threatening or disabling AE (≥ Grade 4 AE per CTCAE v5.0). Discontinuation or dose reduction for Grade 3 AEs other than DILI AEs (see Section 7.7.7) will be at the discretion of the Investigator.

7.7.8.2. 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 the ways to safeguard the interests of the clinical study subjects. The study team is expected to recommend 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

7.7.9. Suspected Unexpected Serious Adverse Reactions

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

- Serious
- Unexpected (i.e., the event is not listed in the Reference Safety Information section 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 of a SUSAR and if it 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 IEC/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 7 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.

7.7.10. 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.

7.7.11. Warnings and Precautions

7.7.11.1. Risk of Urinary Retention

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

7.7.11.2. Angioedema

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®. 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 a patent airway should be promptly provided.

7.7.11.3. Decreased Gastrointestinal Motility

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

7.7.11.4. Controlled Narrow-angle Glaucoma

In subjects 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.

7.7.11.5. Central Nervous System Effects

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

7.7.11.6. Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment

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

7.7.11.7. Elevation of Liver Enzymes

KarXT was associated with transient increases in liver transaminase values, primarily ALT. Most occurred within the first month of starting KarXT treatment and resolved on treatment, suggesting hepatic adaptation to xanomeline. Hepatic safety should be monitored in all subjects receiving KarXT.

8. STATISTICAL CONSIDERATIONS

8.1. STATISTICAL HYPOTHESIS

The primary null hypothesis is that there is no difference in change from baseline to end of Week 6 in PANSS total score between adjunctive KarXT and placebo.

8.2. SAMPLE SIZE DETERMINATION

Approximately 360 subjects will be randomized. The sample size is based on the assumption of a treatment difference of 5 points on the primary efficacy endpoint (change from baseline to Week 6 in PANSS total score), a standard deviation (SD) of 13 points, and a 20% drop out rate. A total of 180 subjects per arm will provide a 90% power to detect a significant difference between treatment groups, using a 2-sided alpha of 0.05. [redacted]

8.3. POPULATIONS FOR ANALYSIS

Table 7: Population for Analysis Description

Population	Description
Enrolled	All subjects who sign the ICF.
Intent-to-Treat (ITT)	All subjects who are randomized to the study.
Modified Intent-to-Treat (mITT)	All subjects in the ITT population who received at least 1 dose of study medication, have a Baseline Positive and Negative Syndrome Scale assessment, and at least 1 post-Baseline Positive and Negative Syndrome Scale assessment. Efficacy analysis will be performed on this population.
Safety	All subjects who received at least 1 dose of the study drug. Safety analysis will be performed on this population.

[redacted]

8.4. STATISTICAL ANALYSES

8.4.1. General Approach

The SAP will be prepared after the protocol is approved. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will complement the protocol and supersede it in case of differences.

All statistical analyses will use SAS® version 9.4 or higher. Summary tables will be organized by treatment group. Descriptive statistics for continuous variables will include the number of subjects (n), mean, SD, coefficient of variation, median, 95% confidence interval, minimum, and maximum values unless otherwise noted. For categorical variables, frequencies and percentages will be provided, and the data will be tabulated by treatment group with the number and proportion of subjects for each category.

All efficacy analyses will be performed using the mITT population.

[redacted]

8.5. EFFICACY ANALYSIS

8.5.1. Primary Estimand

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

The primary clinical question of interest is: *What is the effect of adjunctive KarXT vs adjunctive placebo on the change from Baseline in PANSS total score in adult subjects aged 18 to 65 years (inclusive) at the time of randomization (Visit 3) with a DSM-5 diagnosis of schizophrenia, who are inadequate responders to their current APD (aripiprazole, risperidone, paliperidone or their LAI formulations, ziprasidone, lurasidone, or cariprazine) with PANSS total score of ≥ 70 at time of enrollment, regardless of treatment discontinuations for any reason and regardless of receipt of prohibited antipsychotic medications?*

The primary estimand is described by the following attributes:

1. Population: Adult subjects aged 18 to 65 years (inclusive) at the time of randomization (Visit 3) with a DSM-5 diagnosis of schizophrenia, with PANSS total score of ≥ 70 at time of enrollment who are inadequate responders to one of the following current APDs: aripiprazole, risperidone, paliperidone or their LAI formulations, ziprasidone, lurasidone, or cariprazine. Further details about the population are provided in Section 5.
2. Endpoint: Change from Baseline in PANSS total score at Week 6.

3. Treatment of interest: The randomized treatment (adjunctive KarXT or adjunctive placebo considering the following APDs: aripiprazole, risperidone, paliperidone or their LAI formulations, ziprasidone, lurasidone, or cariprazine) with or without the use of prohibited antipsychotic medications. Further details about the investigational treatment and control are provided in Section 6.

[redacted]

The population-level summary is the difference between treatment groups (adjunctive KarXT vs adjunctive placebo) in mean change from Baseline in PANSS total score at Week 6, obtained from a MMRM.

[redacted]

8.5.2. Analysis of the Primary Efficacy Endpoint

All efficacy analyses will be performed using the mITT population.

For the primary efficacy endpoint, the difference between adjunctive KarXT and adjunctive placebo at Week 6 will be estimated using MMRM. The model will include the change from Baseline PANSS total scores at Weeks 1, 2, 3, 4, and 6 as the response. The treatment difference at Week 6 will be estimated using contrasts. The MMRM will include the treatment group (adjunctive KarXT or adjunctive placebo), visit, and the interaction between the treatment group and visit as fixed factors. Age, sex at birth, Baseline PANSS total score, and the randomization stratification factor of background oral APDs versus LAI formulations and country will be included as covariates in the model.

[redacted]

8.5.4. Key Secondary Endpoint

The key secondary endpoint, change from Baseline to Week 6 in PSP, will be analyzed in a manner similar to the primary endpoint.

[redacted]

8.5.5. Analysis of Secondary Efficacy Endpoints

The analysis methods for the secondary efficacy endpoints will be further detailed in the SAP.

8.6. SAFETY ANALYSIS

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities version 22.1 or higher. The incidence of TEAEs (events with onset dates on or after the start of the study drug) will be summarized for each treatment group separately by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset, duration, relationship, and severity to study drug, action taken with the study drug, treatment of the event, and outcome. The incidence and severity of TEAEs, AESIs, and SAEs will be presented by treatment group.

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 subjects with values outside the limits of the normal range at each time point by treatment group. Similar descriptive summaries will be provided for SAS, BARS, AIMS, body weight, and BMI.

The C-SSRS is a measure of suicidal ideation and behavior. The number of subjects with a lifetime history of suicidal ideation or suicidal behavior will be summarized by treatment.

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

[redacted]

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1. 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, including EU No. 536/2014.

9.1.2. Independent Ethics Committee/Institutional Review Board

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

9.1.3. Informed Consent Process

For each study subject, ICF will be obtained before any protocol-related activities. The subject must be fluent in the language of the ICF to consent. 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 subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The 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 subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

Informed Consent will also be obtained from the informant prior to any protocol-related activities. Informant consent can be done in person or remotely in accordance with local regulations and site processes and prior to any study procedures being conducted at the Screening visit (Visit 1). The informant will continue to interact with the subject throughout the ARISE trials to have firsthand knowledge about the subject's behavior. In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial, and will sign the informant consent in person.

Subject Registry:

The Clinical Trial Registry reduces duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the Informed Consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

At the Screening visit, following Informed Consent and before any other study procedures, site staff (inclusive of US Staff only) that has received training and login access to the database will enter the subject study ID number and authorized subject identifiers. A report from The Clinical Trial Registry will detail any potential protocol violations or dual enrollment attempts will be generated and should be printed for source documentation. The reports will detail each protocol violation detected and specific washout period dates where applicable. Subjects who are identified as verification failures by The Clinical Trial Registry should not be enrolled without documented approval from Karuna or the CRO.

At the last subject contact, The Clinical Trial Registry staff will automatically close out the subject (SFU or ET/EOT) based on an interactive response system.

9.1.4. 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 9.1.5.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the EDC system must correspond to and be supported by source documentation maintained at the study site unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry.

All study forms and records transmitted to the Sponsor must 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 an EDC provider. 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. The EDC provider system strictly enforces controlled access of study material to appropriate parties. Access to both study data and documents is limited to designated personnel on the study. Access is only granted after receipt of a formal request by an approved designee at Karuna, electronic Clinical Outcome Assessment Vendor, or the CRO.

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.

Strict EDC provider standard operating procedures (SOPs) are enforced to protect the confidentiality, integrity, and access of "Protected Health Information" (PHI) when it is stored, transmitted, and maintained. When any PHI is collected in an EDC platform and uploaded to the EDC provider, such PHI data is ONLY accessible to designated staff at the EDC provider and handled in accordance with the EDC provider SOPs. Such data is also only accessible to designated staff at the Sponsor or the Sponsor's designee when such access is properly requested. In such cases, the Sponsor or Sponsor's designee would follow their own SOPs. Access rights to the data are granted and enforced based on the individual's role in conducting the study, strictly limiting access to PHI as defined by the Data Controller (Sponsor), Informed Consent, and local regulations. Additionally, the system can be configured to disallow the collection of PHI on a site-specific basis when required by local regulations.

9.1.5. 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 subjects. 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.

[redacted]

9.1.7. Monitoring

The study will be monitored according to the KAR-012 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 and virtual (telephone) or a combination and contacts, will be made at appropriate times during the study. The Investigator will ensure 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 subject.

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

9.1.8. 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, SOPs, 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.

9.1.9. 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, and regulatory authorities will review and approve this protocol and the ICF. All subjects are required to give informed consent before participation in the study.

9.1.11. 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 subject 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, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be outlined in the clinical study agreement.

9.2. PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

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

9.2.2. 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 would be identified as such before study unblinding during 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 subjects
- One example of a minor deviation 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 subjects

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

10. REFERENCES

[redacted]

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

Barry, M. J., Fowler, F. J., Jr., O'Leary, M. P., et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol.* 1992; 148(5): 1549-1557; discussion 1564.

[redacted]

Bodick, N. C., Offen, W. W., Levey, A. I., et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol.* 1997; 54(4): 465-473.

Bodick, N. C., Offen, W. W., Shannon, H. E., et al. The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. *Alzheimer Dis Assoc Disord.* 1997; 11 Suppl 4: S16-22.

Brannan, S. K., Sawchak, S., Miller, A. C., et al. Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia. *N Engl J Med.* 2021; 384(8): 717-726.

[redacted]

Crismon, L., Argo, T. R. and Buckley, P. F. (2014). Schizophrenia, 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*. 2017.

Emsley, R., Chiliza, B., Asmal, L., et al. The nature of relapse in schizophrenia. *BMC Psychiatry.* 2013; 13: 50.

Farde, L., Suhara, T., Halldin, C., et al. PET study of the M1-agonists [11C]xanomeline and [11C]butylthio-TZTP in monkey and man. *Dementia.* 1996; 7(4): 187-195.

Green, M. F., Kern, R. S. and Heaton, R. K. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* 2004; 72(1): 41-51.

Guy, W. (1976). *EDCEU Assessment Manual for Psychopharmacology – Revised.*, DHEW Publication No ADM 76 338.

HMA. *Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials.* 2014.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., et al. 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.* 2019; 394(10202): 939-951.

Kahn, R. S., Sommer, I. E., Murray, R. M., et al. Schizophrenia. *Nat Rev Dis Primers.* 2015; 1: 15067.

Kaul, I., Sawchak, S., Correll, C. U., et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet.* 2024; 403(10422): 160-170.

Kaul, I., Sawchak, S., Walling, D. P., et al. Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry.* 2024.

Kay, S. R., Opler, L. A. and Lindenmayer, J. P. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl.* 1989; (7): 59-67.

Leucht, S., Cipriani, A., Spineli, L., et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013; 382(9896): 951-962.

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005; 353(12): 1209-1223.

[redacted]

Mirza, N. R., Peters, D. and Sparks, R. G. Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. *CNS Drug Rev.* 2003; 9(2): 159-186.

Nafees, B., van Hanswijck de Jonge, P., Stull, D., et al. Reliability and validity of the Personal and Social Performance scale in patients with schizophrenia. *Schizophr Res.* 2012; 140(1-3): 71-76.

Patel, K. R., Cherian, J., Gohil, K., et al. Schizophrenia: overview and treatment options. *P T.* 2014; 39(9): 638-645.

Posner, K., Brown, G. K., Stanley, B., et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011; 168(12): 1266-1277.

Scheife, R. and Takeda, M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clin Ther.* 2005; 27(2): 144-153.

Sellin, A. K., Shad, M. and Tamminga, C. Muscarinic agonists for the treatment of cognition in schizophrenia. *CNS Spectr.* 2008; 13(11): 985-996.

Shekhar, A., Potter, W. Z., Lightfoot, J., et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry.* 2008; 165(8): 1033-1039.

Staskin, D., Kay, G., Tannenbaum, C., et al. 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.* 2010; 64(9): 1294-1300.

Tandon, R., Marcus, R. N., Stock, E. G., et al. A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: Broad Effectiveness Trial With Aripiprazole (BETA). *Schizophr Res.* 2006; 84(1): 77-89.

Task Force for the Diagnosis Management of Syncope, European Society of Cardiology, European Heart Rhythm Association, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J.* 2009; 30(21): 2631-2671.

Taylor, D., Hanssens, L., Loze, J. Y., et al. Preference of medicine and patient-reported quality of life in community-treated schizophrenic patients receiving aripiprazole vs standard of care: results from the STAR study. *Eur Psychiatry.* 2008; 23(5): 336-343.

Thorn, C. A., Moon, J., Bourbonais, C. A., et al. Striatal, Hippocampal, and Cortical Networks Are Differentially Responsive to the M4- and M1-Muscarinic Acetylcholine Receptor Mediated Effects of Xanomeline. *ACS Chem Neurosci.* 2019; 10(3): 1753-1764.

van Os, J. and Kapur, S. Schizophrenia. *Lancet.* 2009; 374(9690): 635-645.

Wess, J., Eglen, R. M. and Gautam, D. Muscarinic acetylcholine receptors: mutant mice provide new insights for drug development. *Nat Rev Drug Discov.* 2007; 6(9): 721-733.

Wu, E. Q., Shi, L., Birnbaum, H., et al. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. *Psychol Med.* 2006; 36(11): 1535-1540.

11. APPENDICES

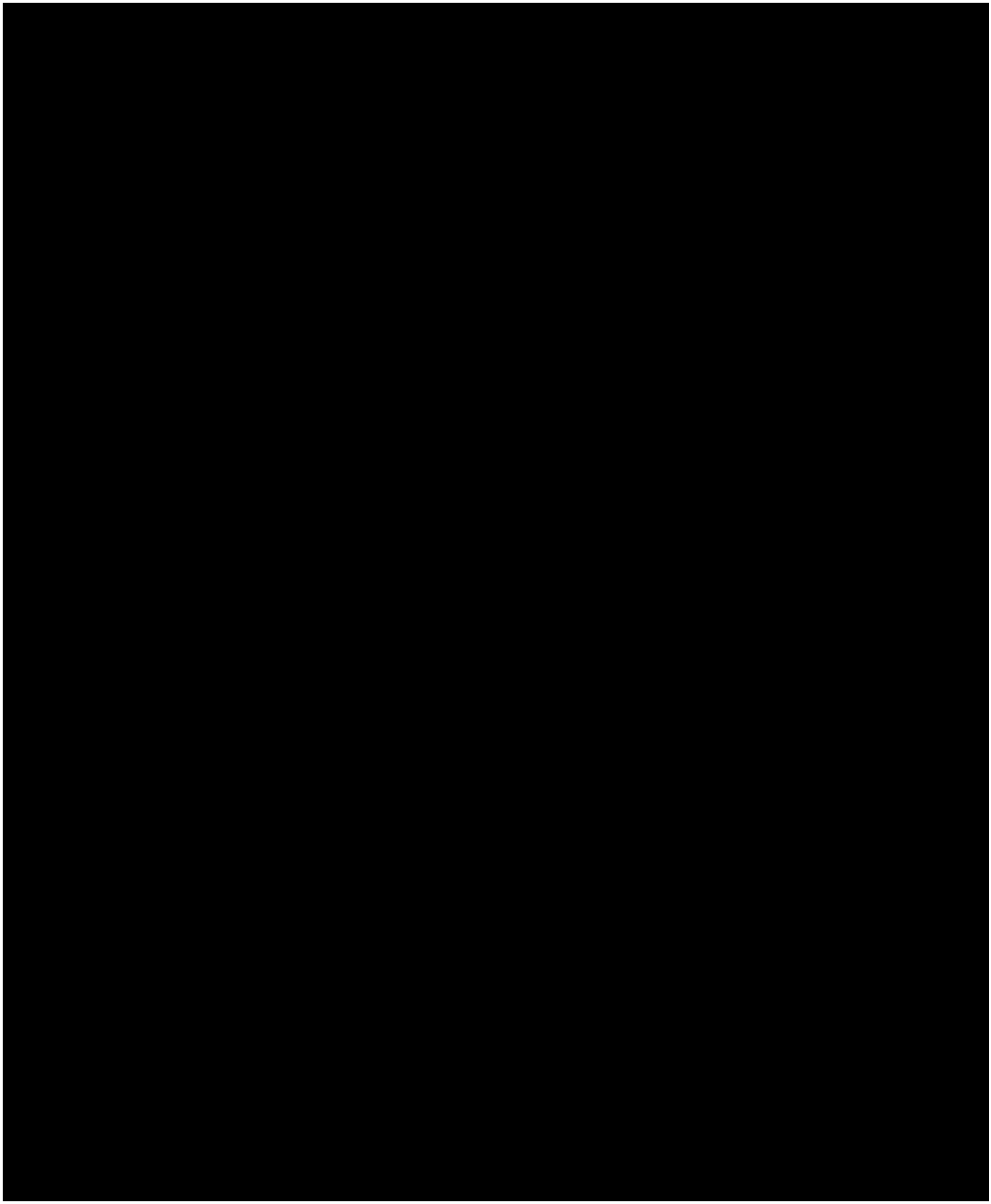
APPENDIX 1. BACKGROUND ANTIPSYCHOTICS DOSING REGIMEN

Antipsychotic drugs	Trade name	Dosing recommendations
Paliperidone	Invega (Schizophrenia)	• Recommended Dose: 3 to 12 mg/day • Maximum Dose: 12 mg/day
	Invega Sustenna®	• Dose range is 117 mg, 156 mg, or 234 mg (intramuscular 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: 3 to 6 mg/day
	Risperidone 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 (subcutaneous injection) o 90 mg (0.6 mL) equivalent to 3 mg oral risperidone o 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 • 1064 mg every 2 months
Ziprasidone	Geodon (oral) (Schizophrenia; Adults)	• Dose range: 40 to 160 mg/day
Lurasidone	Latuda (oral) (Schizophrenia)	• Dose range: 40 to 160 mg/day
Cariprazine	Vraylar and Reagila	• Dose range: 1.5 – 6 mg/day

[redacted]

APPENDIX 3. GUIDANCE FOR ORTHOSTATIC HYPOTENSION

Adverse Event	Parameters
Orthostatic Hypotension	Orthostatic hypotension will be defined as the subject being symptomatic with the below difference in orthostatic vitals between supine and standing • a decrease of systolic BP of 20 mmHg or more • or a decrease in diastolic BP of 10 mmHg or more • or an increase in HR of 30 bpm or more Changes of the orthostatic vitals alone will not be considered an AESI without the subject being symptomatic. If the subject is asymptomatic, with the above difference in orthostatic vitals, it will be captured as an AE.



TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Title Page, Protocol Approval Signatures, Header	5.0 [redacted]	~~5.0~~**6.0** ~~16-Jan-2024~~ **30-Jul-2024**	Updated date and version to v6.0.
Protocol Approval Signatures	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.	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, including European Union No. 536/2014**	Added to align with European Union requirements.
Protocol Approval Signatures	[redacted] Karuna Therapeutics	[redacted] Karuna Therapeutics**, A Bristol Myers Squibb Company**	Updated to reflect accurate signatory.
[redacted]			
Protocol Synopsis Safety Endpoints, Section 3.2.5 **Similar edits in:** **Section 4.1** **Section 7.6**	Spontaneously reported AEs, including TEAEs, serious adverse events (SAEs), and TEAEs leading to study withdrawal	Spontaneously reported AEs, including TEAEs, serious adverse events (SAEs), and TEAEs leading to study **drug** withdrawal	Updated for accuracy.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Safety Endpoints **Similar edits in:** **Schedule of Events** **Abbreviations** **Section 3.2.5** **Section 7.1.1** **Section 7.2.1** **Section 7.2.2** **Section 7.2.3** **Section 7.2.4** **Section 7.2.5** **Section 7.2.6** **Section 7.6** **Section 7.6.1** **Section 8.6**	Simpson-Angus Rating Scale (SARS)	Simpson-Angus ~~Rating~~ Scale (SA~~R~~S)	Updated for accuracy.
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Planned Sample Size** **Protocol Synopsis Statistical Methods and Planned Analyses** **Section 4.1** **Section 8.2** **Section 8.8**	... The study will randomize up to 400 subjects with schizophrenia to adjunctive KarXT or placebo (1:1).	… The study will randomize ~~up to 400~~ **approximately 360** subjects with schizophrenia to adjunctive KarXT or placebo (1:1).	[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Statistical Methods and Planned Analyses** **Section 4.1** **Section 6.4.1**	... The randomization will be stratified by background oral antipsychotic drugs (APDs) vs LAIs. The effect of adjunctive KarXT on atypical antipsychotics is unknown.	… The randomization will be stratified by background oral antipsychotic drugs (APDs) vs LAIs **and country**. The effect of adjunctive KarXT on atypical antipsychotics is unknown.	To align with randomization schedule document dated 27 September 2022.
[redacted]			
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Inclusion/exclusion criteria** **Section 4.1** **Section 5.1** **Section 8.5.1**	Subjects will be outpatients, ≥18 to <60 years old at the time of randomization (Visit 3),...	Subjects will be outpatients, ≥18 to ~~<60~~ **65** years old **(inclusive)** at the time of randomization (Visit 3),...	Increasing allowed subject age to ensure older population of schizophrenia subjects are able to participate in the study.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Duration** **Schedule of Events** **Section 4.1** **Section 7.1**	...The study periods include a [redacted] Screening Period, a 6-week double-blind Treatment Period, and a Safety Follow-up (SFU) Visit (end of Week 7).	...The study periods include [redacted] **Screening Period,** [redacted] a 6-week double-blind Treatment Period, and a Safety Follow-up (SFU) Visit (end of Week 7) **for subjects who do not rollover into the long-term open-label study KAR-013**.	To allow sites flexibility to enroll more quickly in situations where it is warranted.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 7.4			
[redacted]			
Protocol Synopsis Inclusion/exclusion criteria **Similar edits in:** **Section 5.1**	5. The subject has had at least one previous inadequate response to above antipsychotics that was dosed appropriately (within the label) for at least 6 weeks	5. The subject has **an** ~~had at least one previous~~ inadequate response to above antipsychotics that was dosed appropriately (within the label)**, as defined per inclusion criteria 8 and 9** ~~for at least 6 weeks~~	Inclusion criteria #5 is operationalized by inclusion criteria #8, 9, and therefore is redundant and introduces confusion.
Protocol Synopsis Inclusion/exclusion criteria **Similar edits in:** **Section 5.1**	15. Subject has identified a reliable informant/caregiver willing and able to assist with study activities as needed throughout the subject's participation in the study. The informant needs to be physically present at the Baseline visit but can complete the remaining study visits assessments via phone (as needed and as per local regulations). In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial.	15. Subject has identified a reliable informant/caregiver willing and able to assist with study activities as needed throughout the subject's participation in the study. **The informant does not have to be someone responsible for the subject's physical or psychiatric well-being. As needed, t**~~T~~he informant needs to be physically present at the **Screening Visit 1** ~~Baseline visit~~ but can complete the remaining study visits assessments via phone (as needed and as per local regulations). In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial. **Individuals who can serve as an informant for a subject include:** **a. Family member, relative, or partner** **b. Friend, clubhouse staff member (clubhouse model of psychosocial rehabilitation), or day center co-member** **c. Social worker, caseworker, residential facility staff, nurse, or other home care staff**	Informant requirement is significant recruitment challenge; when the site staff sufficiently know a subject, they are typically able to inform on the PANSS as they rate, making notes as applicable on the source. Text was also added to provide site with additional ideas on who could fulfil this role in the study.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		d. Person who interacts with the subject regularly **e. If the subject is well known to the site staff, a site staff member may serve as the informant. Site staff serving as an informant should not have other study responsibilities (i.e., rating scales) delegated to them for that respective subject**	
Protocol Synopsis Inclusion/exclusion criteria **Similar edits in:** **Section 5.2**	7. Significant or severe medical conditions including pulmonary, cardiovascular, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, could jeopardize the safety of the subject or the validity of the study results.	Significant or severe medical conditions including pulmonary, cardiovascular, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, could jeopardize the safety of the subject or the validity of the study results. **Subjects with any of the following lab values at Screening (Visit 1) are excluded:** **a. eGFR < 60 mL/min** **b. Alanine transaminase or aspartate transaminase (AST) > 1.5 x upper limit of normal (ULN)** **c. Total bilirubin > 1.5 x ULN (Subjects with Gilbert's syndrome can be included as long as direct bilirubin is ≤ 1.5 x ULN)**	[redacted]. Excludes subjects with pre-existing hepatic or renal impairment.
Protocol Synopsis Inclusion/exclusion criteria **Similar edits in:** **Section 5.2**	12. Clinically significant abnormal finding on the physical examination, medical history, ECG (QTc of > 450 msec in males and > 470 msec in females), or clinical laboratory results at Screening	12. Clinically significant abnormal finding on the physical examination, medical history, ECG (QTc**F** of > 450 msec in males and > 470 msec in females), or clinical laboratory results at Screening	Added to align with vendor programming.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Inclusion/exclusion criteria and Section 5.2	22. Participation in another clinical study in which the subject was enrolled within 3 months before Screening	22. ~~Participation in another clinical study in which the subject was enrolled within 3 months before Screening~~ **Subjects who received investigational product as part of a clinical trial within 3 months of Screening**	Revised criterion to clarify that subjects who participated in a clinical trial but did not receive investigational product within 3 months of the KAR-012 screening visit would be considered eligible for enrollment.
Protocol Synopsis Inclusion/exclusion criteria and Section 5.2	24. Current involuntary hospitalization or incarceration or on parole probation	24. Current involuntary hospitalization or incarceration or on parole/probation**, unless approved by the Medical Monitor**	[redacted]
Protocol Synopsis Inclusion/exclusion criteria and Section 5.2 **Similar edits in:** **Section 7.1.1**	25. … Note: IPSS will be required only for male subjects ≥ 45 years of age. Subjects already enrolled in the study will have these assessments at their next clinic visit planned after re-consenting to determine current eligibility.	25. … Note: IPSS will be required only for male subjects ≥ 45 years of age. ~~Subjects already enrolled in the study will have these assessments at their next clinic visit planned after re-consenting to determine current eligibility.~~	Removed since all currently enrolled subjects have met this criterion.
Protocol Synopsis Methods and Planned Analyses **Similar edits in:** **Section 8.4.1** **Section 8.7**	General considerations: ... Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), coefficient of variation, median, 90% confidence interval, minimum, and maximum values unless otherwise noted.	General considerations: … Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), coefficient of variation, median, **95** ~~90~~% confidence interval, minimum, and maximum values unless otherwise noted.	Updated to the conventional percentage.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			
Schedule of Events **Similar edits in:** **Section 7.1.2**	Visit 2: Subject eligibility verification process: independent diagnostic verification procedure and identity check using appropriate software/database. Verify eligibility	~~Visit 2: Subject eligibility verification process: independent diagnostic verification procedure and identity check using appropriate software/database. Verify eligibility~~	PANSS score at Visit 2 should not be utilized to determine subject eligibility. Subject eligibility should be based upon PANSS score at Visit 1 and Visit 3.
[redacted]			

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
			[redacted].
Schedule of Events **Similar edits in:** **Section 7.1.1** **Section 7.2.6** **Section 7.6.7**	f. A complete physical examination includes body temperature (orally collected, ° Celsius), general appearance, head/eyes/ears/nose/throat, an examination of thorax and abdomen, assessment of cardiovascular, pulmonary, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.	f. A complete physical examination includes body temperature (orally collected, °~~ Celsius~~), general appearance, head/eyes/ears/nose/throat, an examination of thorax and abdomen, assessment of cardiovascular, pulmonary, **and** musculoskeletal~~, and circulatory~~ systems, palpations for lymphadenopathy, and limited neurological examination.	Updated to align with vendor programming.
Section 2.2.4	To date, in 19 completed clinical studies (conducted by Eli Lilly or Karuna Therapeutics), some for as long as 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 3 completed Phase 1 studies in healthy volunteers [redacted] and 1 completed Phase 2 study (KAR-004) in adult patients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) schizophrenia (Refer to KarXT IB for details). Multiple other Phase 1 and Phase 3 studies are ongoing.	To date, in ~~19~~**32** completed clinical studies (conducted by Eli Lilly or Karuna Therapeutics), ~~some for as long as 3 years of exposure, more than 840~~ **with approximately 1632** 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 ~~3~~**multiple** completed Phase 1 studies in healthy volunteers ([redacted]), ~~and~~ 1 completed Phase 2 study (KAR-004 **findings described below), and multiple completed Phase 3 studies (KAR-007 and KAR-009 findings described below)** in adult~~ patients~~ **subjects** with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) schizophrenia ~~(Refer to KarXT IB for details)~~. Multiple other Phase 1 and Phase 3 studies are ongoing. **Refer to the KarXT IB for details on all completed and ongoing KarXT studies.**	Added to accurately reflect clinical experience to date with KarXT.
Section 2.2.4.5	N/A	*Entirely new section*	Added to accurately reflect clinical

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
			experience to date with KarXT.
Section 2.2.4.6	N/A	*Entirely new section*	Added to accurately reflect clinical experience to date with KarXT.
Section 4.1	Screening Period … The recommended background dosing of aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine, and the minimum detectable levels of drug concentrations are provided in Appendix 1.	Screening Period … The recommended background dosing of aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine~~, and the minimum detectable levels of drug concentrations~~ are provided in Appendix 1.	Removed for correctness.
Section 4.1 and Section 7.6	Safety will be assessed through spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms, SARS, BARS, AIMS, body weight, BMI, vital signs, ECG, International Prostate Symptom Score (IPSS) questionnaire, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), prolactin levels, physical examination and C-SSRS throughout the study as scheduled. Section 7.6 provides complete details on these safety assessments.	Safety will be assessed through spontaneous AEs including **TEAEs, TEAEs leading to discontinuation**, AESIs, procholinergic and anticholinergic symptoms, SA~~R~~S, BARS, AIMS, body weight, BMI, vital signs, ECG, International Prostate Symptom Score (IPSS) questionnaire, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), prolactin levels, physical examination and C-SSRS throughout the study as scheduled. Section 7.6 provides complete details on these safety assessments.	Added for consistency with Safety Endpoints (Synopsis and Section 3.2.5).
Section 4.2	The trial utilizes a common study used to determine the efficacy of an adjunctive treatment.	The ~~trial utilizes a common~~ study **uses a group sequential** design used to determine the efficacy of an adjunctive treatment.	[redacted]
Section 4.4	N/A	**An independent Data Monitoring Committee (DMC) will be established to review accumulated data [redacted]. The DMC charter**	DMC added to facilitate the [redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		will describe the procedures related to the committee operations in greater detail.	
[redacted]			
Section 6.7 [redacted]	… Subjects need to be on stable dosing of monotherapy aripiprazole, risperidone, paliperidone, or their LAIs, ziprasidone, lurasidone, or cariprazine that they have been taking under the same dosing regimen for at least 8 weeks before randomization. Subjects must remain on the same APD during the study; the dose should not be changed during the study.	… Subjects need to be on stable dosing of monotherapy aripiprazole, risperidone, paliperidone, or their LAI formulations, ziprasidone, lurasidone, or cariprazine that they have been taking under the same dosing regimen for at least 8 weeks prior to **Visit 3/Day 1** ~~before randomization~~. **Subjects who are taking LAI formulations but occasionally supplement with oral antipsychotics as needed (PRN) must wash out of the PRN oral antipsychotic for at least one week prior to Visit 3**. Subjects must remain on the same APD during the study; the dose should not be changed during the study.	Clarifies that as needed oral antipsychotics to supplement LAI antipsychotics are not allowed during the study. Based on relatively short half lives of oral antipsychotics, one week is sufficient washout.
Section 7.1.1 **Similar edits in:** **Schedule of Events** **Section 9.1.3**	… • Informed Consent will also be obtained from the informant prior to any protocol-related activities. The informant will continue to interact with the subject throughout the ARISE trials to have firsthand knowledge about the subject's behavior. This can be done either in person or remotely as required by local regulations. In Bulgaria, the informant needs to	… • Informed Consent will also be obtained from the informant prior to any protocol-related activities. **Informant consent can be done in person or remotely in accordance with local regulations and site processes and prior to any study procedures being conducted at the Screening Visit. The informant will continue to interact with the subject throughout the**	Added to provide flexibility because current informant requirements are a significant recruitment challenge.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial, and will sign the informant consent in person.	**ARISE trials to have firsthand knowledge about the subject's behavior.** ~~This can be done either in person or remotely as required by local regulations.~~ In Bulgaria, the informant needs to be physically present at the Baseline visit and should be physically present at all study visits where the Investigator determines that his/her input would be beneficial, and will sign the informant consent in person.	
Section 7.1.1 and Section 7.2.1	For the IPSS, study candidates must have < 5 (almost always) on either Item 1, 3, 5, or 6, or a sum of scores on IPSS Items 1, 3, 5, and 6 of < 9 to be eligible for the study	For the IPSS, study candidates must have < 5 (almost always) on ~~either Item~~ **items** 1, 3, 5, ~~or~~ **and** ~~6~~ ~~or~~ **and** a sum of scores on IPSS Items 1, 3, 5, and 6 of < 9 to be eligible for the study	To accurately reflect eligibility.
Section 7.1.2	Complete the PANSS and CGI-S assessments. Study candidates must have a PANSS total score ≥ 70, CGI-S scale of positive symptoms with a score ≥ 4 (moderate), and PANSS M-Pos Symptom Factor ≥ 4 on 2 (or more) items to continue to the study. [redacted]	Complete the PANSS and CGI-S assessments. ~~Study candidates must have a PANSS total score ≥ 70, CGI-S scale of positive symptoms with a score ≥ 4 (moderate), and PANSS M-Pos Symptom Factor ≥ 4 on 2 (or more) items to continue to the study.~~ [redacted]	Removed for accuracy with eligibility criteria; eligibility from PANSS is determined by Visit 1 and Visit 3.
Section 7.5.1	… The PANSS rating form contains 7 positive symptom scales, 7 negative symptom scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale.	… The PANSS rating form contains 7 positive symptom ~~scales~~ **items**, 7 negative symptom ~~scales~~ **items**, and 16 general psychopathology symptom ~~scales~~ **items.** Subjects are rated from 1 to 7 on each symptom ~~scale~~ **items**.	Updated for correctness and consistency. Each question on a scale is referred to as an item, and other subscales refer to questions as items.
Section 7.6.9	… At Screening, the central ECG reader will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal ECG will be recorded; if the ECG is considered abnormal, the abnormality will be documented	… At Screening, the central ECG reader will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal ECG will be recorded; if the ECG is considered abnormal, the abnormality will be documented	Added to provide clarification to sites on when an ECG can be repeated.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or if artifacts are present.	on the eCRF. **An ECG can be repeated during the Screening Period in the instance clinically significant abnormalities are identified, and if the Investigator deems it appropriate. The ECG should be repeated prior to a screen failure determination being made.** ~~ECGs will be repeated if clinically significant abnormalities are observed or if artifacts are present.~~	
Section 7.6.10	… If a subject has an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 during the treatment period, the subject should be referred to an urologist. The urologist, in collaboration with the study Investigator, should determine whether the subject should be discontinued from the study.	… If a subject has an IPSS score of 5 (almost always) on items 1, 3, 5, or 6, OR a sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9 during the treatment period, the subject should be referred to an urologist. **The study Investigator should take the urologist's input into consideration** ~~urologist, in collaboration with the study Investigator, should~~ **when** determin**ing** ~~e~~ whether the subject should be discontinued from the study.	Updated to clarify that while the Investigator will consider the urologist's recommendation, the Investigator makes the final decision with regard to continued study participation.
Section 7.6.11	Laboratory assessment samples (Table 4) are to be collected at designated visits as detailed in the SOE (Table 1). Blood laboratory samples will be analyzed at a central laboratory.	Laboratory assessment samples (Table 4) are to be collected at designated visits as detailed in the SOE (Table 1). **Laboratory Assessments may also be repeated if results are clinically significant. During the screening period, if the Investigator deems it appropriate to repeat safety laboratory testing, this should be completed prior to a screen failure determination being made.** Blood laboratory samples will be analyzed at a central laboratory.	Added to provide clarification to sites.
Section 7.6.11 (Table 4)	(Urine Analysis) pH Protein Glucose Ketones	(Urine Analysis) pH Protein Glucose Ketones	Added FSH to align with the requirement of FSH level test discussed in [redacted].

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	Indicators of blood and WBCs Specific gravity Urobilinogen	Indicators of blood and WBCs Specific gravity Urobilinogen **FSH** *Corresponding footnote:* **FSH test for post menopausal females at the Screening Visit 1 only.**	
Section 7.7.3	The AESIs will be monitored and include orthostasis, syncope, and LFT elevations inclusive of DILI. AESIs should be recorded as AEs and reported as SAEs if the AESI meets serious criteria. For further guidance on orthostatic hypotension, see APPENDIX 3. DILI monitoring guidelines are provided below in Section 7.7.6	**AESIs will include symptomatic orthostasis (Section 7.7.3.1), syncope (Section 7.7.3.2), and elevated LFTs requiring DILI monitoring (Section 7.7.3.3).** **The Investigator will assess and record any additional information on the AESI in detail which must be submitted within 24 hours of awareness of the event.** **As follow-up information becomes available, the site should update the AESI within 24 hours of awareness of the new information. All relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summaries, post-mortem results, etc.) and all other updated information should be entered in the EDC. The Investigator should follow the subject until the AESI resolves or until the condition becomes chronic in nature, stabilizes, or returns to baseline values (if a baseline value is available).** **7.7.3.1. Symptomatic Orthostasis** **Orthostasis will be defined as the subject is symptomatic and has at least one of the following changes in vital signs from the sitting to standing measurements:**	Added to provide greater details around the definition of an AESI, and to require prompt reporting when an AESI is detected by the sites. The goal is to prevent sites from missing the occurrence of an AESI.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		• A decrease of systolic blood pressure of 20 mmHg or more **• A decrease in diastolic blood pressure of 10 mmHg or more** **• An increase in seated heart rate of 30 bpm or more** **Changes of the orthostatic vital signs alone will not be considered an AESI without the subject being symptomatic.** **7.7.3.2. Syncope** **Syncope is defined as a sudden, transient loss of consciousness. Syncope is due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery (Task Force for the Diagnosis and Management of Syncope, et al., 2009).** **7.7.3.3. Elevated Liver Function Test Requiring Drug Induced Liver Injury Monitoring** **An AESI should be reported as anytime the subject exhibits:** **• ALT and/or AST > 3 × ULN reference range** **All LFT AESIs should also be recorded as an AE and subsequently follow the DILI monitoring criteria as explained in Section 7.7.7.** ~~The AESIs will be monitored and include orthostasis, syncope, and LFT elevations inclusive of DILI.~~ ~~AESIs should be recorded as AEs and reported as SAEs if the AESI meets serious criteria. For~~	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		~~further guidance on orthostatic hypotension, see APPENDIX 3.~~ ~~DILI monitoring guidelines are provided below in Section 7.7.6~~	
Section 7.7.5	SAEs / AESIs reported by subjects or observed by clinical staff after subject has signed the Informed Consent Form must be reported to the Pharmacovigilance group of Catalyst Clinical Research and the Sponsor. Any such SAE / AESI due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. SAEs will be reported directly through the EDC, but as a backup (in case the EDC is not available), sites can use the Catalyst email address as below: Catalyst Clinical Research Pharmacovigilance email address is: Safety@catalysterc.com. … The Investigator must report all additional follow-up evaluations to the Catalyst Clinical Research pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as it is practicable.	SAEs/AESIs reported by subjects or observed by clinical staff after subject has signed the ICF must be reported to the **Sponsor's** pharmacovigilance group ~~of Catalyst Clinical Research and the Sponsor~~. Any such SAE/AESI due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. SAEs will be reported directly through the EDC, but as a backup (in case the EDC is not available), sites can use the Catalyst email address as below: ~~Catalyst Clinical Research~~ **Sponsor's p**harmacovigilance **group** email address**:** ~~is: Safety@catalysterc.com~~ **worldwide.safety@bms.com or Fax to: +1 609 818-3804.** … The Investigator must report all additional follow-up evaluations to the ~~Catalyst Clinical Research~~ **Sponsor's** pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as it is practicable.	Updated for accuracy.
Section 7.7.11.7	Elevated liver enzymes have been reported in previous studies of xanomeline as monotherapy in Alzheimer's disease 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.	**KarXT was associated with transient increases in LFT values, primarily ALT, mostly occurred within the first month of starting KarXT treatment and resolved on treatment, suggesting hepatic adaptation to xanomeline. Hepatic safety should be monitored in all subjects receiving KarXT** ~~Elevated liver enzymes have been reported in previous studies of xanomeline as monotherapy~~	Updated to reflect current clinical trial data.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	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.	~~in Alzheimer's disease 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.~~	
Section 8.1	N/A *Original content moved to Section 8.4.1, shown below as new text.*	**The primary null hypothesis is that there is no difference in change from baseline to end of Week 6 in PANSS Total between adjunctive KarXT and placebo.**	Updated for accuracy with study design and objectives.
Section 8.2	The sample size up to 400 subjects is based on the assumption of a mean treatment difference of 5 points on the primary efficacy endpoint (change from Baseline to Week 6 in the PANSS total score) and a SD of 17 points. Based on these assumptions, 200 subjects per arm will provide 83.5% power to detect a significant difference between treatment groups using a 2-sided alpha of 0.05.	~~The sample size up to 400 subjects is based on the assumption of a mean treatment difference of 5 points on the primary efficacy endpoint (change from Baseline to Week 6 in the PANSS total score) and a SD of 17 points. Based on these assumptions, 200 subjects per arm will provide 83.5% power to detect a significant difference between treatment groups using a 2-sided alpha of 0.05.~~**Approximately 360 subjects will be randomized. The sample size is based on the assumption of a treatment difference of 5 points on the primary efficacy endpoint (change from baseline Week 6 in PANSS total score), a standard deviation (SD) of 13 points, and a 20% drop out rate. A total of 180 subjects per arm will provide 90% power to detect a significant difference**	[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		between treatment groups, using a 2-sided alpha of 0.05. [redacted]	
[redacted]			
Section 8.4.1	All efficacy analyses will be performed using the mITT population. The primary set of analyses will be limited to the subset of subjects who were taking one of the following APDs at study entry: aripiprazole, risperidone, paliperidone or their LAI versions, or ziprasidone, lurasidone, or cariprazine. A secondary, supportive set of analyses will be based on the full set of subjects who were	**The SAP will be prepared after the protocol is approved. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will complement the protocol and supersede it in case of differences.** **All statistical analyses will use SAS® version 9.4 or higher. Summary tables will be**	[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	taking any APD at study entry. The statistical analysis of the primary and key secondary efficacy variables will account for multiplicity by using a fixed-sequence testing procedure. The primary endpoint of change from Baseline to Week 6 in PANSS Total score will be evaluated first. Formal statistical testing of the key secondary endpoint, change from Baseline to Week 6 in PSP score, will be performed only if the primary endpoint is significant at the 2-sided 0.05 alpha level ($P < 0.05$). This will control the overall Type 1 error rate across both hypotheses/endpoints being tested.	**organized by treatment group. Descriptive statistics for continuous variables will include the number of subjects (n), mean, SD, coefficient of variation, median, 95% confidence interval, minimum, and maximum values unless otherwise noted. For categorical variables, frequencies and percentages will be provided, and the data will be tabulated by treatment group with the number and proportion of subjects for each category.** All efficacy analyses will be performed using the mITT population. [redacted] [redacted]	[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 8.5.1	… Robustness of the estimand will be assessed through sensitivity analyses using alternative analysis populations (e.g., Completer population; all subjects included in the mITT population, regardless of current APD at randomization),		

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			
Section 9.1.1	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.	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**, including EU No. 536/2014**.	Added to comply with European Union regulations.
[redacted]			

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			

Abbreviations: AD = Alzheimer's disease; AE = adverse event; AESI = adverse event of special interest; AIMS = Abnormal Involuntary Movement Scale; ALT = alanine transaminase; APD = antipsychotic drug; AST = aspartate transaminase; BARS = Barnes Akathisia Rating Scale; BID = 2 times a day; BMI = body mass index; bpm = beats per minute; [redacted]; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DILI = drug-induced liver injury; DMC = Data Monitoring Committee; DSM-5 = Diagnostic and Statistical Manual–Fifth Edition; ECG = electrocardiogram; eCRF = electronic case report form; EDC = electronic data capture;

eGFR = estimated glomerular filtration rate; [redacted]; [redacted]; GCP = Good Clinical Practice; IB = Investigator's Brochure; IP = investigational product; IPSS = International Prostate Symptom Score; LAI = long-acting injectable; LFT = liver function test; [redacted]; mITT = modified intent-to-treat; N/A = not applicable; PANSS = Positive and Negative Syndrome Scale; [redacted]; PRN = as needed; SAE = serious adverse event; SAP = statistical analysis plan; SAS = Simpson-Angus Scale; SD = standard deviation; SOE = Schedule of Events; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; WBC = white blood cell; [redacted].

[a] [redacted]

1. TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Title Page, Protocol Approval Signatures, Header	4.0 09-Mar-2023	~~4.0~~**5.0** ~~09-Mar-2023~~ **16-Jan-2024**	Updated date and version to v5.0.
Protocol Approval Signatures	[redacted] Karuna Therapeutics	[redacted] Karuna Therapeutics	Updated to reflect accurate signatory body.
Investigator Signature Page	… • Prior to initiating the trial, I will provide the Independent Ethics Committee (IEC), Institutional Review Board (IRB), and regulatory authorities all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by IEC, IRB, and regulatory authorities, I will not modify this protocol without obtaining prior approval from Karuna Therapeutics and of the IEC, IRB, and regulatory authorities. I will submit the protocol amendments and/or any consent form modifications to Karuna Therapeutics and the IEC, IRB, and regulatory … • I ensure that source documents and trial records that include all pertinent observations on each site's trial subjects will be attributable, legible,	… • Prior to initiating the trial, I will provide the Independent Ethics Committee (IEC), Institutional Review Board (IRB), and regulatory authorities**, as applicable,** all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by IEC, IRB, and regulatory authorities, I will not modify this protocol without obtaining prior approval from Karuna Therapeutics and of the IEC, IRB, and regulatory authorities. I will submit the protocol amendments and/or any consent form modifications to Karuna Therapeutics and the IEC, IRB, and regulatory … • I ensure that source documents and trial records that include all pertinent observations on ~~each~~ **the applicable** site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.	Clarified investigator's responsibilities.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	contemporaneous, original, accurate, and complete.		
[redacted]			
Protocol Synopsis Safety Endpoints	• To evaluate the safety and tolerability of adjunctive KarXT compared with placebo when added to risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, and cariprazine for the treatment of schizophrenia	• To evaluate the safety and tolerability of adjunctive KarXT compared with placebo when added to risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, ~~and~~ **or** cariprazine for the treatment of schizophrenia	Corrected for consistency with the body of the protocol.
Protocol Synopsis Safety Endpoints **Similar edits in:** **Section 3.2.5** **Section 7.7.3**	– Adverse events of special interest (AESI) such as orthostasis, and elevated liver function tests (LFTs) requiring drug-induced liver injury (DILI) monitoring	Adverse events of special interest (AESI) such as orthostasis, **syncope,** and elevated liver function tests (LFTs) requiring drug-induced liver injury (DILI) monitoring	Syncope added as an AESI for improved patient safety and accuracy to latest data.
[redacted]			

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Inclusion Criteria #4** **Section 4.1** **Section 5.1 IC #4** **Section 6.7**	Subjects will be outpatients, ≥18 to <60 years old at the time of randomization (Visit 3), with a primary diagnosis of schizophrenia who have been on a stable aripiprazole, risperidone, paliperidone, ziprasidone, lurasidone, or cariprazine regimen for at least 8 weeks at the same dose prior to Screening and continue to experience ongoing positive symptoms despite therapy.	Subjects will be outpatients, ≥ 18 to < 60 years old at the time of randomization (Visit 3), with a primary diagnosis of schizophrenia who have been on a stable aripiprazole, risperidone, paliperidone, **or their LAIs,** ziprasidone, lurasidone, or cariprazine regimen for at least 8 weeks at the same dose prior to ~~Screening~~ **Day 1 (Visit 3)** and continue to experience ongoing positive symptoms despite therapy.	Duration of stable dose of APD for study eligibility updated to properly reflect the desired 8 weeks prior to dosing. Previously was written as 12 weeks prior to dosing. Clarified that the long-acting injectable versions of aripiprazole, risperidone, and paliperidone are allowed, for internal document consistency.
Protocol Synopsis Study Design **Similar edits in:** **Protocol Synopsis Duration**	The duration of the study is approximately 92 days. This includes [redacted] Screening Period, 6-week Treatment Period, and a 1-week safety monitoring visit.	The duration of the study is approximately 92 days. This includes a [redacted] Screening Period, 6-week Treatment Period, and ~~a 1-week safety monitoring visit.~~**an SFU Visit (end of Week 7).**	Revised for consistency with the body of the protocol.
Protocol Synopsis Study Design **Similar edits in:** **Section 4.1** **Section 7.1** **Section 7.1.1**	To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1). For subjects on long-acting injectables it will be sufficient to obtain confirmation that the subject is within the treatment window.	To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1). ~~For subjects on long-acting injectables it will be sufficient to obtain confirmation that the subject is within the treatment window.~~	Updated for clarity, as LAIs should be treated the same as all APDs.
Protocol Synopsis Study Design	Dose of the background antipsychotic medication should not be changed during the study (including the Screening Period).	~~Dose~~ **Subjects are required to remain on the same appropriate approved APD; the dose** of the background ~~antipsychotic medications~~ **APD**	Language revised for improved clarity of background APD dosing requirements.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Similar edits in: **Section 4.1** **Section 6.7**		should not be changed during the study (including the Screening Period).	
Protocol Synopsis **Study Design**	Subjects who are randomized will begin receiving KarXT or matching placebo 2 times per day (BID)	Subjects who are randomized will begin receiving KarXT or matching placebo 2 times per day (BID)	Clarified duration of BID dosing.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis **Inclusion Criteria #4** **Similar edits in:** **Section 5.1 IC #4**	Subject is currently being treated with monotherapy risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine and has been taking this treatment with the same dosing regimen for at least 8 weeks at the time of Screening (supported by documentation)	Subject is currently being treated with **stable dosing of** monotherapy risperidone, paliperidone, aripiprazole, **or their LAIs,** ziprasidone, lurasidone, or cariprazine and has been taking this treatment with the same dosing regimen for at least 8 weeks at the time of ~~Screening~~ **Day 1 (Visit 3)** (supported by documentation)	Clarified eligibility requirement for treatment with APDs.
Protocol Synopsis **Inclusion Criteria #15** **Similar edits in:** **Schedule of Events footnote 'b'** **Section 5.1 IC #15** **Section 7.1.1** **Section 9.1.3**	In Bulgaria, the informant must be physically present at all study visits.	In Bulgaria, the informant ~~must~~ **needs to be physically present at the Baseline visit and should** be physically present at all study visits **when the Investigator determines that his/her input would be beneficial.**	Updated informant attendance requirement to reflect that attendance is at the discretion of the Investigator.
Protocol Synopsis **Exclusion Criteria #3** **Similar edits in:** **Section 5.2 EC #3**	3. Subject has a history of inadequate response to schizophrenia medications defined as: Failure to minimally respond to 2 adequate courses of pharmacotherapy (a minimum of 6 weeks at an adequate dose per the label) a. Having received any trial of clozapine regardless of dose, duration, or indication	3. Subject has a history of ~~inadequate response to~~ **treatment-resistant** schizophrenia ~~medications~~ defined as: **a**. Failure to minimally respond to 2 adequate courses of **APD** pharmacotherapy ~~(a minimum.~~ **Note: Failure to minimally respond is defined as persistence** of **symptoms**~~6 weeks at an~~ **of moderate severity symptoms in 2 or more psychotic symptom domains or persistence of severe symptoms in 1 or more psychotic symptom domains despite** adequate dose ~~per the label)~~ **and duration (6 weeks or longer) of APD treatment.** ~~a. Having received any trial of clozapine regardless of dose, duration, or indication~~	Revised exclusion criteria to exclude treatment-resistant schizophrenia patients and to provide clarity as to what defines this patient group. Clozapine details removed, as deemed unnecessary because the definition above excludes to this.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Exclusion Criteria #5 **Similar edits in:** **Section 5.1 EC #5**	5. Current APD is other than aripiprazole, risperidone, paliperidone, or their LAI versions, ziprasidone, lurasidone, or cariprazine a. olanzapine, quetiapine, or haloperidol is not permitted	5. Current APD is other than aripiprazole, risperidone, paliperidone, or their LAI versions, ziprasidone, lurasidone, or cariprazine ~~a. olanzapine, quetiapine, or haloperidol is not permitted~~	Removed list of prohibited APDs because this is accounted for and in more detail in [redacted] of the protocol.
Protocol Synopsis Exclusion Criteria #13 **Similar edits in:** **Schedule of Events footnote 'd'** **Section 5.2 EC #13** **Section 7.6.12**	13 Urine toxicology screen is positive for non-cannabis or non benzodiazepine substances	13. Urine toxicology screen is positive for ~~non-cannabis or non-benzodiazepine substances~~ **phencyclidine, amphetamines, opiates, cocaine, or alcohol (clinically significant alcohol use in the opinion of the Investigator)**	Urine toxicology screen harmonized across documents for consistency and clarity.
Protocol Synopsis Exclusion Criteria #14 **Similar edits in:** **Section 5.2 EC #14** **Section 6.7** **Section 6.7.1 [section removed]** **Section 11** [redacted]	14. Recent history of receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, divalproex), lithium, tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for as needed anxiolytics (e.g., lorazepam, chloral hydrate) Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors taken at a stable dose for at least 8 weeks prior to Screening may be permitted Mirtazapine may be used as a hypnotic if started at least 8 weeks prior to Screening and at a stable dose	14. **Subject is currently taking, or plans to take while in the study, any prohibited concomitant medication** [redacted] ~~Recent history of receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, divalproex), lithium, tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for as needed anxiolytics (e.g., lorazepam, chloral hydrate)~~ ~~Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors taken at a stable dose for at least 8 weeks prior to Screening may be permitted~~ ~~Mirtazapine may be used as a hypnotic if started at least 8 weeks prior to Screening and at a stable dose~~	Updated to improve clarity [redacted] consolidating the prohibited and concomitant medication information.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Protocol Synopsis Exclusion Criteria #22 **Similar edits in:** **Section 5.2 EC #22**	22. Participation in another clinical study in which the subject received an experimental or investigational drug within 3 months before Screening or has participated in more than 2 clinical studies in the past year	22. Participation in another clinical study in which the subject ~~received an experimental or investigational drug~~ **was enrolled** within 3 months before Screening ~~or has participated in more than 2 clinical studies in the past year~~	Revised for improved readability and clarity.
Protocol Synopsis Exclusion Criteria #24 **Similar edits in:** **Section 5.2 EC #24**	24. Current involuntary hospitalization or incarceration	24. Current involuntary hospitalization or incarceration **or on parole/probation**	Updated exclusion criteria to better define eligibility.
Protocol Synopsis Exclusion Criteria #25 **Similar edits in:** **Schedule of Events** **List of Abbreviations** **Section 4.1** **Section 5.2 EC #25** **Section 7.1.1** **Section 7.2.1** **Section 7.2.5** **Section 7.2.6** **Section 7.3** **Section 7.6** **Section 7.6.10** **Section 7.6.11 (Table 4)**	NA	**25. For all male subjects only, any one of the following:** **a. History of bladder stones** **b. History of recurrent urinary tract infections** **c. Serum prostate specific antigen (PSA) > 10 ng/mL** **d. An International Prostate Symptom Score (IPSS) of 5 (almost always) on either item 1, 3, 5, or 6** **e. A sum of scores on IPSS items 1, 3, 5, and 6 of ≥9** **Note: IPSS will be required only for male subjects ≥ 45 years of age. Subjects already enrolled in the study will have these assessments at their next clinic visit planned after re-consenting to determine current eligibility.**	Exclusion criterion added for male subjects to improve overall subject safety and refine enrolled population.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			
Protocol Synopsis Statistical Methods and Planned Analyses **Similar edits in:** **Section 8.4.1** **Section 8.5.4**	… The key secondary endpoint, change from Baseline to Week 6 in PSP, will be analyzed in a manner similar to the primary endpoint. [redacted]	… The key secondary endpoint, change from Baseline to Week 6 in PSP, will be analyzed in a manner similar to the primary endpoint. [redacted]	Added for internal document consistency.
[redacted]			
Schedule of Events	NA	Description of Change	Updated for consistency and overall clarity of

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		IPSS row added to SOE, refer to redline for reference. Footnote 'q' added and other footnotes rearranged accordingly.	assessments to be performed.
Schedule of Events **Similar edits in:** **Section 7.1.1** **Section 7.2.1** **Section 7.2.4** **Section 7.2.6** **Section 7.6.9**	i. ECGs at all scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or [redacted] analysis. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained	i. ECGs at all scheduled visits will be performed before blood ~~withdrawal~~ **sample collection** for any safety laboratory tests and/or [redacted] analysis. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained	Revised terminology for clarity.
[redacted]			
Section 2.1 **Similar edits in:** **Section 4.2**	Given that KarXT has no direct dopaminergic activity and differs from the D_2 antagonists risperidone, paliperidone, ziprasidone, lurasidone, or the D_2 partial agonist aripiprazole, and D_2 and D_3 partial agonist cariprazine, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their long-acting injectables (LAIs), ziprasidone or lurasidone.	Given that KarXT has no direct dopaminergic activity and differs from the D_2 antagonists risperidone, paliperidone, ziprasidone, lurasidone, ~~or~~ the D_2 partial agonist aripiprazole, and D_2 and D_3 partial agonist cariprazine, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their long-acting injectables (LAIs), ziprasidone ~~or~~**,** lurasidone**, or cariprazine**.	Added for internal document consistency.
Section 2.2.1	Central muscarinic receptors have been hypothesized to be therapeutic treatments for	Central muscarinic receptors have been hypothesized to be therapeutic treatment **target**s	Corrected textual error.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	schizophrenia based on several converging lines of evidence, including both animal and human studies (Wess 2007, Sellin 2008).	for schizophrenia based on several converging lines of evidence, including both animal and human studies (Wess 2007, Sellin 2008).	
Section 4.1	Efficacy assessments (PANSS scores and CGI-S score) will be assessed at scheduled visits. Refer to Section 7.5 for more details.	Efficacy assessments (PANSS scores**,** ~~and~~ CGI-S score**s, and other efficacy endpoints as defined in Section 3.2** ~~CGI-S score)~~) will be assessed at scheduled visits. Refer to Section 7.5 for more details.	Language revised for improved clarity.
Section 5.3	NA	Subjects may be rescreened **one time** on a case-by-case basis upon approval of the Medical Monitor. ~~Such individuals may be allowed to rescreen once within 60 days from date of consent.~~ **Any subject who is considered for rescreen should sign a new ICF.**	Revised statement to screen failure/rescreen language for operational clarity.
Section 5.5	• Clinically significant alcohol use or illegal drug use in the opinion of the Investigator.	• Clinically significant alcohol use or illegal drug use in the opinion of the Investigator **or Sponsor**.	Updated to include Sponsor in clinical judgment call of clinically significant alcohol use or illegal drug use.
Section 5.6 **Similar edits in:** **Section 7.7.5**	If a pregnancy is verified, the subject will be permanently discontinued from study medication. Upon discontinuation from study medication, only procedures that would not expose the pregnant female subject to undue risk will be performed.	If a pregnancy is verified, the subject will be permanently discontinued from **the** study ~~medication~~ **drug**. Upon discontinuation from study ~~medication~~ **drug**, only procedures that would not expose the pregnant female subject to undue risk will be performed **at the ET Visit and the SFU Visit**.	Administrative update for consistency and accuracy in procedures for managing pregnancy.
Section 6.3.1	The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal.	The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, **the amount of study drug returned by each**	Administrative update.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		subject, and the return of materials to the Sponsor or designee for storage or disposal.	
Section 6.3.3	[redacted] All packaging and labeling operations will comply with Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Blister pack wallets of KarXT or placebo capsules will be provided at each visit and will be labeled, "KarXT (Xanomeline/Trospium Cl) or Placebo", recommended storage conditions, the name and address of the manufacturer, and the Investigational Use Statement ("Caution: New Drug – Limited by Federal [US] law to investigational use").	[redacted] All packaging and labeling operations will comply with Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Blister pack wallets of KarXT or placebo capsules will be provided at each visit and will be labeled, "~~"~~KarXT (Xanomeline/Trospium Cl) or Placebo~~"~~**",** recommended storage conditions, [redacted] and [redacted] **other information according to labeling requirements specific to countries participating in the KAR-012 study. Further details on** the [redacted] **product label will be provided in the Pharmacy Manual.**	[redacted]
Section 6.4.1	On Day 1, all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups.	On Day 1~~,~~ **(Visit 3),** all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups.	Updated for clarity.
Section 6.4.1 **Similar edits in:** **Section 6.4.2**	Subjects will be assigned a randomization number through the interactive web response system (IWRS), in accordance with the randomization code generated by [redacted]. Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the first subject discontinued the study.	Subjects will be assigned a randomization number through the interactive web response system (IWRS), in accordance with the randomization code generated by [redacted] **A third-party unblinded statistician**. Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the first subject discontinued the study.	Language revised to remove mention of specific vendors and provide more flexibility.
Section 6.4.2	Unblinding according to the protocol will occur only after the completion of the study.	Unblinding according to the protocol will occur only after ~~the completion of the study~~ **database lock.**	Administrative update.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 6.5	Subjects will be dosed as described in Section 4.1 and in accordance with the SOE (Table 1). KarXT doses were selected based on the results of previous clinical studies (see Section 2.2.4).	Subjects will be dosed as described in Section 4.1 and in accordance with the SOE (Table 1). KarXT doses were selected based on the results of previous clinical studies (see Section 2.2.4). **Per the protocol, subjects will be evaluated for dose adjustments at Visits 3 to 7 and at unscheduled visits.**	Updated for cross-document consistency.
Section 6.7 and Section 6.7.1 [redacted]	Subjects will be asked to report all prior medications they were taking up to 6 months before the study, up to the time of the first dose of study medication on Day 1. All prior medications will be recorded on the eCRF. In addition, the subjects will identify all of the medications that they are currently taking. Restricted prior therapies are provided in Section 5.2. All medications and other treatments taken by the subject during the study, including treatments initiated before the start of the study, must be recorded on the eCRF. All subjects participating in this study must not take the below mentioned prohibited medications for the duration of the study. • Oral antipsychotic medications other than the ones permitted in the trial, monoamine oxidase inhibitors, mood stabilizers (e.g., lithium, olanzapine, quetiapine, haloperidol), anticonvulsants (e.g., lamotrigine, divalproex), tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except	Subjects will be asked to report all prior medications they were taking up to 6 months before the study, up to the time of the first dose of study medication on Day 1. All prior medications will be recorded on the eCRF. In addition, the subjects will identify all of the medications that they are currently taking. ~~Restricted prior therapies are provided in Section 5.2.~~ All medications and other treatments taken by the subject during the study, including treatments initiated before the start of the study, must be recorded on the eCRF. [redacted] ~~All subjects participating in this study must not take the below mentioned~~ **for guidance on allowed and** prohibited medications ~~for the duration of the study~~. ~~• Oral antipsychotic medications other than the ones permitted in the trial, monoamine oxidase inhibitors, mood stabilizers (e.g., lithium, olanzapine, quetiapine, haloperidol), anticonvulsants (e.g., lamotrigine, divalproex), tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for anxiolytics that~~	Consolidated information on allowed and prohibited medications in [redacted] of the protocol to improve clarity.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	for anxiolytics that were taken on an as needed basis (e.g., lorazepam) • Anticholinergic medications including benztropine, diphenhydramine, darifenacin, oxybutynin, etc. During the study (i.e., from the time of Screening visit until study completion), the use of any other concomitant medication(s) during the study period is prohibited without the prior approval of the Investigator unless its use is deemed necessary as in a medical emergency or treatment of non-TEAE. Over the counter medications such as acetaminophen, paracetamol, ibuprofen, aspirin etc., are permitted during the study. After signed ICF is obtained from the subjects, the subjects who are taking the following medications must have the minimum washout periods specified below and not take the medications for the duration of the study. • Eight weeks for antipsychotics (including olanzapine) other than the ones allowed in the study, monoamine oxidase inhibitors, mood stabilizers (e.g., lithium, olanzapine, quetiapine, haloperidol), anticonvulsants (e.g., lamotrigine, divalproex) and tricyclic antidepressants (e.g., imipramine, desipramine) Note: Please direct questions relating to prohibited medications to the Medical Monitor.	~~were taken on an as needed basis (e.g., lorazepam)~~ • ~~Anticholinergic medications including benztropine, diphenhydramine, darifenacin, oxybutynin, etc.~~ During the study (i.e., from the time of Screening visit until study completion), the use of any other concomitant medication(s) ~~during the study period~~ **other** [redacted] is prohibited without the prior approval of the Investigator unless its use is deemed necessary as in a medical emergency or treatment of non-TEAE. Over-the-counter medications such as acetaminophen, paracetamol, **and** ibuprofen~~,~~ ~~aspirin etc.,~~ are permitted during the study. After signed ICF is obtained from the subjects, the subjects ~~who are~~ **will need to be washed out of excluded APDs for 8 weeks before randomization.** **Subjects need to be on stable dosing of monotherapy aripiprazole, risperidone, paliperidone, or their LAIs, ziprasidone, lurasidone, or cariprazine that they have been** taking **under** the ~~following medications~~ **same dosing regimen for at least 8 weeks before randomization. Subjects** must ~~have~~ **remain on** the ~~minimum washout periods specified below and not take the medications for~~ **same APD during the study;** the ~~duration of~~ **dose should not be changed during** the study. • ~~Eight weeks for antipsychotics (including olanzapine) other than the~~	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	6.7.1, Concomitant Medications for Anxiety and/or Sleep aid Subjects are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on an as needed (PRN) basis. However, subjects should refrain from taking benzodiazepines within 12 hours prior to any of the [redacted]. Subjects may also use non-benzodiazepine medications (e.g., zolpidem, zaleplon) as a sleep aid on a PRN basis.	~~ones allowed in the study, monoamine oxidase inhibitors, mood stabilizers (e.g., lithium, olanzapine, quetiapine, haloperidol), anticonvulsants (e.g., lamotrigine, divalproex) and tricyclic antidepressants (e.g., imipramine, desipramine)~~ ~~Note:~~ Please direct questions relating to prohibited **and concomitant** medications to the Medical Monitor. ~~6.7.1, Concomitant Medications for Anxiety and/or Sleep aid~~ ~~Subjects are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on an as needed (PRN) basis. However, subjects should refrain from taking benzodiazepines within 12 hours prior to [redacted]. Subjects may also use non-benzodiazepine medications (e.g., zolpidem, zaleplon) as a sleep aid on a PRN basis.~~	
Section 6.7	… Over the counter medications such as acetaminophen, paracetamol, ibuprofen, aspirin etc., are permitted during the study. …	… Over the counter medications such as acetaminophen, paracetamol, **and** ibuprofen~~,~~ ~~aspirin etc.,~~ are permitted during the study. …	Removed aspirin as an example over-the-counter medication because the other listed medications are preferred.
Section 7.1 **Similar edits in:** **Section 7.1.1**	Screening is a minimum of [redacted]	Screening is a minimum [redacted]	Clarified screening duration and removed requirement for subjects to bring in bottle of prescribed APD because it is not

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	[redacted] During Screening, the site will confirm that the subject is meeting randomization criteria, including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine at Screening. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1). Subject should also be instructed to bring in their bottle of prescribed background antipsychotic medication to Visit 1 to verify adherence.	[redacted] During Screening, the site will confirm that the subject is meeting randomization criteria, including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ziprasidone, lurasidone, or cariprazine at Screening. To be eligible for randomization, subjects need to have detectable levels of background antipsychotic medication (measured at Visit 1). [redacted]	necessary for verifying adherence.
Section 7.2.3	[redacted]		Visit 5 dose modification updated for clarity.
Section 7.3	• All subjects will be followed for 7 days after the last dose of KarXT or matching placebo on Day 42 ± 3	• All subjects **who do not elect to participate in the KAR-013 study** will be followed for 7 days after the last dose of KarXT or matching placebo on Day 42 ± 3	Updated for clarity of safety follow-up obligations.
Section 7.6.10	The IPSS questionnaire is clinician-administered (Barry 1995).	~~The IPSS questionnaire is clinician-administered (Barry 1995).~~	Administrative update
Section 7.6.11 (Table 4)	PT Activated PTT Fibrinogen	PT **PT/INR** Activated PTT Fibrinogen	Added laboratory assessment to inform safety monitoring.
Section 7.6.11	Upon receipt of the laboratory reports from the relevant laboratory vendor, the results must be reviewed by the Investigator or designee. The results of the review will be subsequently logged in the eSource system and signed off by the investigator or designee.	~~Upon receipt of the~~ **All** laboratory reports ~~from the relevant laboratory vendor, the results~~ must be reviewed**, signed, and dated** by the Investigator or designee~~. The results of the review will~~**, and** be ~~subsequently logged in the eSource system and signed off by the~~	Administrative update

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		~~investigator or designee~~ **filed with both the subject's eCRF and medical record (source document) for that visit.**	
Section 7.7.4	SAEs will be reported directly through the EDC / eSource system, but as a backup (in case the EDC / eSource system is not available), sites can use the Catalyst email address as below: Catalyst Clinical Research Pharmacovigilance email address is: Safety@catalystcr.com	SAEs will be reported directly through the EDC ~~/ eSource system~~, but as a backup (in case the EDC~~/ eSource system~~ is not available), sites can use the Catalyst email address as below: Catalyst Clinical Research Pharmacovigilance email address is: Safety@catalystcr.com	Administrative update to reflect the change from eSource to EDC vendor.
Section 7.7.6	• Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease	• ~~Rule~~ **Consider ruling** out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease	Monitoring requirements for DILI updated for flexibility in ruling out hepatitis.
Section 8.6	NA	**The C-SSRS is a measure of suicidal ideation and behavior. The number of subjects with a lifetime history of suicidal ideation or suicidal behavior will be summarized by treatment.**	Statement added for cross-document consistency and clarity.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 9.1.4	… 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. … 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. Regarding data security, data collected on the secure mobile application is stored locally on the mobile device (iPad), synced to a central server, and backed up on an off-location server. Data collected on the secure website is stored on a central server and backed up on an off-location server. In Europe, the central server where the data is originally synced to is located in Frankfurt, Germany. Data collected is encrypted and uploaded/synced via additionally encrypted transmission to secure servers where access is strictly limited as defined by the Data Controller (Sponsor), Informed Consent, and local regulations.	… Data on eCRFs transmitted via the ~~web-based data~~ **EDC** 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. … 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. ~~Regarding data security, data collected on the secure mobile application is stored locally on the mobile device (iPad), synced to a central server, and backed up on an off-location server. Data collected on the secure website is stored on a central server and backed up on an off-location server. In Europe, the central server where the data is originally synced to is located in Frankfurt, Germany. Data collected is encrypted and uploaded/synced via additionally encrypted transmission to secure servers where access is strictly limited as defined by the Data Controller (Sponsor), Informed Consent, and local regulations.~~	Administrative update to reflect the change from eSource to EDC vendor.
Section 9.1.5	The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be	The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be	Administrative update to reflect the change from eSource to EDC vendor.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	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. In the US, pertinent source documents are uploaded to the EDC platform. The following datapoints in KAR-012 are expected to be initially captured on paper as source and then entered into the EDC platform, as applicable per local and site's requirements: • ICF – this will be signed by the subject/informant as applicable on paper, the date of consent will be captured in the EDC platform • Demographics • Psychiatric history • Medical history • Concomitant medications • AE/SAE information • Site eligibility review • MINI All data collected can be indicated to be "derived from source" at a form level. This will flag whether the data was entered directly into the EDC platform app on the iPads as eSource (Direct Data Capture) or entered after being captured from another source such as paper (source data). This flag will indicate to the study monitors whether the form will require Source Data Verification or will require Source Data Review only.	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.~~ ~~In the US, pertinent source documents are uploaded to the EDC platform. The following datapoints in KAR-012 are expected to be initially captured on paper as source and then entered into the EDC platform, as applicable per local and site's requirements:~~ ~~• ICF – this will be signed by the subject/informant as applicable on paper, the date of consent will be captured in the EDC platform~~ ~~• Demographics~~ ~~• Psychiatric history~~ ~~• Medical history~~ ~~• Concomitant medications~~ ~~• AE/SAE information~~ ~~• Site eligibility review~~ ~~• MINI~~ ~~All data collected can be indicated to be "derived from source" at a form level. This will flag whether the data was entered directly into the EDC platform app on the iPads as eSource (Direct Data Capture) or entered after being captured from another source such as paper (source data). This flag will indicate to the study monitors whether the form will require Source Data Verification or will require Source Data Review only.~~	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	Sites can access and download their site and patient-specific data through a secure web portal and subsequently upload the data into their medical records. Also, sites can download PDFs of all eCRF pages including completed instruments and integrated third party data like ECG data, exactly as they are displayed on the iPads/website holding the eSource data.	~~Sites can access and download their site and patient-specific data through a secure web portal and subsequently upload the data into their medical records. Also, sites can download PDFs of all eCRF pages including completed instruments and integrated third-party data like ECG data, exactly as they are displayed on the iPads/website holding the eSource data.~~	

[redacted]

Abbreviations: AE = adverse event; AESI = adverse event of special interest; APD = antipsychotic drug; DILI = drug-induced liver injury; LAI = long-acting injectable; NA = not applicable; SAE = serious adverse event.

TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	Fi	[redacted]	
References	NA	**Chen, Y.H., DeMets, D.L., and Lan, K.K. (2004). Increasing the sample size when the unblinded [redacted] is promising. Stat Med 23, 1023-1038.**	New reference added for completeness

[redacted]

1. TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis, Title Page, Sponsor Signature Page, Header	~~15-October-2021~~	**08-April-2022**	Corrected date to v3.0 issue
Synopsis/Rationale **Synopsis/Study Design** **Synopsis/Inclusion Criteria #5** **Section 4.1 Description of Overall Study Design** **Section 4.2 Scientific Rationale for Study Design** **Section 6.1.1 Concomitant Medications for Anxiety and/or Sleep aid**	Risperidone, paliperidone, aripiprazole or their long-acting injectable [LAI] formulations, quetiapine, ziprasidone, and lurasidone are widely prescribed for the long-term treatment of schizophrenia. Many patients with schizophrenia have an inadequate response to these antipsychotic therapies and continue to be symptomatic, including persistent positive symptoms such as hallucinations and delusions, despite the antipsychotic treatment. Quetiapine up to doses of 200 mg at bedtime would also be permitted as a concomitant medication for the treatment of insomnia in subjects being treated with risperidone, paliperidone, aripiprazole, quetiapine, ziprasidone, or lurasidone. Given that KarXT has a different mechanism of action from the dopamine antagonists (D2) risperidone, paliperidone, quetiapine, ziprasidone, or lurasidone and the D2 partial agonist aripiprazole, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their LAIs, quetiapine, ziprasidone or lurasidone. As such, adjunctive KarXT might fulfill an important unmet need for schizophrenic patients.	Risperidone, paliperidone, aripiprazole or their long-acting injectable [LAI] formulations, ~~quetiapine~~, ziprasidone, and lurasidone are widely prescribed for the long-term treatment of schizophrenia. Many patients with schizophrenia have an inadequate response to these antipsychotic therapies and continue to be symptomatic, including persistent positive symptoms such as hallucinations and delusions, despite the antipsychotic treatment. ~~Quetiapine up to doses of 200 mg at bedtime would also be permitted as a concomitant medication for the treatment of insomnia in subjects being treated with risperidone, paliperidone, aripiprazole, quetiapine, ziprasidone, or lurasidone.~~ Given that KarXT has a different mechanism of action from the dopamine antagonists (D2) risperidone, paliperidone, ~~quetiapine,~~ ziprasidone, or lurasidone and the D2 partial agonist aripiprazole, adjunctive KarXT may provide additional efficacy (particularly on positive symptoms) in patients having an inadequate response to risperidone, paliperidone, aripiprazole, or their LAIs, ~~quetiapine,~~ ziprasidone or lurasidone. As such, adjunctive KarXT might fulfill an important unmet need for schizophrenic patients.	[redacted]

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis/Study Design / Screening Period **Synopsis/Figure 1. Study Design Schematic** **Synopsis/Duration** **Table 1. Schedule of Events** **Section 7.2.5 Visit 7**	The study periods include [redacted] Screening Period, a 6-week double-blind Treatment Period, and a 1-week Safety Follow-up (SFU) Visit. Visit Window at Visit 3 = ± 3	The study periods include [redacted] Screening Period, a 6-week double-blind Treatment Period, and a 1-week Safety Follow-up (SFU) Visit Visit Window at Visit 3 = ~~± 3~~ **+ 12**	[redacted]
Synopsis/Study Design/Screening Period **Synopsis/Inclusion Criteria #7** **Section 7.1 Screening Visits** **Section 7.1.1 Visit 1** **Section 7.1.2 Visit 2** **Section 7.2.1 Visit 3**	During Screening the site will confirm that the subject is meeting randomization criteria including detectable plasma concentration of risperidone, paliperidone, aripiprazole, quetiapine, ziprasidone or lurasidone at Screening. To be eligible for randomization, subjects taking oral background antipsychotic medication (not long-acting injectables) will need 80% adherence with their prescribed antipsychotic dosing [redacted] For subjects on long-acting injectables it will be sufficient to obtain confirmation that the subject is within the	During Screening the site will confirm that the subject is meeting randomization criteria including detectable plasma concentration of risperidone, paliperidone, aripiprazole, ~~quetiapine,~~ ziprasidone or lurasidone at Screening. To be eligible for randomization, subjects ~~taking oral~~ **need to have detectable levels of** background antipsychotic medication (~~not long-acting injectables) will need 80% adherence with their prescribed antipsychotic~~ [redacted] subjects on long-acting injectables it will be	[redacted]

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		Dose of the background antipsychotic medication should not be changed during the study (including the Screening phase)	Clarify dose of antipsychotic medication should be consistent throughout the study.
Synopsis/Rationale/Study Design/Study Design Schematic **Synopsis/Inclusion Criteria #4** **Synopsis/Exclusion Criteria #5** **Section 4.2 Scientific Rationale for Study Design** **APPENDIX 1**	Footnote a: Participants should be on risperidone, paliperidone, aripiprazole, or their long-acting injections (LAI), quetiapine, ziprasidone or lurasidone as background antipsychotics	Footnote a: Participants should be on risperidone, paliperidone, aripiprazole, or their long-acting injections (LAI), ~~quetiapine,~~ ziprasidone or lurasidone as background antipsychotics	Quetiapine as an antipsychotic background is not permitted
Synopsis/Inclusion Criteria #10 **Section 7.1.1 Visit 1** **Section 7.1.2 Visit 2** **Section 7.2.1 Visit 3**	11. PANSS Marder Positive symptom factor ≥ 4 on two items (PANSS items, delusions, hallucinations, grandiosity, suspiciousness and persecution, stereotyped thinking, somatic concern, unusual thought content or lack of judgment and insight), at Screening (Visit 1) and randomization (Day 1, Visit 3)	~~11.~~ **10.** PANSS Marder Positive symptom factor ≥ 4 on ~~two~~ **2 (or more)** items (PANSS items, delusions, hallucinations, grandiosity, suspiciousness and persecution, stereotyped thinking, somatic concern, unusual thought content or lack of judgment and insight), at Screening (Visit 1) and randomization (Day 1, Visit 3)	Clarify numerical criteria on PANSS

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis/Exclusion Criteria #2	The subject has a history of moderate to severe alcohol use disorder or substance use disorder (other than nicotine or caffeine) within the past 12 months a. A screening subject with mild substance use disorder within the 12 months before Screening must be discussed and agreed upon with the Medical Monitor before being allowed into the study b. Subjects who test positive for cannabis at Screening may be permitted to enroll in consultation with the Medical Monitor if the subject's pattern of use is not indicative of a substance use disorder	The subject has a history of moderate to severe ~~alcohol use disorder or~~ substance use disorder (other than nicotine ~~or caffeine~~) within the past 12 months a. A screening subject with mild substance use disorder within the 12 months before Screening must be discussed ~~and agreed upon~~ with the Medical Monitor before being allowed into the study b. Subjects who test positive for cannabis at Screening may be permitted to enroll in consultation with the Medical Monitor if the subject's pattern of use is not indicative of a **moderate to severe** substance use disorder	Clarify level of substance use disorder
Synopsis/Exclusion Criteria #6	Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia	Subjects who are ~~newly~~ diagnosed **with schizophreniform disorder** or are experiencing their first treated episode of schizophrenia	Clarify disease under study
Synopsis/Exclusion Criteria #12	Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at Screening	Clinically significant abnormal finding on the physical examination, medical history, ECG, (**QTc of > 450 msec in males and > 470 msec in females),** or clinical laboratory results at Screening	Clarify ECG QTC wave exclusionary parameters
Synopsis/Exclusion Criteria #14	Recent history of receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, depakote), lithium, tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for as- needed anxiolytics (e.g., lorazepam, chloral hydrate) a. Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors taken at a stable dose for at least 8 weeks prior to Screening may be permitted	Recent history of receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, depakote), lithium, tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for as- needed anxiolytics (e.g., lorazepam, chloral hydrate) a. Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors taken at a stable dose for at least 8 weeks prior to Screening may be permitted	Clarify dose for Mirtazapine

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	b. Mirtazapine may be used as a hypnotic if started at least 8 weeks prior to Screening	b. Mirtazapine may be used as a hypnotic if started at least 8 weeks prior to Screening **and at a stable dose**	
Synopsis/ Statistical Methods and Planned Analyses /Primary Efficacy Endpoint **Section 8.5.2 Analysis of the Primary Efficacy Endpoint**	The MMRM will include the treatment group (adjunctive KarXT or adjunctive placebo), visit, and the interaction between the treatment group and visit as fixed factors. Site, age, sex at birth, and Baseline PANSS Total score will be used as covariates in the model. [redacted]	The MMRM will include the treatment group (adjunctive KarXT or adjunctive placebo), visit, and the interaction between the treatment group and visit as fixed factors. ~~Site~~**Country**, age, sex at birth, and Baseline PANSS Total score will be used as covariates in the model. [redacted]	Clarify to use Country instead of Sites as a factor in the statistical model
Table 1. Schedule of Events		**Electronic or paper Informed Consent (subject)** **Electronic or paper** Informed Consent (~~paper or electronic)~~ **informant)**[b] Footnote b: **Informant consent can be done in person or remotely**	Clarify that electronic or paper informed consent can be collected from both the subject and the informant. Confirm that informant consent can be performed remotely.

[redacted]

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
			[redacted]
Table 1. Schedule of Events	Footnote h: Vital signs taken at supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in beats/minute (bpm)	Footnote h: Vital signs taken at supine and standing **approximately** after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. HR is measured in beats/minute (bpm)	[redacted]
Table 1. Schedule of Events	Footnote t: Optional COVID-19 testing (PCR) may be performed at any visit based on the Investigator's discretion. If a subject tests positive for COVID-19 during the study, he/she may be quarantined, and any scheduled visits should be rescheduled at the discretion of the Investigator. If the subject requires hospitalization, an SAE should be reported, and the subject should be followed up. In the US mandatory timepoints are done by the central lab and optional are done locally. [redacted]	Footnote t: Optional COVID-19 testing (**antigen or** PCR) may be performed at any visit based on the Investigator's discretion. If a subject tests positive for COVID-19 during the study, he/she may be quarantined, and any scheduled visits should be rescheduled at the discretion of the Investigator. If the subject requires hospitalization, an SAE should be reported, and the subject should be followed up. In the US mandatory timepoints are done by the central lab and optional are done locally. ~~For the Ukrainian sites, all COVID-19 testing will be done centrally.~~	[redacted]

[redacted]

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 2.2.3 Nonclinical Studies	No evidence of mutagenicity or treatment effects on reproduction, fertility, or fetal parameters has been demonstrated in animals following the administration of xanomeline. There are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).	No evidence of mutagenicity or treatment effects on reproduction, fertility, or fetal parameters has been demonstrated in animals following the administration of xanomeline. There are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). ~~Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).~~**Based on animal data, trospium chloride is predicted to have a low probability of increased risk of adverse development outcomes, above background risk. Adverse development findings were not observed to correlate with dose in rats or in rabbits. No increased risk above background was observed in rats and rabbits treated at an exposure approximately equivalent to the maximal recommended human dose (MRHD) of 40 mg. Trospium chloride should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus.**	Change is to align with the October 2020 Trospium USPI Section 8.1 update
Section 5.3 Screen Failure & Re-screening	Individuals who sign the eICF to participate in the study and then do not subsequently meet all the requirements for safety laboratory assessments are not enrolled in the study and are categorized as Screen Failure. Subjects may be rescreened on a case-by-case basis upon approval of the Medical Monitor. Such individuals may be allowed to rescreen once within 30 days.	Individuals who sign the eICF to participate in the study and then do not subsequently meet all ~~the requirements for safety laboratory assessments~~ **inclusion/exclusion criteria** are not enrolled in the study and are categorized as Screen Failure. Subjects may be rescreened on a case-by-case basis upon approval of the Medical Monitor. Such individuals may be allowed to rescreen once within ~~30~~ **60** days.	Clarify that screen fail is related to not meeting the inclusion/exclusion criteria. Re-screen period is extended to 60 days.
Section 6.5 Study Treatment Compliance	Treatment compliance will be evaluated by on-site pill count and adherence confirmed by	Treatment compliance will be evaluated by on-site pill count. **Number of pills dispensed,** and	Clarify the process for IP accountability

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	[redacted]The planned dose, actual administered dose, and dosing date and time will be recorded on the appropriate eCRF. See Section 6.2.1 for details.	[redacted]~~The planned dose, actual administered dose, and dosing date and time~~ **returned (for each dispensation visit)** will be recorded on the appropriate eCRF. ~~See Section 6.2.1 for details.~~ [redacted]	and study drug adherence.
Section 7.1.1 Visit 1 **Section 9.3.1 Electronic Informed Consent**	During Screening, the following procedures must be performed and recorded for each study candidate • Participants will sign the ICF on their first visit before any study-related procedures are performed, including screening evaluations. ICF can be paper or electronic • Collect demographic information • Perform a urine pregnancy test for WOCP, if positive perform a confirmatory serum pregnancy test	During Screening, the following procedures must be performed and recorded for each study candidate • Participants will sign the ICF on their first visit before any study-related procedures are performed, including screening evaluations. ICF can be paper or electronic **Informed Consent will also be obtained from the informant prior to any protocol-related activities. This can be done either in person or remotely** • Collect demographic information • ~~Perform a urine pregnancy test for WOCP, if positive perform a confirmatory serum pregnancy test~~ **A serum pregnancy test for WOCP should be done at Visit 1, and urine pregnancy tests should be done at other visits. A serum pregnancy test should be done to confirm any positive urine pregnancy test**	Highlight that informant consent will be obtained at Visit 1. Clarify process for serum pregnancy test.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 7.1.1 Visit 1	• Perform the MINI, version 7.0.2, a psychiatric evaluation to confirm the DSM-5 criteria for schizophrenia and does not meet psychiatric exclusionary criteria ○ MINI should be performed before PANSS assessment	• Perform the MINI, version 7.0.2, a psychiatric evaluation to confirm the DSM-5 criteria for schizophrenia and does not meet psychiatric exclusionary criteria ○ **If possible**, MINI should be performed before PANSS assessment	[redacted]
Section 7.1.1 Visit 1		• **Subject should be instructed to bring in their bottle of prescribed background antipsychotic medication to Visit 1 to verify adherence. For subjects on long-acting injectables it will be sufficient to obtain confirmation that the subject is within the treatment window**	
Section 7.2.1 Visit 3 **Section 7.2.4 Visit 6**		• **Collect a blood sample for the analysis of the plasma concentration of the background antipsychotic drug**	
Section 7.2.5 Visit 7	• Dispense study drug by giving the subject 1 wallet	• Dispense study drug by giving the subject ~~1 wallet~~ **2 wallets**	
Section 7.2.6 Visit 8	• In the absence of dose-limiting AEs the dose will be maintained at KarXT 125/30 mg or its matching placebo based on the PI's judgment until the last dose	• ~~In the absence of dose-limiting AEs the dose will be maintained at KarXT 125/30 mg or its matching placebo based on the PI's judgment until the last dose~~ • **Collect the used study drug wallets from the subjects**	

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Section 7.3 Visit 9	• Subjects will be discharged from the study. This is the end of the study	• ~~Subjects will be discharged from the study. This is the end of the study~~	This is an outpatient study.
Section 7.4 Unscheduled Visits	The PI may at his/her discretion arrange for a subject to have unscheduled assessments • Urine drug and alcohol screen.	The PI may at his/her discretion **(and in consultation with Medical Monitor)** arrange for **an Unscheduled Visit and conduct any protocol specific assessment that is deemed necessary. At** a ~~subject to have unscheduled~~ **minimum, the following** assessments **should be considered at an Unscheduled Visit:** • ~~Urine drug and alcohol screen.~~	Clarify the process for unscheduled visit and what assessments should be considered.
Section 7.6.5 **Demographics, and Medical and Psychiatric History**	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 8.7. All clinical abnormalities not present at Baseline or described in the past medical history and subsequently identified as clinically noteworthy must be recorded as AEs.	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 8.7~~.Section 7.7. All clinical abnormalities not present at ~~Baseline~~ Screening or described in the past medical history and subsequently identified as clinically noteworthy must be recorded as AEs.	Clarify the starting period for recording of AEs
Section 7.6.10 Laboratory Assessments	All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the subject'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 up until repeat test results return to normal, stabilize, or are no longer clinically significant.	~~All~~ **Upon receipt of the** laboratory reports **from the relevant laboratory vendor, the results** must be reviewed, ~~signed, and dated~~ by the Investigator~~. A legible copy of all reports must~~ **or designee. The results of the review will** be ~~filed with both the subject's eCRF and medical record (source document) for that visit.~~ **subsequently logged in the eSource system and signed off by the investigator or designee.** 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	Clarify process on recording laboratory reports in the eSource system

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.	
Section 7.7.1 Definition of Adverse Events	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 (except those related to the indication under study) 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.	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 (except those related to the indication under study) 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. **In addition, all novel coronavirus (COVID-19) related events should be reported as AEs.**	Clarify Covid-19 as an AE to be reported.
Section 7.7.3 Adverse Event of Special Interest	The AESIs will be monitored and include orthostasis and LFT elevations inclusive of DILI. AESIs should be recorded as AEs and reported as SAEs when appropriate.	The AESIs will be monitored and include orthostasis and LFT elevations inclusive of DILI. AESIs should be recorded as AEs and reported as SAEs ~~when appropriate~~**if the AESI meets serious criteria. For further guidance on orthostatic hypotension, see APPENDIX 3.** **DILI monitoring guidelines are provided below in Section 7.7.6**	Clarify reporting for AESIs.
Section 7.7.4 Serious Adverse Event Reporting	An SAE occurring from the time the first dose of the study drug is administered, during the study, or within 1 week of stopping the treatment must be reported to the Pharmacovigilance group of Catalyst Clinical Research and will be communicated to the Sponsor. Any such SAE due to any cause,	~~An SAE occurring from~~ **SAEs / AESIs reported by subjects or observed by clinical staff after subject has signed** the ~~time the first dose of the study drug is administered, during the study, or within 1 week of stopping the treatment~~ **Informed Consent Form** must be reported to the Pharmacovigilance group of Catalyst Clinical	Clarify when SAE/AESI reporting starts

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event.	Research and ~~will be communicated to~~ the Sponsor. Any such SAE / **AESI** due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event.	
Section 7.7.9 Suspected Unexpected Serious Adverse Reactions	The Investigator will assess whether or not an event is causally related to study treatment. The Sponsor [or their designee Clinical Research Organization (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 IEC/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 Investigator will assess whether or not an event is causally related to study treatment. The Sponsor [or their designee ~~Clinical~~ **Contract** Research Organization (CRO)] will consider the Investigator's assessment and determine whether the event meets the criteria **of a SUSAR and if it 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 IEC/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~~ **7** 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.	Clarify events that meet the criteria for reporting.
Section 9.3.1 Electronic Informed Consent Process	If local regulations do not allow eICF, then paper ICFs are permitted.	If local regulations do not allow eICF, then paper ICFs are permitted. **There may be other situations where paper ICFs are permitted.**	Clarify where electronic or paper ICFs is permitted.

[redacted]

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
[redacted]			
		• **a decrease of systolic blood pressure of 20 mmHg or more** • **or a decrease in diastolic blood pressure of 10 mmHg or more** • **or an increase in heart rate of 30 bpm or more**	

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
		Changes of the orthostatic vitals alone will not be considered an AESI without the subject being symptomatic. If the subject is asymptomatic, with the above difference in orthostatic vitals, it will be captured as an AE.	

[redacted]

1. TABULAR SUMMARY OF REVISIONS IMPLEMENTED IN THE AMENDED PROTOCOL

The major revisions to **Protocol KAR-012 v2.0** include changes to inclusion criteria and clarification that all study personal will be blinded. Administrative and minor editing changes that do not affect the content or conduct of the protocol has been incorporated.

Bolded text indicates new content, ~~strike-through~~ shows deleted text. Only the changed text in a section will be shown. An ellipsis, or series of dots (…), is used to indicate that unchanged text before and/or after the addition or revision is not shown. For changes that affect multiple sections of the protocol, the change is listed once at the first instance below, and each subsequent protocol section incorporating that change is also listed at that point. Changes to the reference section are not documented. The administrative and minor editing are not elaborated on in this document but are found in v1.0 to 2.0 tracked change document, that accompanies this summary of revisions.

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis, Title Page, Sponsor Signature Page, Header	~~24 August 2021~~	**15-October-2021**	Corrected date to v2.0 issue
Synopsis /Schedule of Events (SOE)/Section 7.1.1 Inclusion Criteria #2	Subject is capable of providing signed electronic informed consent form (eICF) before any study assessments will be performed (SOE)Informed Consent	Subject is capable of providing signed electronic informed consent form (eICF) before any study assessments will be performed. **If local regulations do not allow eICF, then paper ICFs are permitted** SOE-Informed Consent **(paper or electronic)**	Paper informed consent is now explicitly permitted.

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
Synopsis /Screening Visit/Baseline Visit Inclusion Criteria #8	To be eligible for randomization, subjects will need 80% adherence with their prescribed antipsychotic dosing [redacted] and pill count during the Screening period	To be eligible for randomization, subjects **taking oral background antipsychotic medication (not long-acting injectables** will need 80% ~~compliance~~ adherence with their prescribed antipsychotic dosing using [redacted] and ~~pill count~~ **site confirmation** during the Screening period, which is defined as ~~[~~(doses taken with the [redacted] + doses self-reported + site-reported doses) ~~–(intentionally non-adherent doses)]~~ / expected doses**.** [redacted]**. For subjects on long-acting injectables it will be sufficient to obtain confirmation that the subject is within the treatment window**	Clarification and inclusion for subjects on long-term injectables
Synopsis / Inclusion Criteria #15	Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the Investigator	Subject resides in a stable living situation ~~after discharge,~~ in the opinion of the Investigator	This is an outpatient study therefore discharge is incorrect.
Synopsis/Inclusion Criteria #16	Subject has identified a reliable informant/ caregiver/clinical support team willing and able to assist with study activities as needed throughout the subject's participation in the study. An informant is needed at the Baseline visit as well as at the end of the study for relevant assessments. An informant may not be necessary if the subject has been the patient of the Investigator for ≥ 1 year.	Subject has identified a reliable informant/ caregiver~~/clinical support team~~ willing and able to assist with study activities as needed throughout the subject's participation in the study. **The informant needs to be physically present at the Baseline visit but can complete the remaining study visits assessments via phone (as needed)**. ~~An informant may not be necessary if the subject has been the patient of the Investigator for ≥ 1 year."~~	Clarification that informant visit can be phone visit except for first baseline. Informant should be "physically present at baseline, the rest of the visits can be on the phone
Synopsis/Exclusion Criteria #19	Unable to taper and discontinue a concomitant medication that would preclude participation in	Unable to taper and discontinue a concomitant medication that would preclude participation in the	Antihistamines are allowed, however due

[redacted]

Section in Amended Protocol	Original Text	Revised Text	Rationale for Change
	the double-blind adjunctive treatment (e.g., cannot stop anticholinergic or antihistamine)	double-blind adjunctive treatment (e.g., cannot stop anticholinergic ~~or antihistamine~~)	to the anticholinergic activity of diphenhydramine (Benadryl), this is not allowed.
Section 2.3.1	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 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 following new frequently observed AEs: increased LFT, tachycardia, fatigue and chills have been reported.**	Additional observed AEs have been included, based on safety data.
Section 6.3.1	At the study site, the randomization schedule will be accessible only to authorized unblinded pharmacy personnel or designee. Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the first subject discontinued the study.	~~At the study site, the randomization schedule will be accessible only to authorized unblinded pharmacy personnel or designee.~~ Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the first subject discontinued the study.	No study personnel will be unblinded.

[redacted]

[redacted]