1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults with DSM-5 Schizophrenia

Protocol Number: KAR-009

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 33 Arch Street Suite 3110 Boston, MA 02110 Tel: (857) 449-2244 Email: info@karunatx.com
Protocol Version:	1.2
Protocol Date:	09 August 2021

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults with DSM-5 Schizophrenia

Protocol Number: KAR-009

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

Sponsor Signatory

Steve Brannan, MD
Chief Medical Officer
Karuna Therapeutics

DocuSigned by:
Steve Brannan
Signer Name: Steve Brannan
Signing Reason: I approve this document
Signing Time: 8/10/2021 | 7:23:01 AM PDT
A275B43612EA45F1BBF1FFEABA426D7D
Signature
8/10/2021
Date (DD-Mmm-YYYY)

Inder Kaul, MD, MPH
Vice President, Clinical Development
Karuna Therapeutics

DocuSigned by:
Inder Kaul
Signer Name: Inder Kaul
Signing Reason: I approve this document
Signing Time: 8/10/2021 | 11:01:46 AM EDT
3FC6022AD2EE4E4E95B5064D0EC6A7FE
Signature
8/10/2021
Date (DD-Mmm-YYYY)

Contract Research Organization Signatory

Patrick Keenan, MD
Senior Medical Director
Syneos Health

DocuSigned by:
Patrick keenan
Signer Name: Patrick Keenan
Signing Reason: I have reviewed this document
Signing Time: 8/16/2021 | 7:15:43 AM PDT
ADE491EF29BB4B57A2686CFBB3896757
Signature
8/16/2021
Date (DD-Mmm-YYYY)

Biostatistician

Christian Graven
Senior Biostatistician
Veristat

DocuSigned by:
Signer Name: Christian Graven
Signing Reason: I have reviewed this document
Signing Time: 8/10/2021 | 10:32:22 AM EDT
F2271F50594641238A6F4B19DFEB33CB
Signature
8/10/2021
Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults with DSM-5 Schizophrenia

Protocol Number: KAR-009

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

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

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults with DSM-5 Schizophrenia
Protocol Number:	KAR-009
Study Sites:	Approximately 10 sites in the United States and 10 sites in Ukraine
Phase of Development:	Phase 3
Objectives:	**Primary Objective** The primary objective of the study is to evaluate the efficacy of KarXT (a fixed combination of xanomeline and trospium chloride [xanomeline 125 mg/trospium 30 mg] twice daily [BID]) versus placebo in reducing Positive and Negative Syndrome Scale (PANSS) total scores in adult inpatients with a Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objectives**: The secondary objectives of the study are: • To evaluate the reduction of PANSS positive score in subjects treated with KarXT versus placebo • To evaluate the improvement in Clinical Global Impression-Severity (CGI-S) results in subjects treated with KarXT versus placebo • To evaluate the reduction of PANSS negative score in subjects treated with KarXT versus placebo • To evaluate the reduction of PANSS Marder Factor negative symptoms score in subjects treated with KarXT versus placebo • To evaluate the safety and tolerability of KarXT • To assess the pharmacokinetics (PK) of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia **Exploratory Objectives**: The exploratory objectives of this study are: • To evaluate the change in cognition measuring core domains of impairment in schizophrenia using Cambridge Neuropsychological Test Automated Battery (CANTAB) • To evaluate the change in prolactin levels after administration of KarXT • To evaluate the single nucleotide polymorphisms (SNPs) regarding schizophrenia subtypes and SNPs related to drug metabolism.
Study Endpoints:	**Primary Endpoint:** • Change from baseline in PANSS total score at Week 5 **Secondary Endpoints:** Efficacy Endpoints: • Change from baseline in PANSS positive score at Week 5 • Change from baseline in PANSS negative score at Week 5 • Change from baseline in PANSS Negative Marder Factor score at

	Week 5 • CGI-S score at Week 5 • Percentage of PANSS responders (a 30% change in PANSS total score) at Week 5 Safety Endpoints: • Spontaneously reported adverse events (AEs) including AEs of special interest (AESIs) • Spontaneously reported procholinergic and anticholinergic symptoms • Simpson-Angus Scale (SAS) • Barnes Akathisia Rating Scale (BARS) • Abnormal Involuntary Movement Scale (AIMS) • Body weight, body mass index, waist circumference • Orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, urinalysis, and drug screen • 12-lead electrocardiogram (ECG) • Physical examination • Suicidal ideation scale with the use of Columbia Suicide Severity Rating Scale (C-SSRS) Pharmacokinetic Endpoints: • Area under the plasma concentration-time curve (AUC) • Maximum observed plasma concentration (C_{max}) • Time to maximum observed plasma concentration (T_{max}) Exploratory Endpoints: • Change in cognition measuring core domains of impairment in schizophrenia using CANTAB • Change from baseline in prolactin levels at Week 5 • Prediction of response based on SNP schizophrenia subtypes, and SNPs related to KarXT metabolism for both efficacy and tolerability
Study Design:	This is a Phase 3 randomized, double-blind, parallel-group, placebo-controlled, multicenter inpatient study in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia. Subjects will be randomized (1:1 ratio) to receive either KarXT or placebo for a treatment period of 5 weeks. Subjects will start on a lead-in dose of KarXT 50/20 (xanomeline 50 mg/trospium 20 mg) BID for the first 2 days (Days 1 and 2) followed by KarXT 100/20 (xanomeline 100 mg/trospium 20 mg) BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who were increased to KarXT 125/30 BID, depending on clinical response and tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Dosing must not change after Visit 7 (Day 21) of the study and may be decreased for tolerability reasons no more than once during the study. In addition, dose escalation to KarXT 125/30

	BID may not occur outside of the permitted visit window for Visit 5/Day 8. A safety follow-up visit (Visit 11/ Day 42 + 5 days) will be performed for all those subjects who do not rollover in to the long-term open-label study KAR-008. The study is designed to test the hypothesis that treatment with KarXT in adult schizophrenia subjects with acute psychosis will result in significantly greater reduction (ie, improvement) in the primary and secondary endpoints at Week 5 from baseline compared with placebo. The endpoints are set up as a hierarchical list and step down through the statistical testing of each endpoint using an alpha of 0.05. Statistical testing of change from baseline to Week 5 in PANSS positive score, PANSS negative score, and PANSS Negative Marder Factor score, CGI-S score at Week 5, and percentage of PANSS responders will be performed only if the primary endpoint is significant at the 0.05 alpha level ($P \leq 0.05$), and testing would continue through a preordered list of key secondary efficacy endpoints. If at any point $P > 0.05$, then formal statistical testing would stop. This will control the overall Type 1 error rate across all hypotheses/endpoints being tested.
Selection of Subjects:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years, inclusive, at screening. 2. Subject is capable of providing informed consent. a. A signed informed consent form must be provided before any study assessments are performed. b. Subject must be fluent (oral and written) in English (applicable to the Unites States) or local language (Ukrainian or Russian applicable to Ukraine) to consent 3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2. 4. Subject is experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 2 months before screening. a. The subject requires hospitalization for this acute exacerbation or relapse of psychotic symptoms. b. If already an inpatient at screening, has been hospitalized for less than 2 weeks for the current exacerbation at the time of screening. 5. Positive and Negative Syndrome Scale total score between 80 and 120, inclusive. a. Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items: i. Item 1 (P1; delusions) ii. Item 2 (P2; conceptual disorganization) iii. Item 3 (P3; hallucinatory behavior) iv. Item 6 (P6; suspiciousness/persecution)

	6. Subjects with no change (improvement) in PANSS total score between screening and baseline (Day -1) of more than 20%. 7. Subject has a CGI-S score of ≥4 at screening and baseline (Day -1) visits. 8. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 5 half-lives or 1 week, whichever is longer, before baseline (Day -1). 9. Subjects taking a long-acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®) before baseline visit (Day -1). 10. Subject is willing and able to be confined to an inpatient setting for the study duration, follow instructions, and comply with the protocol requirements. 11. Body mass index must be ≥18 and ≤40 kg/m^2. 12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator. 13. Subject has an identified reliable informant/caregiver. An informant/caregiver is needed at the screening and baseline visits as well as at the end of the study for relevant assessments (site staff may act as informant while the subject is an inpatient). An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year. 14. Women of childbearing potential (WOCBP) , or men whose sexual partners are WOCBP, must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and APPENDIX 1. **Exclusion Criteria:** 1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening). Exclusionary disorders include, but are not limited to, moderate to severe alcohol use disorder (within the past 12 months), substance (other than nicotine or caffeine) use disorder within the past 12 months (use of cannabis at screening will result in screen failure with the allowance to rescreen at a later date if no moderate to severe substance use disorder is determined), major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and post-traumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment. a. A screening subject with mild substance abuse disorder within the 12 months before screening must be discussed and agreed upon with the medical monitor before they can be allowed into the study. 2. Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia. 3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results. 4. Subjects with HIV, cirrhosis, biliary duct abnormalities,

	hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test results. 5. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma. 6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months. 7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following: a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening or answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Nonsuicidal, self-injurious behavior is not exclusionary. 8. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening. 9. Subjects cannot currently (within 5 half-lives or 1 week, whichever is longer, before baseline [Day -1]) be receiving oral antipsychotic medications; monoamine oxidase inhibitors; anticonvulsants (eg, lamotrigine, Depakote); tricyclic antidepressants (eg, imipramine, desipramine); selective serotonin reuptake inhibitors; or any other psychoactive medications except for as needed anxiolytics (eg, lorazepam, chloral hydrate). 10. Pregnant, lactating, or less than 3 months postpartum. 11. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements. 12. Positive test for coronavirus (COVID-19) within 2 weeks before screening and at screening. 13. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that preclude study participation. 14. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening. 15. Subject has a history of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months. 16. Subjects with prior exposure to KarXT. 17. Subjects who experienced any adverse effects due to xanomeline or trospium. 18. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 3 months before screening. 19. Risk of violent or destructive behavior. 20. Current involuntary hospitalization or incarceration.
Planned Sample Size:	A total of approximately 246 adult subjects (aged 18 to 65 years, inclusive) are planned to be randomized in a 1:1 ratio to 2 treatment groups, either KarXT or placebo.

Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium), oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium), oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium), oral (Days 8 to 35, if tolerated)
Reference Therapy:	Matching placebo BID oral
Treatment Duration:	Total study duration is up to 8 weeks, including a 7-day screening phase (up to a 7-day extension of the screening phase is allowed, if necessary), a 5-week treatment period, and a 7-day follow-up period (only for subjects who do not rollover to KAR-008 study). Subjects completing this study will have the option of rolling over into a long-term open-label study (KAR-008) in which every subject will receive KarXT.
Efficacy Assessments:	PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S score will be evaluated at scheduled visits.
Safety Assessments:	Spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms, SAS, BARS, AIMS, body weight, body mass index, waist circumference, orthostatic vital signs, ECG, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), prolactin levels, physical examination, and C-SSRS will be evaluated throughout the study as scheduled.
Pharmacokinetic Assessments:	AUC, C_{max}, and T_{max} will be estimated at scheduled visits.
Statistical Methods and Planned Analyses:	Intent-to-treat (ITT) population: All subjects who are randomized to the study will be included in the ITT population. Modified ITT (mITT) population: All subjects who are randomized, received at least 1 dose of study drug, have a baseline PANSS assessment, and at least 1 postbaseline PANSS assessment will be included in the mITT population and will be used in the efficacy analysis. Safety population: All subjects who received at least 1 dose of study drug will be included in the safety population and will be used in the safety analysis. PK population: All subjects who have an evaluable PK profile will be included in the PK population and will be used in the PK analysis. Subjects must have received at least 1 dose of active study drug and have at least 1 measurable plasma concentration of study drug. The primary efficacy endpoint of the study is the change from baseline in PANSS total score at Week 5. The difference between KarXT and placebo will be estimated using a mixed model for repeated measures. The key secondary endpoints are the change from baseline to Week 5 in PANSS positive score, PANSS negative score, and PANSS Negative Marder Factor score, CGI-S score at Week 5, and percentage of PANSS responders at Week 5. The statistical analysis of the primary and key secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. This testing procedure will control the overall Type 1 error rate across all hypotheses/endpoints being tested. Assuming the treatment difference in the change from baseline in PANSS total score at Week 5 is 8 points between KarXT and placebo (standard deviation 16), a sample size of approximately 172 subjects (86 evaluable subjects per arm) will result in a power of 90.3% for a 2-sided alpha of 0.05

	($P \leq 0.05$). With an anticipated dropout rate of 30%, a total of 246 subjects are estimated to be enrolled.

3 TABLE OF CONTENTS

1 FINAL CLINICAL STUDY PROTOCOL 1
2 SYNOPSIS 5
3 TABLE OF CONTENTS 12
3.1 List of In-text Tables 15
3.2 List of In-text Figures 17
4 LIST OF ABBREVIATIONS 18
5 INTRODUCTION 20
5.1 Background on Schizophrenia 20
5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride) 20
5.2.1 Nonclinical Studies 22
5.2.2 Completed Clinical Studies 25
5.3 Clinical Risks/Benefits of KarXT and Study Rationale 33
6 STUDY OBJECTIVES AND ENDPOINTS 35
6.1 Study Objectives 35
6.1.1 Primary Objective 35
6.1.2 Secondary Objectives 35
6.1.3 Exploratory Objectives 35
6.2 Study Endpoints 36
6.2.1 Primary Endpoint 36
6.2.2 Secondary Endpoints 36
6.2.2.1 Efficacy Endpoints 36
6.2.2.2 Safety Endpoints 36
6.2.3 Pharmacokinetic Endpoints 36
6.2.4 Exploratory Endpoints 37
7 INVESTIGATIONAL PLAN 38
7.1 Description of Overall Study Design and Plan 38
7.2 Discussion of Study Design 41
7.3 End of Study 41
7.4 Independent Safety Monitoring Committee 41
8 SELECTION OF STUDY POPULATION 42
8.1 Inclusion Criteria 42
8.2 Exclusion Criteria 43
8.3 Rescreening 44

8.4 Study Withdrawal, Removal, and Replacement of Subjects 45
8.4.1 Pregnancy 46
8.5 Completion of the Study or Lost to Follow-up 47
8.6 Study Termination 47
9 TREATMENTS 48
9.1 Details of Study Treatments 48
9.1.1 Identity of Study Treatments 48
9.1.2 Packaging and Labelling 49
9.1.3 Study Drug Storage 49
9.1.4 Study Drug Retention 49
9.2 Dose Schedule 49
9.2.1 Visit 2b/Day 1 Randomization and Dosing 49
9.2.2 Visit 3/Day 3 and/or Visits Occurring on Weekends/Holidays 50
9.2.3 Visit 5/Day 8 Dosing and PK Considerations and Visit 8/Day 28 PK Considerations 50
9.2.4 Visit 10/Day 35 Dosing 50
9.3 Measures to Minimize Bias: Study Treatment Assignment 50
9.3.1 Method of Study Treatment Assignment 50
9.3.2 Blinding 51
9.4 Dose Modification 52
9.5 Treatment Accountability and Compliance 52
9.6 Prior and Concomitant Therapy 52
9.6.1 Prior and Concomitant Medications 52
9.6.2 Concomitant Medications for Anxiety and/or Sleep aid 53
10 STUDY PROCEDURES 54
10.1 Informed Consent 61
10.2 Study Procedures 61
11 EFFICACY ASSESSMENTS 62
11.1 Positive and Negative Syndrome Scale 62
11.2 Clinical Global Impression–Severity 62
12 SAFETY ASSESSMENTS 63
12.1 Demographics, and Medical and Psychiatric History 63
12.2 Vital Signs 63
12.3 Physical Examination 64
12.4 Weight, Height, Body Mass Index, Waist Circumference 64

12.5 Electrocardiograms 64
12.6 Laboratory Assessments 64
12.6.1 Blood Sampling for Pharmacogenetics 66
12.7 Adverse Events 66
12.7.1 Adverse Events 66
12.7.2 Adverse Events of Special Interest 68
12.7.3 Serious Adverse Events 68
12.7.4 Serious Adverse Event Reporting 69
12.7.5 Drug-Induced Liver Injury 69
12.7.6 Trial Discontinuation Criteria Other than DILI and Pregnancy 70
12.7.6.1 Individual Stopping Criteria 70
12.7.6.2 Trial Stopping Rules 70
12.7.7 Suspected Unexpected Serious Adverse Reactions 71
12.7.8 Pregnancy 73
12.7.9 Overdose 73
12.8 Cambridge Neuropsychological Test Automated Battery 73
12.9 Simpson-Angus Scale 74
12.10 Barnes Akathisia Rating Scale 74
12.11 Abnormal Involuntary Movement Scale 75
12.12 Columbia-Suicide Severity Rating Scale 75
12.13 Functional Constipation Inquiry 75
12.14 Mini International Neuropsychiatric Interview Version 7.0.2 76
12.15 Change in Prolactin 76
13 PHARMACOKINETICS 77
13.1 Pharmacokinetic Sampling 77
13.1.1 Blood Samples 77
13.2 Pharmacokinetic Analytical Methodology 78
14 STATISTICAL ANALYSIS 79
14.1 Determination of Sample Size 79
14.2 Analysis Populations 79
14.3 General Statistical Considerations 80
14.4 Efficacy Analysis 80
14.4.1 Primary Estimand 80
14.4.2 Analysis of the Primary Efficacy Endpoint 81
14.4.3 Analysis of Secondary Efficacy Endpoints 81

14.5 Safety Analysis 82
14.6 Pharmacokinetic Analysis 82
14.7 Interim Analysis 82
14.8 Handling of Missing Data 83
15 STUDY MANAGEMENT 84
15.1 Approval and Consent 84
15.1.1 Regulatory Guidelines 84
15.1.2 Independent Ethics Committee/Institutional Review Board 84
15.1.3 Informed Consent 84
15.2 Data Handling 85
15.3 Source Documents 85
15.4 Record Retention 86
15.5 Monitoring 86
15.6 Quality Control and Quality Assurance 87
15.7 Protocol Amendment and Protocol Deviation 87
15.7.1 Protocol Amendment 87
15.7.2 Protocol Deviations 87
15.8 Ethical Considerations 87
15.9 Financing and Insurance 88
15.10 Publication Policy/Disclosure of Data 88
16 REFERENCES 89
17 APPENDICES 92
APPENDIX 1. CONTRACEPTION GUIDELINES 93
APPENDIX 2. FUNCTIONAL CONSTIPATION INQUIRY 94

3.1 List of In-text Tables

Table 1 Study Design 40
Table 2. Schedule of Assessments 55
Table 3. Laboratory Assessments 65
Table 4. Classification of Adverse Events by Intensity 67
Table 5. Classification of Adverse Events by Relationship to Study Drug 68
Table 6 Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery 74
Table 7 Statistical Testing Procedure 80

3.2 List of In-text Figures

Figure 1 Change from Baseline in PANSS Total Scores (KAR-004).....29
Figure 2 Change from Baseline in PANSS-Positive Scores (KAR-004).....30
Figure 3 Change from Baseline in CGI-S (KAR-004).....31
Figure 4 Change from Baseline in PANSS-Negative Scores (KAR-004).....32

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
APD	antipsychotic drug
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CTS	Clinical Trial Subject
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure

Abbreviation	Definition
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
MCC	microcrystalline cellulose
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
NCI	National Cancer Institute
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic(s)
PRN	as needed
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	thrice daily
TK	toxicokinetic
T_{max}	Time to maximum observed plasma concentration
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VCT	Verified Clinical Trials Registry
WOCBP	women of child bearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability[1]. The prevalence of schizophrenia is between 0.6% and 1.9% in the United States (US) population[2]. Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the US is 5.1 per 1000 lives[3]. It is found equally in males and females, with males usually having an earlier onset of symptoms[4].

The mainstay for treating schizophrenia is antipsychotic drugs (APDs)[5]. All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia, and they consequently have limited use today. The second-generation agents that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia[6,7,8]. These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations[9,10]. Thus there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies[11,12]. There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS)[13]. However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors but preferentially stimulates M_1 and M_4 receptors and binding to M_1 and M_4 receptors in the CNS is thought to be responsible for the drug's potential therapeutic effects

(Roth, unpublished data). A recent study reports that xanomeline is a very potent M_4 muscarinic agonist in vivo, measured by various second messenger assays[14]. Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate[15].

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

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

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

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist which binds to and antagonizes all five muscarinic receptor subtypes[19]. It is a commonly used generic drug 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[19]. Several human subject studies have demonstrated that trospium does not appreciably cross the blood brain barrier, consistent with the drug's quaternary ammonium structure[20].

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

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

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

The purpose of the current study is to evaluate the safety and efficacy of KarXT (xanomeline 125 mg/trospium 30 mg) administered twice daily (BID) in adult inpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia. A placebo arm is included to provide test sensitivity.

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

5.2.1 Nonclinical Studies

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

The acute toxicity of xanomeline tartrate was evaluated in mice and rats. All animals were observed for 2 weeks for mortality and clinical signs of intolerance, and then necropsied for gross examinations. In-life findings attributed to the test article included excessive muscarinic-mediated pharmacology, such as excessive salivation, hypoactivity, ataxia, soft stools, exophthalmos, ocular discharge, tremors, and convulsions, with survivors typically appearing normal by Days 3 or 4. Gross findings at necropsy were generally unremarkable (eg, gas-distended or mucous-filled gastrointestinal [GI] tracts after oral dosing).

KarXT-301 was a 14-day, repeat dose study of KarXT in rats where relatively high doses of xanomeline and trospium were given, with either xanomeline alone or in combination with trospium. Seven groups of 10 rats/sex/group were administered either vehicle (reverse osmosis water); xanomeline alone at 37, 75, 150, or 300 mg/kg/day (split into BID doses, every 12 hours); or xanomeline/trospium combination dosages of 150/200 mg/kg/day or 225/400 mg/kg/day, respectively (split into BID doses, every 12 hours).

Satellite animals were included for the collection of plasma after the first and last doses for the determination of drug concentrations of each parent drug in support of toxicokinetic (TK) assessments.

There was no target-organ toxicity revealed by clinical pathology or by gross or microscopic assessments. All intolerance could be attributed to recognized pharmacology of either test article.

No dose-related ophthalmic observations were noted. Findings were not indicative of specific target organ toxicity. In short, no new hazard was identified.

Clinical observations noted in most animals administered 300 mg/kg/day xanomeline included hypoactivity, clear oral discharge, dilated pupils, irregular or labored respiration, and rough haircoat, among other observations. These findings are generally consistent with the anticipated pharmacology of xanomeline.

Three TK animals in the low-dose combination group died or were euthanized in extremis. It is unclear to what extent the combination treatment effects versus the different handling of these animals (including 3 plasma samplings per animal) contributed to these deaths. If gavage accidents were involved (as happened with some TK animals), then they were not detected at gross necropsy. There was no microscopic evidence of toxicity was seen in any toxicity animals in this group or in the higher-dose combination group.

Three toxicology and 3 TK animal deaths (total of 6) occurred in the high-dose combination group. Two toxicology animals had evidence of gavage accidents. For the third, the cause of death was undetermined, and a test article-related effect cannot be ruled out, but degeneration/regeneration of esophageal muscular is indicated some dosing-related trauma. If gavage accidents were involved, then they were not detected at gross necropsy. There was no evidence of target organ microscopic findings in GI tract or any other tissue of any animal, including the early death toxicity animals.

A pharmacodynamics-mediated reduction in GI motility is consistent with the anti-muscarinic effects of trospium on intestinal musculature. Fecal retention, malabsorption, cessation of eating, dehydration, and rapid deterioration followed with continued dosing. Cessation of dosing in the high dose combination animals that survived led to rapid recovery, implying the deleterious effects had been pharmacodynamics-related. No effects on food consumption were seen in any xanomeline-alone group. The lack of microscopic findings in the GI tract of any early death or surviving animal implies that the adverse effects were pharmacologically mediated rather than direct target organ toxicity.

Twenty-eight Day Repeat-Dose Studies with Xanomeline in Rats and Monkeys: Rats were fed xanomeline tartrate at 0%, 0.05%, 0.1%, or 0.2% daily and monkeys were fed xanomeline tartrate daily at 0, 5, 12.5, or 30 mg/kg. All animals survived until necropsy. Safety findings in rats included reduced body weight in the high dose group, increases in gamma-glutamyl-transferase, cholesterol, and bilirubin, slight decreases in triglycerides, bile duct hyperplasia, higher serum potassium (males), and lower serum globulin (females). Findings in monkeys were dose related and included signs of intolerance such as emesis, salivation, diarrhea, hypoactivity, weight loss, and treatment-related tachycardia in the high-dose animals.

Forty-Day Repeat Dose Study of KarXT in Rats (KarXT-302): Six groups of 15 rats/sex/group were given vehicle, xanomeline alone at 75 or 150 mg/kg/day, trospium alone at 100 mg/kg/day, or xanomeline/trospium combination at doses of 75/50 mg/kg/day or 150/100 mg/kg/day, with

all doses split into BID doses. Satellite rats (TK animals) were included for collection of plasma after the first and last doses to determine concentrations of each drug. Dosing was initially planned to be 90 days but was terminated after 40 days because of unexpected deaths in the TK animals. No target organ toxicity was seen. Safety findings included pharmacologically mediated constipation in the trospium alone and combination groups and mild biliary hyperplasia in the high-dose xanomeline alone and combination groups. There were 4 unscheduled deaths in TK animals; 2 in the high-dose xanomeline alone group (150 g/kg/day) and 2 in the high-dose combination group (150 mg/kg/day xanomeline plus 100 mg/kg/day trospium). Both xanomeline-only animals had necropsy gross findings of a gavage accident, and cause of death could not be determined. All toxicology animals survived to their scheduled sacrifice. Sponsor considers that the volume depletion and trauma of multiple bleeds (3 per animal), followed by reduced absorption of fluids and nutrients secondary to reduced GI motility with continued BID dosing explains the greater demise of TK animals relative to toxicity animals.

Based on the results of the 90-day rat toxicology study, oral administration of trospium chloride and xanomeline tartrate alone or in combination to Crl:CD (SD) rats BID (12 hours ± 60 minutes apart) at dosage levels of 25 and 50 mg/kg/dose trospium chloride, 37 and 75 mg/kg/dose xanomeline tartrate, and a combination of 37/25, 75/25, and 75/50 mg/kg/dose xanomeline tartrate/trospium chloride for a minimum of 90 days resulted in minimal to moderate bile duct hyperplasia in the livers of the xanomeline tartrate and combination (xanomeline tartrate and trospium chloride) group males. Although there were no notable differences in the incidence of bile duct hyperplasia when comparing the single vs combination groups, there was an increased severity observed in the combination group males (specifically the 75/25 and 75/50 mg/kg/dose combination group males) when compared with the xanomeline tartrate group males at the terminal euthanasia. The bile duct hyperplasia was considered adverse in the high-dose xanomeline tartrate group males and in the 75/25 and 75/50 mg/kg/dose combination group males due to instances of moderate severity. Therefore, the no-observed-adverse-effect level was considered to be 50 mg/kg/dose for trospium chloride, 37 mg/kg/dose for xanomeline tartrate, and 37/25 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. At these doses for males, mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 146,000 pg•hr/mL for xanomeline, and 4510 + 111,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. At these dosages for females, mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium; 267,000 pg•hr/mL for xanomeline; and 16,700 + 171,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. The absence of bile duct hyperplasia in females cannot be explained from differences in drug exposure. At the recovery euthanasia, bile duct hyperplasia was still present but was limited to minimal severity, and there was a decreased incidence in both the xanomeline tartrate and combination group males. There was also no notable difference in severity between the single vs combination groups at the recovery euthanasia. Given the decreased incidence/severity, in combination with the improved histologic appearance of bile ducts at the recovery euthanasia (i.e., smaller/flattened epithelium, noninflammatory, and an absence of portal bridging), changes at the recovery euthanasia were

consistent with a partial resolution of bile duct hyperplasia. With an absence of correlating serum liver enzyme elevations, bile acid alterations or hepatocellular degeneration, necrosis or regeneration, and with the apparent reversibility after cessation of treatment, these findings appear to have been tolerable by the affected animals. Therefore, the maximum tolerated dose was considered to be 50 mg/kg/dose for trospium chloride, 75 mg/kg/dose for xanomeline tartrate, and 75/50 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. For males, corresponding mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium; 822,000 pg•hr/mL for xanomeline; and 133,000 + 276,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. For females, corresponding mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium; 2,090,000 pg•hr/mL for xanomeline; and 17,600 + 950,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

In summary, no new findings on the "combination" of xanomeline and trospium (KarXT) were discovered; toxicology studies revealed the familiar exaggerations of systemic and CNS muscarinic effects that had previously been seen with xanomeline or trospium at high doses. Target organ findings with xanomeline alone were limited to biliary hyperplasia in the 28-day rat study but not the 28-day or 12-month monkey study, though similar findings were described in a 6-month monkey study. With KarXT, biliary hyperplasia was not observed in the 14-day rat study but was reported in the 40-day rat study. Notably, these hyperplastic findings are not thought to represent pre-neoplastic lesions, because they were of low severity; no fibrosis or associated hepatocellular changes, and no significant effects were seen on hepatobiliary-related serum chemistry.

5.2.2 Completed Clinical Studies

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

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

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008[18]. In this pilot study, the effects of xanomeline were examined in 20 subjects with schizophrenia utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric Rating Scale total scores and PANSS total scores (ie, 24-point change over placebo, P = 0.04). In the cognitive test battery, subjects in the xanomeline group showed improvements relative to placebo in some of the cognitive domains of verbal learning and short-term memory function.

These studies demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

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

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

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

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

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

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes which may have contributed to syncope and postural dizziness in those subjects. Two subjects (both in the xanomeline alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline alone group.

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

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

Study KAR-002 was a Phase 1, double-blind, randomized, multiple-dose adaptive design pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. Subjects received either 100 mg xanomeline + 20 mg trospium BID or placebo. The first cohort of this study was stopped after 1.5 days when the US FDA put the program on hold due to a preliminary rat finding in the 14-day study. This study used a new formulation of KarXT in which xanomeline and trospium were combined into a single dose form and given BID. Safety findings included an increase in orthostatic complaints. Caution should be used in drawing conclusions from this study, as subjects did not have time to reach steady state plasma levels from dosing, as only 3 doses were given.

Study KAR-003 was a Phase 1, double-blind, randomized, multiple-dose, adaptive design, inpatient pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. The primary objective of this study was to assess the safety and tolerability of 7 days of daily administration of KarXT at various dose combinations, administered BID. Subjects received either KarXT or placebo (3:1 ratio). All subjects on KarXT received 2 days of 50 mg xanomeline + 20 mg trospium BID, and then increased to different doses for Days 3 to 7. This study also used the new formulation of KarXT in which xanomeline and trospium were combined into a single dosage form and given BID.

There was a relatively high degree of variability in xanomeline and trospium exposures between individuals in all cohorts, which is consistent with previous results with KarXT, xanomeline-alone, and trospium-alone. Peak plasma concentrations were observed at a median time of 2.0 hours for xanomeline and 1.0 hour for trospium across all treatment groups and study days.

Although there was insufficient data to draw a definitive conclusion regarding the impact of trospium on the pharmacokinetics (PK) and bioavailability of xanomeline, or the impact of xanomeline on the PK and bioavailability of trospium, the PK results suggest that neither drug had a meaningful impact on the PK behavior of the other drug.

During the 2-day lead-in phase, the most common AEs (≥20% of subjects) when all the subjects completed dosing were dry mouth, nausea, and constipation. For the treatment groups that completed dosing, although the incidence of TEAEs was lower in the KarXT 100/20 BID

(66.7%) group compared to KarXT 125/40 group (88.9%), the incidence of cholinergic TEAEs (nausea, vomiting, diarrhea, sweating, and excess salivation) was similar between the 2 groups. The most commonly reported TEAEs (≥20% of subjects in either treatment group) in these groups were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. For the treatment groups that did not complete dosing (KarXT 150/20 BID group and KarXT 150/40 BID group), the cholinergic TEAEs were generally higher compared to the treatment groups that completed dosing.

Overall, anticholinergic TEAEs appeared to occur primarily in the treatment groups that were dosed with 40 mg trospium BID (KarXT 150/40 BID and KarXT 125/40 BID groups), particularly when paired with 125 mg xanomeline BID, suggesting to consider slightly lowering the trospium dose from 40 mg BID in future studies. All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. Treatment-emergent AEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

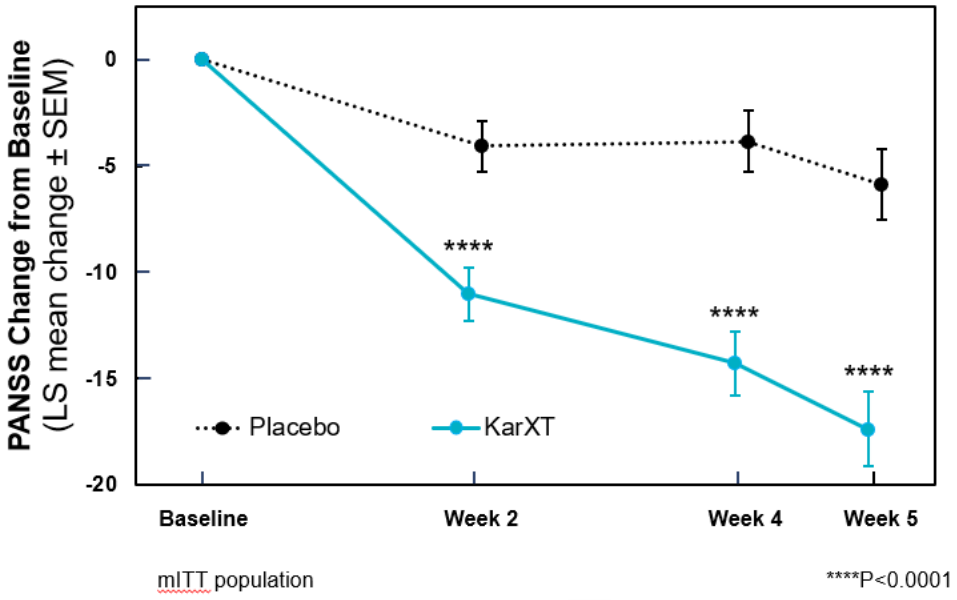
Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT 125/30 BID versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from previous dose increase of 100/20 BID. The clinical portion of this study was completed and clinical study report is in progress. No new safety concerns have arisen during this study.

The KAR-004 trial results are unambiguous regarding efficacy, where not only the primary outcome measure showed a robust separation from placebo, but the additional sensitivity and secondary outcome measures were consistently robust as well.

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. The KarXT group showed an adjusted mean improvement of 17.40 points at Week 5 compared to an adjusted mean 5.85 point improvement in the placebo group for a difference of 11.56 points in the total PANSS score (Figure 1). Substantial significant differences were also seen between KarXT and placebo at Weeks 2 and 4; moreover, the difference appears to be widening with each successive time point. In addition, sensitivity analyses of the primary

outcome measure all showed the same strong differences from placebo attesting to the robustness of the finding in Completer, last observation carried forward, and Per Protocol populations (all with $p < 0.0001$). Also, analyses exploring missingness via imputation for missing data at random or not missing at random also showed strong separation (both with $p < 0.0001$). The Cohen's d effect size observed in this trial was 0.75.

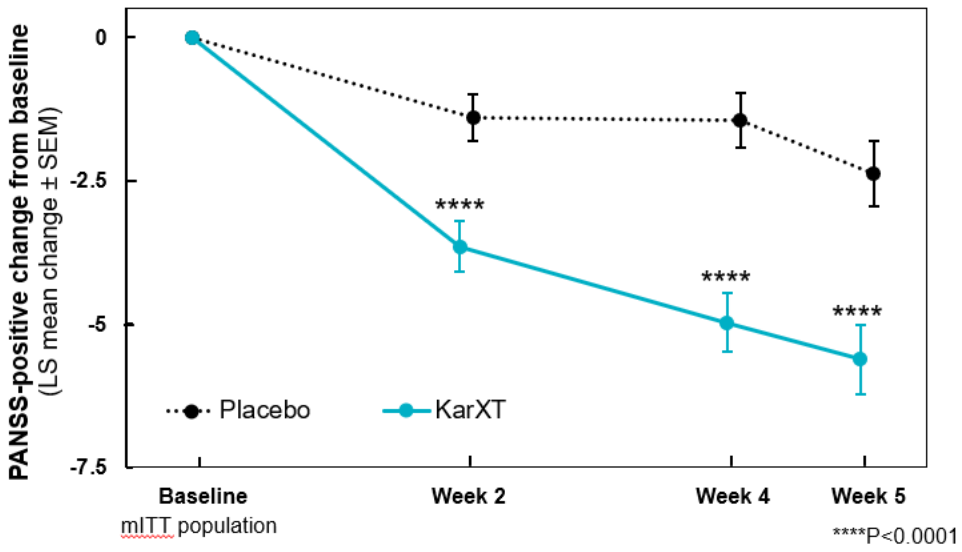
Figure 1 Change from Baseline in PANSS Total Scores (KAR-004)



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

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

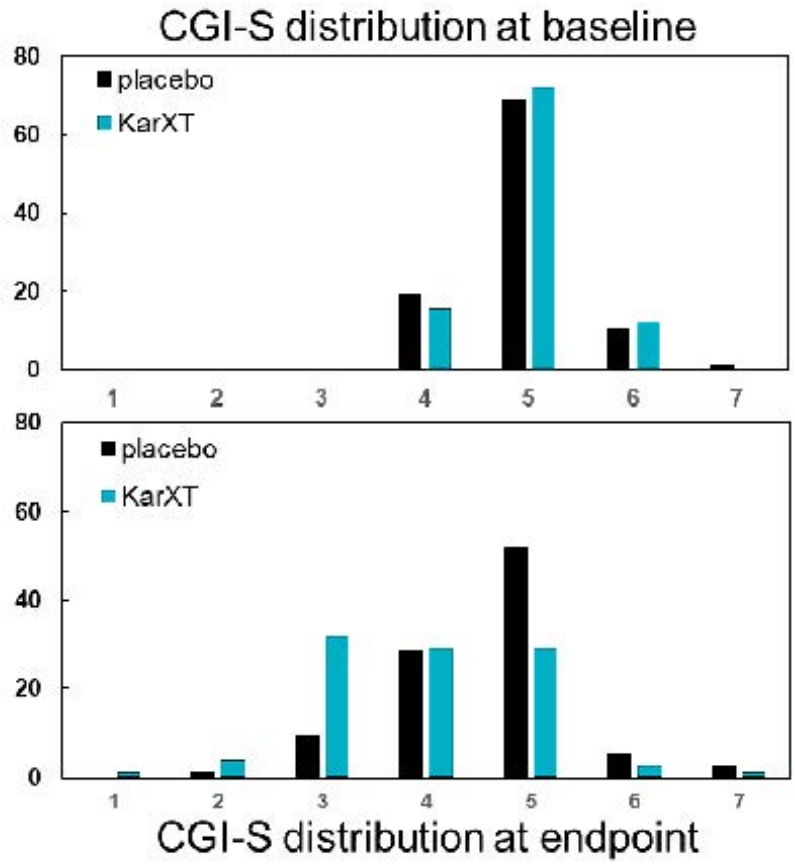
Figure 2 Change from Baseline in PANSS-Positive Scores (KAR-004)



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

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

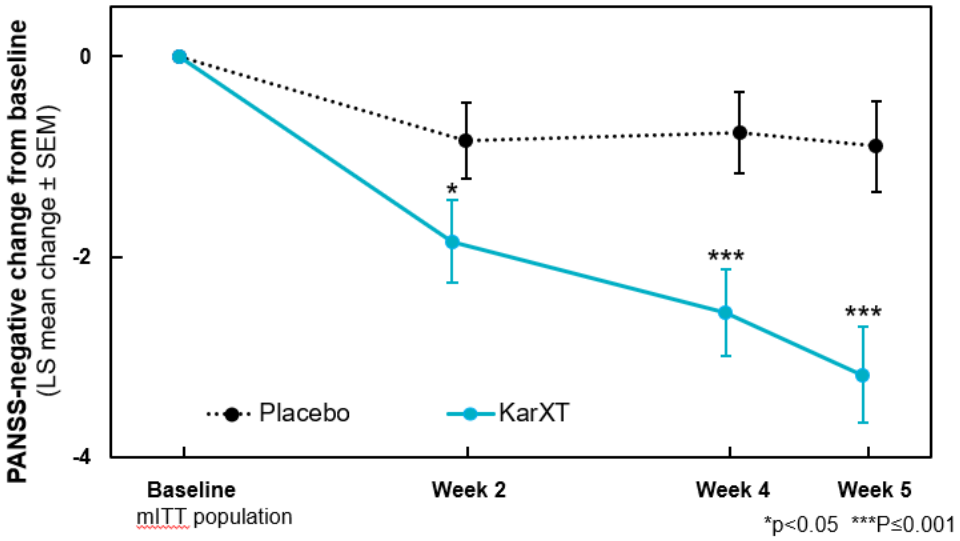
Figure 3 Change from Baseline in CGI-S (KAR-004)



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

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

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



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

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

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo
- Most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were rated as severe, and none led to discontinuations
- One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.
- No syncope or mean changes in BP were seen
- A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after week 2 was seen
- One subject (on KarXT) was discontinued due to an elevated gamma-glutamyl transpeptidase
- There were no new safety findings associated with KarXT that have not been observed with either xanomeline-alone or trospium-alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available antipsychotics for the treatment of schizophrenia.
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and extrapyramidal symptoms.

Another Phase 3 study (KAR-007) is planned at approximately 20 study sites in the US.

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium. The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared with all available APDs. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($P < 0.0001$) separation from placebo (-17.4 KarXT vs -5.9 placebo) at Week 5. KarXT, as compared with placebo, demonstrated highly significant reduction in PANSS total scores ($P < 0.0001$) at all post randomization time points (Weeks 2, 4, and, 5) with a calculated effects size (Cohen's d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all post randomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

More than 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium, or as the fixed dose combination drug KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the US for 12 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

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

intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.

KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies. The current tolerability and AE profile and the efficacy of KarXT justify further development of KarXT in this patient population by advancing to Phase 3 trials.

Subjects assigned to active study drug may benefit by improvement in schizophrenia symptoms. Since subjects will be having an acute psychotic event, subjects will be hospitalized where the clinical staff is available to help them 24 hours a day. In addition, the inpatient setting represents an important venue for research, examining the effects of KarXT and helps to eliminate or reduce to the extent possible, subjectivity and bias. Furthermore, this inpatient setting will also enhance measurable quality standards as well as increased adherence.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of KarXT 125/30 BID versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the reduction of PANSS positive score in subjects treated with KarXT versus placebo
- To evaluate the improvement in CGI-S results in subjects treated with KarXT versus placebo
- To evaluate the reduction of PANSS negative score in subjects treated with KarXT versus placebo
- To evaluate the reduction of PANSS Marder Factor negative symptoms score in subjects treated with KarXT versus placebo
- To evaluate the safety and tolerability of KarXT
- To assess the PK of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia

6.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate change in cognition measuring core domains of cognitive impairment in schizophrenia using the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- To evaluate the change in prolactin levels after administration of KarXT
- To evaluate the single nucleotide polymorphisms (SNPs) regarding schizophrenia subtypes and SNPs related to drug metabolism

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoint of this study is change from baseline in PANSS total score at Week 5

6.2.2 Secondary Endpoints

6.2.2.1 Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from baseline in PANSS positive score at Week 5
- Change from baseline in PANSS negative score at Week 5
- Change from baseline in PANSS Negative Marder Factor score at Week 5
- CGI-S score at Week 5
- Percentage of PANSS responders (a 30% change in PANSS total score) at Week 5

6.2.2.2 Safety Endpoints

The safety endpoints of this study are as follows:

- Spontaneously reported AEs including AEs of special interest (AESI)
- Spontaneously reported procholinergic and anticholinergic symptoms
- Simpson-Angus Scale (SAS)
- Barnes Akathisia Rating Scale (BARS)
- Abnormal Involuntary Movement Scale (AIMS)
- Body weight, body mass index (BMI), waist circumference
- Orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, urinalysis, and drug screen
- 12-lead ECG
- Physical examination
- Suicidal ideation scale with the use of Columbia Suicide Severity Rating Scale (C-SSRS)

6.2.3 Pharmacokinetic Endpoints

The PK endpoints of this study are as follows:

- Area under the plasma concentration-time curve (AUC)

- Maximum observed plasma concentration (C_{max})
- Time to maximum observed plasma concentration (T_{max})

6.2.4 Exploratory Endpoints

- Change in cognition measuring core domains of cognitive impairment in schizophrenia using CANTAB
- Change from baseline in prolactin levels at Week 5
- Prediction of response based on SNP schizophrenia subtypes, and SNPs related to KarXT metabolism for both efficacy and tolerability

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, inpatient clinical study in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia is designed to test the hypothesis that treatment with KarXT will result in significantly greater reduction (ie, improvement) in the primary and secondary endpoints at Week 5 from baseline compared with placebo. Total study duration is up to 8 weeks, including a 7-day screening phase (up to a 7-day extension of the screening phase is allowed, if necessary), a 5 week treatment period, and a 7-day follow-up period (only for subjects who do not rollover to KAR-008 study). Subjects completing this study will have the option of rolling over into a long-term open-label study (KAR-008) in which every subject will receive KarXT. Study staff should discuss KAR-008 protocol participation with potential subjects prior to the final day of participation in the acute study, via use of the provided recruitment materials.

Screening Period:

Screening of subjects will take place in 7 days or less before Day -1 (Days -8 to -2). Up to a 7-day extension of the screening time is allowed, if necessary.

A suitable number of subjects will be screened to randomize approximately 246 subjects across approximately 10 sites in the US and 10 sites in Ukraine. Subjects will be randomized through the IWRS in a 1:1 ratio to receive either KarXT or placebo for a treatment duration of 5 weeks.

Treatment Period:

In the treatment period, all subjects assigned to KarXT will start on a lead-in dose of KarXT 50/20 (xanomeline 50 mg/trospium 20 mg) BID for the first 2 days (Days 1 and 2) followed by KarXT 100/20 (xanomeline 100 mg/trospium 20 mg) BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on clinical response and tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Dosing must not change after Visit 7 (Day 21) of the study and may be decreased for tolerability reasons no more than once during the study. In addition, dose escalation to KarXT 125/30 BID may not occur outside of the permitted visit window for Visit 5/Day 8.

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

Efficacy assessments (PANSS scores and CGI-S score) will be assessed at scheduled visits. Refer to Section 11 for more details.

Safety will be assessed through spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms, cognition testing, SAS, BARS, AIMS, body weight, BMI, waist circumference, orthostatic vital signs, ECG, clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), prolactin levels, physical examination, and C-SSRS will be evaluated throughout the study as scheduled. Section 12 provides complete details on these safety assessments.

Details on PK assessments are provided in Section 13.

Safety Follow-up Period:

A safety follow-up visit (Visit 11/ Day 42 + 5 days) will be performed for all those subjects who do not rollover into the long-term open-label study KAR-008.

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

Table 1 presents the study design.

Table 1 Study Design

Phase:	Screening	Inpatient Treatment									End of Treatment /Early Termination	Safety Follow-up
Day:	Days -8 to -2	Day -1	Day 1	Day 3 +1 day	Day 7 ±2 days	Day 8 -1/+2 days	Day 14 ±2 days	Day 21 ±2 days	Day 28 ±2 days	Day 32 +1 day	Day 35 -2 days[c]	Day 42 +5 days
Visit:	Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Xanomeline / trospium (KarXT)*:	N/A		50/20 BID	100/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[a]	125/30 BID (Option: 100/20 BID)[a]	125/30 BID (Option: 100/20 BID)[a]	125/30 BID[b]	125/30 BID[b]	125/30 BID[b]	
Comment:	Up to a 7-day extension to the screening phase is allowed.	Baseline	2-day lead-in dose	Upward titration of dose		Upward titration of dose	Downward dose adjustment allowed according to clinical response/tolerability		No dose adjustment allowed (after Day 21)			For subjects who do not enter in to rollover Study (KAR-008)

Abbreviation: BID = twice daily.

* All the KarXT doses are in mg.

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

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

c. The last dose of study drug will be administered the morning of Visit 10.

7.2 Discussion of Study Design

A randomized, double-blind, parallel-group, placebo-controlled study design is suitable for conducting any interventional studies. This design will minimize bias and provide reference data for comparison of efficacy and safety parameters of the investigational drug.

Schizophrenia is a long-term mental disorder which requires a chronic therapy. A 5-week treatment duration is considered an acceptable treatment duration to observe clinically significant response (ie. primary endpoint can be achieved). The 5-week treatment duration is substantiated by the statistically significant outcome of the KAR-004 study of the same duration.

7.3 End of Study

A subject will have fulfilled the requirements for study completion when the subject has completed all study periods, including the End of Study visit (Visit 10/Day 35 [End of Treatment/Early Termination] for subjects who roll over into KAR-008 or Visit 11/Day 42 [Follow-up] for subjects who do not roll over into the KAR-008 study) as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

Subjects completing this study will have the option of rolling over into a long-term open-label study (KAR-008) in which every subject will receive KarXT, following completion of Visit 10/Day 35 of the current study (KAR-009).

Note: A safety follow-up visit will be performed 1 week after the End of Treatment/Early Termination visit (Visit 10) for subjects who have completed Visit 10/Day 35 but do not rollover in to the long-term open-label study KAR-008.

7.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety and tolerability data from the clinical study. The ISMC will include 3 clinicians and a reporting statistician. This committee will be responsible, on a periodic basis, for confirming the safety and tolerability of KarXT throughout the study, with particular focus on assessing for any new toxicities that might be involved with KarXT.

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

8 SELECTION OF STUDY POPULATION

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

8.1 Inclusion Criteria

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

1. Subject is aged 18 to 65 years, inclusive, at screening.
2. Subject is capable of providing informed consent.
   a. A signed informed consent form must be provided before any study assessments are performed.
   b. Subject must be fluent (oral and written) in English (applicable to the US) or local language (Ukrainian or Russian applicable to Ukraine) to consent.
3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2.
4. Subject is experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 2 months before screening.
   a. The subject requires hospitalization for this acute exacerbation or relapse of psychotic symptoms.
   b. If already an inpatient at screening, has been hospitalized for less than 2 weeks for the current exacerbation at the time of screening.
5. Positive and Negative Syndrome Scale total score between 80 and 120, inclusive.
   a. Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items:
      i. Item 1 (P1; delusions)
      ii. Item 2 (P2; conceptual disorganization)
      iii. Item 3 (P3; hallucinatory behavior)
      iv. Item 6 (P6; suspiciousness/persecution)
6. Subjects with no change (improvement) in PANSS total score between screening and baseline (Day -1) of more than 20%.
7. Subject has a CGI-S score of ≥4 at screening and baseline (Day -1) visits.
8. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 5 half-lives or 1 week, whichever is longer, before baseline (Day -1).
9. Subjects taking a long-acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®) before baseline visit (Day -1).
10. Subject is willing and able to be confined to an inpatient setting for the study duration,

follow instructions, and comply with the protocol requirements.

11. BMI must be ≥18 and ≤40 kg/m^2.
12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator.
13. Subject has an identified reliable informant/caregiver. An informant/caregiver is needed at the screening and baseline visits as well as at the end of the study for relevant assessments (site staff may act as informant while the subject is an inpatient). An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year.
14. Women of childbearing potential (WOCBP) , or men whose sexual partners are WOCBP, must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and APPENDIX 1.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening). Exclusionary disorders include, but are not limited to, moderate to severe alcohol use disorder (within the past 12 months), substance (other than nicotine or caffeine) use disorder within the past 12 months (use of cannabis at screening will result in screen failure with the allowance to rescreen at a later date if no moderate to severe substance use disorder is determined), major depressive disorder, bipolar I or II disorder, schizoaffective disorder, obsessive compulsive disorder, and post-traumatic stress disorder. Symptoms of mild mood dysphoria or anxiety are allowed as long as these symptoms are not the primary focus of treatment.
    a. A screening subject with mild substance abuse disorder within the 12 months before screening must be discussed and agreed upon with the medical monitor before they can be allowed into the study.
2. Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia.
3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, GI, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
4. Subjects with HIV, cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test results.
5. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.

7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (C-SSRS – ideation) with the most recent episode occurring within the 2 months before screening or answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring within the 12 months before screening. Nonsuicidal, self-injurious behavior is not exclusionary.
8. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.
9. Subjects cannot currently (within 5 half-lives or 1 week, whichever is longer, before baseline [Day -1]) be receiving oral antipsychotic medications; monoamine oxidase inhibitors; anticonvulsants (eg, lamotrigine, Depakote); tricyclic antidepressants (eg, imipramine, desipramine); selective serotonin reuptake inhibitors; or any other psychoactive medications except for as needed anxiolytics (eg, lorazepam, chloral hydrate).
10. Pregnant, lactating, or less than 3 months postpartum.
11. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
12. Positive test for coronavirus (COVID-19) within 2 weeks before screening and at screening.
13. Subjects with extreme concerns relating to global pandemics, such as COVID-19, that preclude study participation.
14. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.
15. Subject has a history of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months.
16. Subjects with prior exposure to KarXT.
17. Subjects who experienced any adverse effects due to xanomeline or trospium.
18. Participation in another clinical study in which the subject received an experimental or investigational drug agent within 3 months before screening.
19. Risk of violent or destructive behavior.
20. Current involuntary hospitalization or incarceration.

8.3 Rescreening

Individuals who sign the informed consent form (ICF) to participate in the study but who do not subsequently meet all the requirements for safety laboratory assessments and therefore do not enroll (screen failures) may be rescreened, upon approval of the medical monitor on a case by case basis. Such individuals may be allowed to rescreen up to 1 time. When re-testing within the

same screening procedure, only the exclusionary laboratory tests will be repeated once in case the exclusionary laboratory result was not due to a pathological condition and was occasional (except for individuals who have positive serology results).

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be discharged from the study site, if clinically warranted after completing all the Visit 10/early termination assessments as indicated in the Schedule of Assessments (Table 2).

Note: A safety follow-up visit will be performed 1 week after the End of Treatment/Early Termination visit (Visit 10) for those subjects who do not roll over into the long-term open-label study KAR-008.

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 will not re-enter the study.

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

- progressive disease
- unacceptable toxicity or AE
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request. The reason for subject withdrawal will be noted on the eCRF
- on the basis of the investigator's clinical judgement
- 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 (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a study subject is off study drug for >5 days in a row])

- violation of entry criteria; ie, subjects who are enrolled but are later discovered not to meet entry criteria
- development of suicidal or assaultive behavior
- alcohol or illegal drug use
- pregnancy, as indicated in Section 12.7.8. Any study subject who becomes pregnant while participating in the study will be unblinded to study treatment randomization. If she is found to be on active treatment assignment, she will be followed until her pregnancy reaches term
- Sponsor's decision to discontinue 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. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who leave the unit or are lost to follow-up. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved (regardless of whether they enroll in the long-term open-label study KAR-008) or the subject is considered to be in stable condition.

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

8.4.1 **Pregnancy**

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

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

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

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

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

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the study drug. Upon discontinuation from the study, only those procedures that would not expose the pregnant female subject to undue risk will be performed. See Section 12.7.8 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a pregnancy report will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAE (Section 12.7.4).

8.5 Completion of the Study or Lost to Follow-up

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

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

8.6 Study Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or 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 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.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, one of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the freebase equivalent of xanomeline and trospium according to the desired dose strength. In addition to the active ingredients, the drug beads contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish-orange hydroxypropyl methylcellulose hard capsules. Placebo will be prepared in matching capsules; therefore, an unblinded pharmacist will be required to dispense study drug in a blinded fashion to personnel who will be responsible for administration of IP to the subject. For the 2-day lead-in period (Days 1 and 2), subjects randomized to active drug will receive capsule strength KarXT 50/20 BID, followed by 2 capsules of KarXT 50/10 mg BID or a dosage of 100/20 BID for a total daily dosage of 200/40 mg xanomeline/trospium chloride for the remainder of Week 1 (Days 3 to 7). At the beginning of Week 2, dosing may be increased to 2 capsules of KarXT 62.5/15 mg or a dosage of 125/30 BID for a total daily dosage of 250/60 mg xanomeline/trospium chloride, depending on clinical response and tolerability. Investigators have the option to return a subject to KarXT 100/20 BID for the remainder of the treatment period, but dosing must not change after Visit 7 of the study.

KarXT 50/10 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish-orange, hydroxypropyl methylcellulose hard capsule.

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

KarXT 62.5/15 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish-orange, hydroxypropyl methylcellulose hard capsule.

Placebo is composed of sugar spheres pf011, 850/1000 suglets, 99.05% colorcon, and 10.05% talc in a size 0, Swedish-orange, hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements.

9.1.2 Packaging and Labelling

The study packaging and labelling will be performed by Corealis Pharma, located in Laval, Quebec, Canada, Catalent Pharma Solutions, located in Winchester, Kentucky (labelling for the US sites), and Catalent Pharma Solutions, located in Philadelphia, Pennsylvania (labelling for Ukrainian sites). All packaging and labelling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

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

Further details on labelling of investigational products will be provided in the Pharmacy Manual.

9.1.3 Study Drug Storage

KarXT and placebo must be stored at controlled room temperature 15°C-25°C in a secured location with no access to unauthorized personnel.

9.1.4 Study Drug Retention

Study drug not used in KAR-009 may be used for the long-term extension study (KAR-008). Therefore, unused study drug for this particular study must be retained until completion or termination of the KarXT program, and written authorization from the Sponsor has been received. The unused study drug can be reassigned in the IWRS to subjects in the KAR-008 study. All unused and used study drug must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused study drug may be disposed until fully accounted for by the study monitor.

9.2 Dose Schedule

The first dose of the study drug will be administered in the morning of Day 1. The last dose will be administered in the morning of Visit 10 (Day 35 -2 days). The study drug should be administered daily BID on an empty stomach ie, at least 1 hour before a meal or 2 to 3 hours after a meal. Some considerations for dosing and PK blood withdrawals are provided in the subsections below.

9.2.1 Visit 2b/Day 1 Randomization and Dosing

- The first dose will be administered in the morning, and the evening dose will be administered 12 ± 0.5 hours after the morning dose.
- All subjects must be administered 4 dosages of the KarXT 50/20 or placebo before dose escalation to KarXT 100/20 or placebo BID.

9.2.2 Visit 3/Day 3 and/or Visits Occurring on Weekends/Holidays

- If dose escalation to the KarXT 100/20 or placebo level is confirmed by investigator order on Visit 3/Day 3, that dose is to be administered in the morning.
- When Day 3 occurs on a weekend, it is expected that the complete Visit 3 will be performed, and the subject's dose will be escalated on Day 3.
- If completion of the visit is not possible on Day 3, the +1-day visit window may be used. In this instance, the dose will not be escalated until the study visit occurs. In all cases, the subject must have had at least 4 doses of KarXT 50/20 or placebo before escalating to KarXT 100/20 or placebo.
- This may result in only 4 days of the KarXT 100/20 or placebo dose at Visit 5/Day 8, which is acceptable.
- All subjects must be administered 8 doses of the KarXT 100/20 or placebo before dose escalation to KarXT 125/30 or placebo BID.

9.2.3 Visit 5/Day 8 Dosing and PK Considerations and Visit 8/Day 28 PK Considerations

- If dose escalation to the KarXT 125/30 or placebo level is confirmed by investigator order on Visit 5/Day 8, that dose is to be administered in the morning (after the predose PK blood draw) to allow for serial postdose PK blood draws per protocol (Table 2, Footnote p).
- Should the use of visit windows be necessary, serial PK sampling must accompany the actual day of dose escalation for Visit 5.
- For Visit 8, serial PK sampling is meant to capture the PK profile of the subject's final KarXT dose level (125/30 or 100/20) after multiple doses; therefore, there must be no changes in dose for at least 7 days prior to Visit 8. PK sampling must accompany the actual day of Visit 8 if a window is used.

9.2.4 Visit 10/Day 35 Dosing

- All subjects will receive their final dose of KarXT or placebo on the morning of Visit 10/Day 35.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

At Screening, the interactive web response system (IWRS) will assign a unique subject identification number to the subject known as the Subject Number. This number will be associated with the subject throughout the study. Every subject who signs an ICF must be

entered into the IWRS regardless of eligibility in order to obtain a Subject Number. This 9-digit number will consist of a 3-digit study code and a 3-digit site identification followed by a 3-digit subject number assigned sequentially within each site, starting at 001.

On Day -1, all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups. Subjects will be assigned a randomization number through the IWRS, in accordance with the randomization code generated by the authorized personnel at VERISTAT. At the study site, the randomization schedule will only be accessible 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 former discontinued the study.

9.3.2 **Blinding**

An IWRS will allocate treatment based on a prespecified randomization list generated by VERISTAT. Active and placebo study drug will be provided in bulk to each site participating in the study. For each dose, study drug and packaging will be identical in size, shape, color, and appearance (see Section 9.1.2). No other study site personnel (except the pharmacist or other designated unblinded individual), subjects, informants/caregivers, Sponsor personnel, or Sponsor designees (eg, Sponsor's Medical Monitor) will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. Both active study drug and placebo will be supplied as identical matching capsules. This prevents bias on the part of the study staff and the subject to influence the results of the study.

If an investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Sponsor/medical monitor must be obtained in such instances.

VERISTAT 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 wellbeing, the investigator may break the randomization code for just that subject via the IWRS, by which system the unblinding will be captured after consultation and agreement with the medical monitor/Sponsor. The unblinding and its cause will also be documented in the eCRF. Unblinding according to the protocol will occur only after completion of the study.

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

appropriate course of action is to stop the investigational drug and treat the signs and symptoms resulting from the AE.

The members of the ISMC will be unblinded as they review the safety data from the study.

9.4 Dose Modification

Subjects will be dosed as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The study drug doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments at Visits 5, 6, and 7 and at unscheduled visits. No dose adjustments are allowed after Visit 7. No other dose modifications are permissible in this study except those specified in this protocol.

9.5 Treatment Accountability and Compliance

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

Administration of study drug will be supervised by study site personnel to ensure compliance.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment bulk supply and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor or designee until accountability has been fully monitored through the end of the study. Study drug accountability will be assessed periodically by the assigned unblinded study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Subjects will be asked for 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.

Restricted prior therapies are provided in Section 8.2.

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

During the study (ie, from the time of screening visit until study completion), subjects will refrain from the use of any new concomitant medications without the specific prior approval of the investigator. The administration of any other concomitant medications during the study

period is prohibited without the prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, dates of use, and time of use (only for concomitant medications used on an as-needed [PRN] basis).

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

- Within 5 half-lives or 1 week, whichever is longer, before baseline (Day -1), subjects could not have taken oral antipsychotic medications, MAO inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate).
- Subjects taking a long acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®).

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

9.6.2 Concomitant Medications for Anxiety and/or Sleep aid

Subjects are allowed to take benzodiazepines (up to 6 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on a PRN basis. Subjects may also use non-benzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid also on a PRN basis. Study sites must record the use of such medications in the eCRF on a per-administration basis and subject's source document. Note: Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.6 specifies laboratory assessment samples to be obtained. See Sections 11, 12, and 13 for additional details regarding efficacy, safety, and PK assessments, respectively.

Table 2. Schedule of Assessments

PROCEDURE	SCREENING PHASE	TREATMENT PHASE										SAFETY FOLLOW-UP[v]	Unscheduled Visit(s)[b]
VISIT	1 (Day -8 to -2)[a]	2a (Day -1)	2b (Day 1)	3 (Day 3 +1 day)	4 (Day 7 ±2 days)	5 (Day 8 -1/+2 days)	6 (Day 14 ±2 days)	7 (Day 21 ±2 days)	8 (Day 28 ±2 days)[u]	9 (Day 32 +1 day)	10/ET (Day 35 -2 days)	11 (Day 42 +5 days)	
WEEKS PAST RANDOMIZATION	NA	0			1		2	3	4		5	6	
Written informed consent	X												
Collect demographic information (date of birth, sex, race)	X												
Pregnancy test (females of childbearing potential only)[c]	X	X									X	X	
Urine test for drugs of abuse and alcohol testing[d]	X	X											X
Review of inclusion/exclusion criteria	X	X											
Subject eligibility verification process	X												
Medical, psychiatric, and medication history	X												
Complete physical examination[e]	X										X	X	
Spontaneous AEs[f]		X	X	X	X	X	X	X	X	X	X	X	X

PROCEDURE	SCREENING PHASE	TREATMENT PHASE										SAFETY FOLLOW-UP[v]	Unscheduled Visit(s)[b]
VISIT	1 (Day -8 to -2)[a]	2a (Day -1)	2b (Day 1)	3 (Day 3 +1 day)	4 (Day 7 ±2 days)	5 (Day 8 -1/+2 days)	6 (Day 14 ±2 days)	7 (Day 21 ±2 days)	8 (Day 28 ±2 days)[u]	9 (Day 32 +1 day)	10/ET (Day 35 -2 days)	11 (Day 42 +5 days)	
WEEKS PAST RANDOMIZATION	NA	0			1		2	3	4		5	6	
Review of concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Height (Screening only) and body weight, BMI, waist circumference	X	X									X	X	
Orthostatic vital signs: BP and heart rate[g]	X		X	X	X	X	X	X	X	X	X	X	X
Resting 12-lead ECG[h]	X		X						X		X		
Blood samples for hematology, coagulation, and serum chemistry and urine sample for urinalysis[i]	X							X			X	X	X
COVID-19 testing[j]	X												X
Blood sample for prolactin[k]		X						X			X		
Blood sample for viral serology[l]	X												
Blood sample for DNA testing		X											

PROCEDURE	SCREENING PHASE	TREATMENT PHASE										SAFETY FOLLOW-UP[v]	Unscheduled Visit(s)[b]
VISIT	1 (Day -8 to -2)[a]	2a (Day -1)	2b (Day 1)	3 (Day 3 +1 day)	4 (Day 7 ±2 days)	5 (Day 8 -1/+2 days)	6 (Day 14 ±2 days)	7 (Day 21 ±2 days)	8 (Day 28 ±2 days)[u]	9 (Day 32 +1 day)	10/ET (Day 35 -2 days)	11 (Day 42 +5 days)	
WEEKS PAST RANDOMIZATION	**NA**	**0**			**1**		**2**	**3**	**4**		**5**	**6**	
Functional constipation inquiry[m]		X		X	X	X	X	X	X	X	X	X	X
Admission of subject to inpatient unit[n]	X												
Randomization/ assignment of subject randomization number		X											
Determination of dose adjustment						X	X	X					X
Study drug provided (randomized, double-blind) and administered daily BID[o]			X	X	X	X	X	X	X	X	X		X
Blood samples for PK analysis[p]						X			X		X		X
MINI version 7.0.2[q]	X												
Positive and Negative Syndrome Scale (PANSS) for schizophrenia[r]	X	X					X	X	X		X	X	
C-SSRS[s]	X	X			X		X	X	X		X	X	X
CGI-S Scale	X	X			X		X	X	X		X		
Cognition testing[t]	X	X						X		X			
Simpson-Angus		X			X		X	X	X		X	X	

PROCEDURE	SCREENING PHASE	TREATMENT PHASE										SAFETY FOLLOW-UP[v]	Unscheduled Visit(s)[b]
VISIT	1 (Day -8 to -2)[a]	2a (Day -1)	2b (Day 1)	3 (Day 3 +1 day)	4 (Day 7 ±2 days)	5 (Day 8 -1/+2 days)	6 (Day 14 ±2 days)	7 (Day 21 ±2 days)	8 (Day 28 ±2 days)[u]	9 (Day 32 +1 day)	10/ET (Day 35 -2 days)	11 (Day 42 +5 days)	
WEEKS PAST RANDOMIZATION	NA	0			1		2	3	4		5	6	
Rating Scale													
Barnes Rating Scale for Akathisia		X			X		X	X	X		X	X	
Abnormal Involuntary Movement Scale (AIMS)		X			X		X	X	X		X	X	
Discuss participation in KAR-008[w]								X					

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

a. Up to a 7-day extension of the screening phase is allowed, if needed.
b. Other assessments as needed.
c. A serum pregnancy test for females of childbearing potential should be done at screening, and urine pregnancy tests should be done at other visits.
d. A National Institute on Drug Abuse-5 urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed at screening and at Visit 2a (baseline). If a subject leaves the study site, they should have a urine drug screen and test for alcohol (breathalyzer or urine alcohol level) upon returning to the study site.
e. A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat, examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.
f. AEs as reported by subjects or observed by clinical staff and occurs from Day -1. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgement) is reported during a scheduled visit or if there is a dose adjustment or a relevant/significant AE reported during an unscheduled visit (no multiple draws).
g. Vital signs taken 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. Heart rate is measured in beats/minute. During treatment, beginning with Day 1, orthostatic vital signs should occur 2 (±1) hours after morning dosing. Orthostatic vital signs are only required after the morning dose of the specified visit days, but additional orthostatic vital sign monitoring is allowed at the investigator's discretion. It would be acceptable, for example, to do orthostatic vital signs BID after dosing increases for a day or 2 for

subjects where it seems warranted, but this should not be done automatically.

h. ECG on Day 1 will be done at 2 hours + 15 minutes post morning dose. ECGs at all other scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or PK analysis. During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained.
i. Refer to Table 3 for individual laboratory tests. For urinalysis, a urine dipstick will be performed at the site, and the sample will be sent to the central laboratory in case of abnormalities.
j. Optional COVID-19 test may be performed at unscheduled visits based on the Investigator's discretion.
k. Blood sample for prolactin must be obtained before the morning dose of the study drug at scheduled visits (except at Visit 2a).
l. All subjects must have the following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, HIV-1 antibody, and HIV-2 antibody. If the subject tests positive for anti-HCV antibody, then HCV RNA via polymerase chain reaction should be performed to confirm or rule out active infection.
m. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form scale; see APPENDIX 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
n. If an eligible subject is not already an inpatient, the subject should be admitted to the inpatient unit.
o. Starting on Day 1, study drug is administered daily BID (first dose of study will be administered in the morning of Day 1, and evening dose will be administered 12 ± 0.5 hours after the morning dose and after last PK sampling [for Visits 5 and 8] is completed), on an empty stomach ie, at least 1 hour before a meal or 2 to 3 hours after a meal by the study staff, with the last dose administered on the morning of Visit 10. All subjects must receive at least 4 dosages of the 50/20 BID before dose escalation to KarXT 100/20 BID.
p. For Visit 5/Day 8 and Visit 8/Day 28, 7 PK blood draws are required: before the morning dose, and at 0.5 hour ± 5 minutes, 1 hour ± 5 minutes, 2 hours ± 10 minutes, 4 hours ± 10 minutes, 8 hours ± 10 minutes, and 12 hours ± 10 minutes after the morning dose (Note: The 12-hour samples must be collected before administration of the evening dose). PK blood draws at Visit 5 must be drawn in relation to the first dose of KarXT 125/30 for subjects who are escalated in the morning of Visit 5/Day 8 -1/+2 days. PK blood must also be drawn in relation to the morning dose for subjects who are not escalated at Visit 5/Day 8 -1/+2 days. For Visit 10/ET, a single PK blood sample should be withdrawn before discharge (preferably in the morning after the last dose of the study drug). One PK blood sample may also be drawn if a relevant/ significant AE is reported during a scheduled visit or if there is a dose adjustment or a relevant/significant AE reported during an unscheduled visit (no multiple draws). For an ET Visit that is related to an AE, the collection of a PK blood sample is not optional and should be drawn before discharge.
q. MINI should be performed before PANSS assessment.
r. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments (except MINI) for all visits at which it is performed. The PANSS assessment includes the Marder Factor.
s. C-SSRS first time use lifetime, other times use "Since Last Visit" version. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
t. During screening, subjects will complete each of the CANTAB tests for familiarization purposes. These same tests will then be administered on Visits 2a, 7, and 9. Note: Cognition testing cannot be done within 8 hours of receiving benzodiazepine or sleep medications.
u. There must be no changes in dose for at least 7 days leading up to Visit 8.
v. Safety follow-up visit will be performed 1 week (Day 42 +5 days) after Visit 10/ET for subjects who do not rollover in to the long-term open-label study KAR-008.
w. Study staff should discuss KAR-008 protocol participation with potential subjects prior to the final day of participation in the acute study, via use of the

provided recruitment materials.

10.1 Informed Consent

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

10.2 Study Procedures

Assessments and their timings are to be performed as outlined in the Schedule of Assessments (Table 2). Section 12.6 specifies laboratory assessment samples to be obtained.

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

Efficacy assessments are described in Section 11 and include PANSS and CGI-S scores.

Safety assessments are described in Section 12 and include spontaneous AEs; AESIs, procholinergic and anticholinergic symptoms; cognition testing (CANTAB); SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); prolactin levels; physical examination; and C-SSRS.

PK assessments are described in Section 13 and include estimation of AUC, C_{max}, and T_{max}.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and after discussion with the medical monitor.

Study discontinuation procedures are described in Sections 8.4 and 8.6.

11 EFFICACY ASSESSMENTS

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

11.1 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[22]. The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210. The PANSS assessment includes the Marder Factor.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments (except MINI at screening) for all visits at which it is performed.

11.2 Clinical Global Impression–Severity

The CGI-S is a rating scale completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The 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[23].

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

12 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs; AESIs; procholinergic and anticholinergic symptoms; cognition testing [CANTAB]; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, prolactin, and drug screen]; physical examination; and C-SSRS) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

12.1 Demographics, and Medical and Psychiatric History

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

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

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

12.2 Vital Signs

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

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

12.3 Physical Examination

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

12.4 Weight, Height, Body Mass Index, Waist Circumference

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

12.5 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 2). During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements will be obtained. ECG at Day 1 will be performed 2 hours (+ 15 minutes) post morning dose. ECGs at all other scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

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

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

12.6 Laboratory Assessments

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

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
Prolactin		
Coagulation	**Serology[a]**	**COVID-19**
PT Activated PTT Fibrinogen	HBV HCV HIV	
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 central laboratory for confirmation of the result.		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; Hb = hemoglobin; HBV = Hepatitis B; HCG = human chorionic gonadotropin; Hct = hematocrit; HCV = Hepatitis C; HIV = Human Immunodeficiency virus; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

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

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

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

Blood and abnormal urine (microscopic analysis) samples will be analyzed at a central laboratory facility. Urine samples will first be analyzed by dipstick at the site. If the results of the dipstick indicate abnormalities to be further investigated, the sample will be sent to the central laboratory, and a microscopic analysis will be performed. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed 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 with until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for drug-induced liver toxicity, detailed in Section 12.7.5, during the study.

Other Laboratory Assessments:

A National Institute on Drug Abuse-5 urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick at screening and at Visit 2a (baseline).

Alcohol testing is performed using a breathalyzer or urine alcohol test.

If a subject leaves the study site, they should have a urine drug screen test and test for alcohol (breathalyzer or urine alcohol test) upon returning to the study site.

12.6.1 Blood Sampling for Pharmacogenetics

A blood sample may be collected at baseline (Day -1) for exploratory pharmacogenetic analysis. Approximately 9 mL of blood may be collected for subsequent DNA extraction. The samples will be stored at a central laboratory facility, where DNA will be extracted and retained. The collection, storage, shipping, processing of the blood samples, and the analytical methods to be used will be detailed in the laboratory manual.

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

The details on the statistical analysis will be provided either in the statistical analysis plan (SAP) or the clinical study report.

12.7 Adverse Events

12.7.1 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. Changes in these

conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant vital signs and laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period, and these will be recorded 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?" The eCRF will be completed at the end of the study as soon as the results of the final laboratory tests are available.

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

For the purposes of this study, the period of observation for collection of AEs extends from the time immediately after the administration of study drug on Day 1 until the End of Study (Visit 10 for subjects who roll over and Visit 11 for subjects who do not roll over to Study KAR-008 study) or early termination. Follow up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

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

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

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

Table 4. Classification of Adverse Events by Intensity

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

Table 5. Classification of Adverse Events by Relationship to Study Drug

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

Abbreviation: AE, adverse event.

12.7.2 Adverse Events of Special Interest

The AESIs will be monitored and include orthostasis and liver function test elevations inclusive of DILI.

AEs of special interest should be recorded as AEs and reported as SAEs when appropriate.

12.7.3 Serious Adverse Events

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

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective treatment of a pre-existing, nonworsening 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, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 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.

12.7.4 Serious Adverse Event Reporting

An SAE occurring from the time first dose of the study drug is administered, during the study, or within 1 week of stopping the treatment must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using email.

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

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

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

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

12.7.5 Drug-Induced Liver Injury

The sponsor has incorporated the following for monitoring of the drug induced liver injury:

- *An increase of serum ALT or AST to >3 × upper limit of normal (ULN) should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).*
- *Close observation should be initiated with ALT or AST >3 × ULN:*
  - *Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. 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 (eg, international normalized ratio, direct bilirubin).*
  - *Consider gastroenterology or hepatology consultations.*
- *Discontinuation of treatment should be considered if:*
  - *ALT or AST >8 × ULN*
  - *ALT or AST >5 × ULN for more than 2 weeks*
  - *ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)*
  - *ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)*
- *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 to resolution of elevated liver enzymes.*
- *Gamma-glutamyl transpeptidase elevations alone should not prompt drug discontinuation.*

12.7.6 Trial Discontinuation Criteria Other than DILI and Pregnancy

12.7.6.1 Individual Stopping Criteria

Based on NCI CTCAE v5.0, the study drug will be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs, other than DILI AEs, (see Section 12.7.5) will be at the discretion of the investigator.

12.7.6.2 Trial Stopping Rules

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

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

12.7.7 Suspected Unexpected Serious Adverse Reactions

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

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

The investigator will assess whether or not an event is causally related to study treatment. The Sponsor (or their designee Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the 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 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.

Warnings and Precautions

Risk of Urinary Retention:

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

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride

should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility:

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

Controlled Narrow-angle Glaucoma:

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

Central Nervous System Effects:

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

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment:

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

Elevation of liver enzymes:

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

12.7.8 **Pregnancy**

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

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

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

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

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

12.7.9 **Overdose**

The investigator must immediately notify the Sponsor of any occurrence of overdose with study drug. Overdose should be managed with symptomatic and supportive care.

12.8 Cambridge Neuropsychological Test Automated Battery

The computerized CANTAB provides an objective measure of cognitive function correlated to neural networks (Table 6). A short cognitive battery measuring core cognitive domains of impairment in schizophrenia (ie, as per Brief Assessment of Cognition Schizophrenia key

cognitive domains) will be employed for this study, and it will take approximately 30 minutes to complete. These CANTAB tests meet MATRICS workshop criteria[24]. Subjects will have 1 familiarization session with the CANTAB tests during the screening visit and will subsequently complete the same test battery on Visits 2a (baseline), Visit 7, and Visit 9. Subjects perform the test on a provisioned iPad with data immediately uploaded to the CANTAB Connect cloud-based platform (WiFi permitting).

Cognition testing cannot be done within 8 hours of receiving benzodiazepine or sleep medications.

Table 6 Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery

CANTAB Tests	MATRICS Cognitive Domain	Outcome Measures
Rapid visual information processing	Sustained attention/vigilance	**A' Prime:** Signal detection measure of how good the subject is at detecting the target sequence (string of three numbers); regardless of response tendency
Verbal recognition memory	Verbal memory and new learning	**Free Recall:** The total number of words that are correctly recalled from the presentation phase by the subject during the immediate free recall stage
Spatial Span	Working memory	**Forward Span Length:** The longest sequence of boxes successfully recalled by the subject
One-touch stockings of Cambridge	Executive Function Planning/Problem Solving	**Problems Solved on First Choice:** The total number of assessed trials where the subject chose the correct answer on their first attempt

Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

12.9 Simpson-Angus Scale

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

12.10 Barnes Akathisia Rating Scale

The BARS is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity[25].

12.11 Abnormal Involuntary Movement Scale

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

12.12 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[26]. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

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

12.13 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass[27]. The stool is often hard and dry[28]. Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement[29]. The normal frequency of bowel movements in adults is between 3 per day and 3 per week[27]. Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, APPENDIX 2 (Longswreth,1486,C3)[30].

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and had been shown to be a useful tool in clinical practice and research[31]. A sample Bristol Stool Form Scale is located in APPENDIX 2.

As a measure of anticholinergic effects, at each visit (except at Visit 2a), subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools and pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation[29,32].

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

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

12.14 Mini International Neuropsychiatric Interview Version 7.0.2

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

12.15 Change in Prolactin

Blood samples to assess the change in prolactin levels will be obtained on Visit 2a/Day -1, Visit 7/Day 21 ± 2 days, and Visit 10/Day 35 -2 days/Early Termination (ET). At each of these visits (except Visit 2a), blood sample must be collected before the morning dose of the study drug.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

Blood samples for PK analysis of KarXT levels will be collected at the time points indicated in the Schedule of Assessments (Table 2). Approximately 6 mL of blood to be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

Serial blood samples to measure plasma concentrations of xanomeline and trospium will be obtained on Visit 5/Day 8 -1/+2 days (first dose of fixed titration period) and Visit 8/Day 28 ± 2 days. Blood samples will be obtained at the following time points on these days:

PK Sample	Timing of Collection	Collection Window
1	Before morning dose	
	After morning dose	
2	0.5 hours	± 5 min
3	1 hour	± 5 min
4	2 hours	± 10 min
5	4 hours	± 10 min
6	8 hours	± 10 min
7	12 hours after (but before the evening dose)	± 10 min

It is very important that the exact time of each PK draw and dosing times are recorded in the eCRF and that PK samples are collected within the specified times of collection.

Should the use of visit windows be necessary, serial PK sampling must accompany the actual day of potential dose escalation for Visit 5.

For Visit 8, serial PK sampling is meant to capture the PK profile of the subject's final KarXT dose level (125/30 or 100/20) after multiple doses. If visit windows are used for Visit 8, the PK sampling should occur at least 7 days after Visit 7 is completed, and there must be no changes in dose for at least 7 days leading up to Visit 8. PK sampling must accompany the actual day of Visit 8.

Note: A single PK sample should be drawn before discharge (preferably in the morning after the last dose of the study drug) at Visit 10/Day 35 -2 days or ET. In addition, one PK sample may be drawn if a relevant/significant AE is reported during a scheduled visit or if there is a dose adjustment or relevant/significant AE reported during an unscheduled visit (no multiple draws). For an ET Visit that is related to an AE, the collection of a PK blood sample is not optional and should be drawn before discharge.

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

13.2 Pharmacokinetic Analytical Methodology

Concentrations of trospium and xanomeline will be determined from plasma PK samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 STATISTICAL ANALYSIS

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

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean and standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

14.1 Determination of Sample Size

Assuming treatment difference of change from baseline in PANSS total score at Week 5 is 8 points between drug and placebo (standard deviation 16), a sample size of approximately 172 (86 evaluable subjects per arm) will result in a power of 90.3% for a 2-sided alpha of 0.05 ($P \leq 0.05$). With a dropout rate of 30%, a total of 246 subjects are estimated to be enrolled.

14.2 Analysis Populations

Intent-to-Treat Population

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

Modified ITT Population

All subjects who are randomized, received at least 1 dose of study drug, have a baseline PANSS assessment, and at least 1 post-baseline PANSS assessment will be included in the mITT population and will be used in the efficacy analysis.

Safety Population

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

PK Population

All subjects who have an evaluable PK profile will be included in the PK population and will be used in the PK analysis. Subjects must have received at least 1 dose of active study drug and have at least 1 measurable plasma concentration of study drug.

14.3 General Statistical Considerations

All efficacy analyses will be performed using the mITT population. 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 5 in PANSS total score will be evaluated first. The endpoints are set up as a hierarchical list and step down through the statistical testing of each endpoint using an alpha of 0.05. Statistical testing of change from baseline to Week 5 in PANSS positive score, PANSS negative score, and PANSS Negative Marder Factor score, CGI-S score at Week 5, and percentage of PANSS responders will be performed only if the primary endpoint is significant at the 0.05 alpha level ($P \leq 0.05$), and testing would continue through a pre-ordered list of key secondary efficacy endpoints. If at any point $P > 0.05$, then formal statistical testing would stop. This will control the overall Type 1 error rate across all hypotheses/endpoints being tested. Table 7 outlines the testing procedure.

Table 7 Statistical Testing Procedure

KarXT vs Placebo
1. Change from baseline in PANSS total score at Week 5
2. Change from baseline in PANSS positive score at Week 5
3. Change from baseline in PANSS negative score at Week 5
4. Change from baseline in PANSS Negative Marder Factor score at Week 5
5. CGI-S score at Week 5
6. Percentage of PANSS responders (a 30% change in PANSS total score) at Week 5

14.4 Efficacy Analysis

14.4.1 Primary Estimand

The population of the primary estimand is among adult inpatients (aged 18-65 years) with a DSM-5 diagnosis of schizophrenia, confirmed by MINI for schizophrenia, who are acutely psychotic and hospitalized with PANSS score of 80 to 120 at time of enrollment, defined according to the inclusion/exclusion criteria. Subjects will receive flexible dose KarXT, whereby a subject receiving 100/20 (xanomeline 100 mg/trospium 20 mg) may be titrated upwards to KarXT 125/30 on Day 8. All subjects who are increased to 125/30 BID will have the option to return to KarXT 100/20, but may not change their dose after Visit 7 (Day 21) or decrease their dose for tolerability reasons more than once. The primary analysis will be executed on the mITT population, including all subjects with a baseline and at least 1 post-baseline PANSS measurement, grouped as randomized.

The variable is the change from baseline in PANSS total score at Week 5.

Intercurrent events:

- Discontinuation from study treatment prior to the completion of the 5 weeks of efficacy assessments: While on treatment strategy where efficacy results recorded prior to subject discontinuation from the study will be included in the analysis
- Use of concomitant medication for anxiety and/or sleep aid: Treatment policy strategy where results will be used regardless of concomitant medications for anxiety and/or sleep aid

The population level summary is the difference between treatment groups (KarXT vs placebo) in mean change from baseline in PANSS at Week 5, obtained from a mixed model repeated measures (MMRM).

Robustness of the estimand will be assessed through sensitivity analyses using alternative methods for handling of missing data and accounting for use of concomitant medications for anxiety and/or sleep aid (eg, subgroup by use of concomitant medication or including use of such concomitant medications as time-varying covariate in the MMRM).

14.4.2 **Analysis of the Primary Efficacy Endpoint**

The primary efficacy endpoint of the study is the change from baseline in PANSS total score at Week 5. The difference between KarXT and placebo at Week 5 will be estimated using an MMRM. The model will include the change from baseline PANSS total scores at Week 2, Week 3, Week 4, and Week 5 as the response. Within-subject correlation will be accounted for using an unstructured covariance matrix. Fixed effects will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit, site, age, sex, and baseline PANSS total score. Low-enrolling sites may be pooled, if necessary, for modeling purposes. The algorithm for pooling sites will be specified in the SAP.

Sensitivity analyses of the primary efficacy endpoint may be performed on an observed case basis, using multiple imputation techniques, and classifying treatment dropouts as treatment failures. Alternative time-varying parameterizations of dose level and use of concomitant medication for anxiety and/or sleep aid may also be included in sensitivity analyses. In addition, alternative covariance matrices for the MMRM may be investigated. The sensitivity analyses of the primary endpoint will be specified in the SAP.

14.4.3 **Analysis of Secondary Efficacy Endpoints**

The continuous secondary endpoints (change from baseline to Week 5 in PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S) will be analyzed in the same manner as the primary efficacy analysis (ie, using MMRM).

The categorical secondary endpoint (percentage of PANSS responders at Week 5) will be compared between the treatment groups (KarXT and placebo) using the Cochran-Mantel-Haenszel test.

The statistical analysis of the primary and key secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. This testing procedure will control the overall Type 1 error rate across all hypotheses/endpoints being tested.

14.5 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 study drug, treatment of event, and outcome.

Orthostatic 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 limits of the normal range at each time point by treatment group. Similar descriptive summaries will be provided for SAS, BARS, change in cognition (CANTAB), AIMS, body weight, BMI, and waist circumference.

14.6 Pharmacokinetic Analysis

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

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

PK parameters for xanomeline and trospium will be derived from plasma concentration data using noncompartmental methods. Actual time elapsed from dosing will be used to estimate all individual PK parameters. The primary PK parameters of interest will include C_{max}, T_{max}, and AUC from 0 to 12 hours (or from 0 to the last measurable concentration). Additional parameters (not limited to the following) such as the elimination half-life, clearance, and volume of distribution will be determined if the data permit.

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

14.7 Interim Analysis

No interim analysis is planned for this study.

14.8 Handling of Missing Data

Several different methods to handle the missing data in the primary efficacy endpoint analysis may be used.

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

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 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.

15.1.2 Independent Ethics Committee/Institutional Review Board

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

15.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal 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 principal 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 the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A caregiver informed consent (Ukraine only) should be obtained before any data pertaining to him or her and the subject is collected.

Subject Registry (for the US only):

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

At the screening visit, following informed consent and before any other study procedures, site staff that have received training and login information access (www.subjectregistry.com) to the database will enter the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts will be generated and should be printed for source documentation. The reports will detail each protocol violation detected and specific washout period dates where applicable. Participants who are identified as verification failures by CTS or VCT should not be enrolled without documented approval from Karuna or Syneos Health.

At the last subject contact, CTSdatabase and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on interactive response system (IXRS).

15.2 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 15.3.

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

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

15.3 Source Documents

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

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

Data recorded on source documents will be transcribed 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.

15.4 Record Retention

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

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

15.5 Monitoring

The study will be monitored according to the KAR-009 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 remote (telephone) or a combination and contacts will be made at appropriate times during the study. The Principal Investigator will assure him/her and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

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

15.6 Quality Control and Quality Assurance

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

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

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

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

15.7.2 Protocol Deviations

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

All protocol deviations will be tracked in the Clinical Trial Management System. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

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

15.8 Ethical Considerations

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

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

15.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

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

15.10 Publication Policy/Disclosure of Data

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

16 REFERENCES

1. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *P T*. 2014;Sep 39(9):638-645.
2. van Os J, Kapur S. Schizophrenia. *Lancet.* 2009 Aug 22;374(9690):635-645.
3. Wu EQ, Shi L, Birnbaum H, Hudson T, Kessler R. Annual prevalence of diagnosed schizophrenia in the USA: a claims data analysis approach. *Psychol Med*. 2006 Nov;36(11):1535-1540.
4. Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, New York: McGraw-Hill; 2014:1019–1046.
5. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. 2004;72(1):41-51.
6. Huhn M, Nikolakopoulou A, Schnider-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.
7. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
8. 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.
9. Emsley R, Chiliza B, Asmal L, Harvey BH. The nature of relapse in schizophrenia. BMC Psychiatry. 2013;13:50.
10. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. *Nat Rev Dis Primers*. 2015;1:15067.
11. Sellin AK, Shad M, Tamminga, C. Muscarinic agonists for the treatment of cognition in schizophrenia. *CNS Spectr.* 2008 Nov;13(11):985-996.
12. Wess J, Eglen RM, Gautam D. Muscarinic acetylcholine receptors: mutant mice provide new insights for drug development. *Nat Rev Drug Discov.* 2007 Sep;6:(9):721-733.
13. Mirza NR, Peters D, Sparks RG. Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. *CNS Drug Rev.* 2003 Summer;9(2):159-186.
14. Thorn CA, Moon J, Bourbonais CA, 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(8):3910.
15. 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.
16. Bodick NC, Offen WW, Levey AI, et al. Effect of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol*. 1997;54(4):465-473.

17. Bodick NC, Offen WW, Shannon HE, et al. The selective muscarinic agonist xaqnomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer's disease. *Alzheimer Dis Assoc Disord*. 1997; 11 Suppl 4:S16-22.

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

19. Staskin D, Sand P, Zinner N, Dmochowski R, Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder; results from a multicenter phase III trial. *J Urol*. 2007;178(3 Pt 1):978-983; discussion 983-984.

20. Scheife R, 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.

21. Brannan SK, Paul SM and Breier A. Xanomeline plus trospium: A novel strategy to enhance pro-muscarinic efficacy and mitigate peripheral side effects. Proceedings of the ASCP annual meeting 2019.

22. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

23. Guy W. EDCEU Assessment Manual for Psychopharmacology – Revised. Rockville, MD, US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976:534-7. DHEW Publication No ADM 76-338.

24. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophrenia Bulletin. 2005 Jan;31(1):5-19.

25. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989 May;154 (5):672–676.

26. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007 Jul;164(7):1035-1043.

27. Chatoor D, Emmanuel A. Constipation and evacuation disorders. *Best Pract Res Clin Gastroenterol*. 2009;23(4):517–530.

28. Constipation. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/digestive-diseases/constipation/all-content. February 2015. Accessed 28 Mar 2020.

29. American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medicalposition statement on constipation. *Gastroenterology*. 2013 Jan;144(1):211–217.

30. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology.* 2006 Apr;130(5):1480–1491.

31. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997 Sep;32(9):920–924.

32. Locke GR III, Pemberton JH, Phillips SF. American Gastroenterological Association Medical Position Statement: guidelines on constipation. *Gastroenterology*. 2000 Dec;119(6):1761–1766.

33. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 27 Mar 2020.

17 APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

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

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

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

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

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant before receiving study drug on Day 1 and continuing until 30 days after the last dose of study drug. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

APPENDIX 2. FUNCTIONAL CONSTIPATION INQUIRY

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

Symptoms ≥3 months; onset ≥6 months before diagnosis

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

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

[a] ≥25% of defecations.

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

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

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

2 Bristol Stool Form Scale