[redacted]

STATISTICAL ANALYSIS PLAN

STUDY SPONSOR:	Karuna Therapeutics 33 Arch Street Suite 3110 Boston, MA 02110 Tel: (857) 449-2244 Email: info@karunatx.com
SPONSOR REPRESENTATIVE:	[redacted] MD, [redacted] 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-007
PROTOCOL VERSION AND DATE:	Version 1.4: 09 August 2021
NAME OF TEST DRUG:	KarXT
PHASE:	Phase 3
METHODOLOGY:	Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter
ANALYSIS PLAN DATE:	28 June 2022
ANALYSIS PLAN VERSION:	Version 3.0
AUTHOR:	[redacted]

[redacted]

APPROVAL 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
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[redacted]

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

[redacted]

[redacted]

TABLE OF CONTENTS

Section **Page**

Section **Page**

TABLES INCLUDED IN THE TEXT

Page

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of Covariance
ATC	Anatomic therapeutic chemical class
AUC	Area under the concentration versus time curve
BARS	Barnes Akathisia Rating Scale
BID	Twice daily
BMI	Body Mass Index
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
C_{max}	Maximum plasma concentration
CGI-S	Clinical Global Impression–Severity
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
DILI	Drug induced liver injury
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	12-lead electrocardiogram
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMC	Independent Safety Monitoring Committee
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
LS	Least Squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Model Repeated Measures
mITT	Modified Intent-to-Treat
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PANSS	Positive and negative syndrome scale
PK	Pharmacokinetic
PMM	Pattern Mixture Models

Abbreviation	Definition
PP	Per-Protocol
PT	Preferred term
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SNP	Single nucleotide polymorphism
SOC	System organ class
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
WBC	White blood cell (count)

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

This document presents the statistical analysis plan (SAP) for Study KAR-007, 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 Diagnostic and Statistical Manual–Fifth Edition (DSM-5) Schizophrenia. This SAP is based upon protocol version 1.4 dated 09 August 2021.

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this study.

In addition, the SAP is intended to clarify many of the details of the more limited discussion in the statistical section of the protocol. Therefore, the SAP will expand on and may modify the plans outlined in the study protocol. If changes are made to the plans outlined in the protocol, the SAP will supersede the relevant contents of the protocol.

1.1.2. Study Objectives

1.1.2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of KarXT 125/30 (125 mg xanomeline, 30 mg trospium) twice daily (BID) versus placebo in reducing Positive and Negative Syndrome Scale (PANSS) total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia.

1.1.2.2. 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 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 improvement in Clinical Global Impression–Severity (CGI-S) results in subjects treated with KarXT versus placebo

- To evaluate the percentage of subjects seeing a 30% reduction in PANSS total 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

[redacted]

- [redacted]
- [redacted]
- [redacted]

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a 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, designed to test the hypothesis that treatment with KarXT will result in significantly greater reduction (ie, improvement) in PANSS total score 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.

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.

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 adverse events (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.

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.

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.

1.2.2. Randomization Methodology

On Day -1, all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups. Up to 246 subjects are planned to be randomized (123 per group).

Randomization will be stratified by site. Although the randomization will target balance by site, this does not guarantee balance overall; however, with sufficient sample size within each site, balance should be maintained.

Subjects will be assigned a randomization number through the interactive web response system (IWRS) in accordance with the randomization code generated by the authorized personnel at [redacted] 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. [redacted] will generate and maintain the security of the randomization code.

1.2.3. Stopping Rules and Unblinding

The availability of any new adverse safety information related to KarXT may result in stopping of the study. An Independent Ethics Committee (IEC) / Institutional Review Board (IRB) or the Sponsor either on its own or on the recommendation of the Independent Safety Monitoring Committee (ISMC), may take such actions. An investigator may take such actions at their own site.

The safety and tolerability aspects of KarXT will be overseen by an Independent Safety Monitoring Committee (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 may recommend to the Sponsor whether to:

a. Continue the clinical study without modification

b. Continue the clinical study with modification

c. Terminate the study

At a subject level, based on National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0, study drug will be discontinued in any subject who has a ≥ Grade 4 AE. [redacted]

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 electronic case report form (CRF). Otherwise, unblinding according to the protocol will occur only after completion of the study.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 2.

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	

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	
Spontaneous AEs[f]		X	X	X	X	X	X	X	X	X	X	X	X
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
[redacted]													
Blood sample for viral serology[l]	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	
[redacted]													
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	

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	
C-SSRS[s]	X	X			X		X	X	X		X	X	X
CGI-S Scale	X	X			X		X	X	X		X		
[redacted]													
Simpson-Angus Rating Scale		X			X		X	X	X		X	X	
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 protocol Table 3 for individual laboratory tests. For urinalysis, a urine dipstick will be performed at the site and the sample will be sent to central lab in case of abnormalities.
j. Optional COVID-19 test may be performed at unscheduled visits at the Investigator's discretion.
[redacted]
l. 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.
[redacted]
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 drawn 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.

[redacted]

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.

1.2.5. Efficacy, Pharmacokinetic, and Safety Endpoints

1.2.5.1. Efficacy Endpoints

The primary efficacy endpoint is change from baseline in PANSS total score at Week 5.

The secondary efficacy endpoints are:

- 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
- Change from baseline in CGI-S score at Week 5
- Percentage of PANSS responders (at least 30% reduction in PANSS total score) at Week 5

1.2.5.2. Pharmacokinetic Endpoints

The pharmacokinetic endpoints are:

- Area under the plasma concentration-time curve (AUC)
- Maximum observed plasma concentration (C_{max})
- Time to maximum observed plasma concentration (T_{max})

Blood samples for PK analysis of KarXT levels will be collected at the time points indicated in the Schedule of Assessments (Table 2). Pharmacokinetic parameters to be determined 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.

1.2.5.3. Safety Endpoints

The safety endpoints are:

- Spontaneously reported AEs including adverse events of special interest (AESIs)
- Spontaneously reported procholinergic and anticholinergic symptoms
- Simpson-Angus Scale
- 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): 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 the Columbia Suicide Severity Rating Scale (C-SSRS)

2. ANALYSIS POPULATIONS

2.1. Population Definitions

The following analysis populations will be evaluated and used for presentation and analysis of the data:

- 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 post-baseline PANSS assessment will be included in the mITT population and will be used in the efficacy analysis.
- Completer Population: All mITT subjects who have a valid PANSS total score at Week 5. The Completer population will be used for a sensitivity analysis of the primary efficacy endpoint.
- Per-Protocol Population (PP): All subjects who were randomized, received at least one dose of study medication, have a baseline and at least one post-baseline PANSS assessment, and have no major protocol deviations. The PP population will be used for a sensitivity analysis of the primary efficacy endpoint.
- 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 mITT population is the primary population for the analysis of efficacy parameters. The PK population is the primary population for the analysis of PK parameters. The Safety population is the primary population for the analysis of safety parameters. Efficacy analyses will be conducted based on treatment as randomized while safety analyses will be conducted based on treatment received.

2.2. Protocol Violations

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 CSR. 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 for the ITT population. All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Assuming treatment difference of 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 (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.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the 2-sided, 0.05 level of significance. Summary statistics will be presented, as well as the confidence intervals (CIs) on selected parameters, as described in sections below.

3.3. Computing Environment

Unless otherwise noted, all descriptive statistical analyses will be performed using [redacted]. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary version March 2018 or newer. CDISC database will conform to SDTM Implementation Guide 3.2 and ADaM Implementation Guide 1.1

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug. If multiple values are present for the same date, the values from the last assessment will be used as the baseline unless otherwise specified.

3.5. Methods of Pooling Data

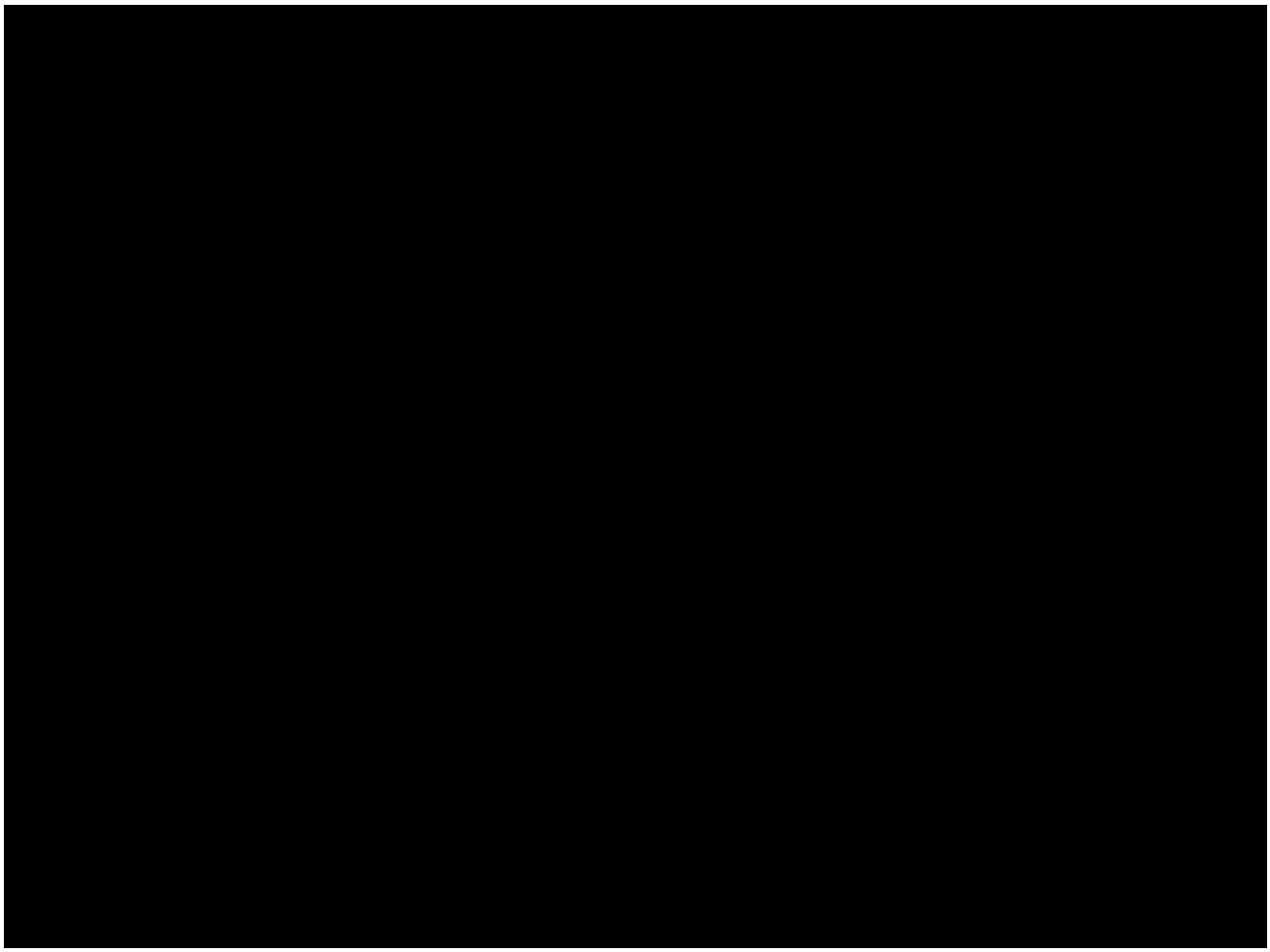
For analyses not stratified by site, data from all study centers will be combined. For analyses stratified by site, study centers with two or fewer subjects of any treatment group will be pooled and considered as one 'Other' site in the analysis.

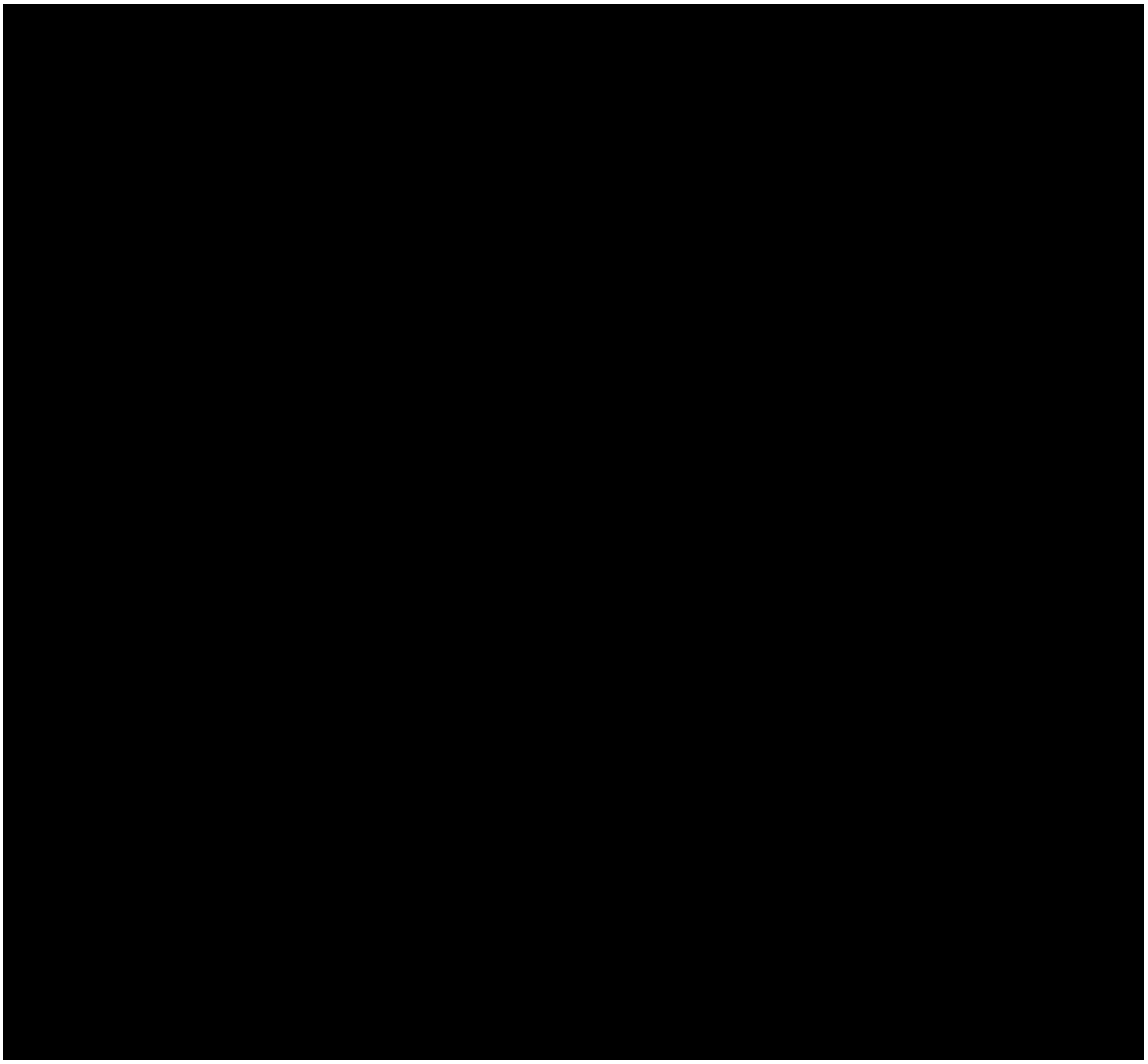
3.6. Adjustments for Covariates

The analysis of the primary and continuous secondary efficacy endpoints will be adjusted for site, age, and gender (male versus female). Sites may be pooled as noted in the previous section. Details are provided in the relevant efficacy analysis section.

3.7. Multiple Comparisons/Multiplicity

In order to account for multiplicity, the Sponsor has pre-specified a step-down procedure (hierarchical order of testing) to control the overall Type-1 error rate across all primary and secondary efficacy endpoints. The secondary endpoints are presented according to the Sponsor-specified hierarchical order in Section 4.3.3.





3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

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

- For the primary efficacy analysis, a 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 (LOCF). In this analysis, the missing values will be replaced by the last available 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).

When tabulating AE data, partial dates will be handled to more accurately determine whether an event was treatment-emergent.

AE start dates that are missing or incomplete will be handled as follows:

(1) Missing Day Only

- If the month and year are the same as the month and year of the first dose date, the first dose date will be used.

- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.

- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2) Missing Day and Month

- If the year is the same as the year of the first dose date, the first dose date will be used.

- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.

- If the year is after the year of first dose date, January 1 will be assigned to the missing fields.

(3) Missing Day, Month, and Year

- The first dose date will be used.

If the stop date is non-missing and the imputed start date is after the reported stop date, the stop date will be used as the start date. If the stop date is missing and the imputed start date if after a patient's date of discontinuation, the date of discontinuation will be used.

AE stop dates that are missing or incomplete will be handled as follows:

(1) Missing Day Only

- The last day of the month will be assigned as the missing day.

(2) Missing Day and Month

- December 31 will be assigned to missing fields.

(3) Missing Day, Month, and Year

- The event will be regarded as ongoing.

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

3.11. Visit Windows

All data will be tabulated per the evaluation visit as recorded on the CRF, even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. Note, if the circumstance arises where an unscheduled or additional visit falls within two separate nominal visit windows (see for Example Day 7 and Day 8 in the Schedule of Assessments), the unscheduled or additional visit will be considered for the earlier of the two nominal visits.

3.12. Interim Analyses

No interim analysis is planned for this study.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and will include the number screened, the number randomized, the number treated in total, the number dosed with KarXT, the number dosed with placebo, the number in each analysis population, the number of subjects who completed treatment, and the number who withdrew prior to completing treatment and reason(s) for withdrawal. Subject disposition will be summarized by treatment and overall.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented. Subject disposition will include all patients screened.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented by treatment group and overall. Age, height, weight, and BMI at baseline will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). The number and percentage of subjects in each gender, ethnicity, race category, and child-bearing potential status will also be presented. Subject demographics and baseline characteristics will be summarized for each of the ITT, mITT, and Safety populations. Subject demographics and baseline characteristics will also be presented in by-patient listings.

Medical history will be summarized in a table by MedDRA System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall for the ITT population. A by-patient listing of medical history will also be provided.

4.3. Efficacy Evaluation

4.3.1. Primary Estimand

The primary clinical question of interest is: *What is the treatment effect of KarXT vs placebo at Week 5 on the change from baseline in PANSS total score in qualified subjects as defined in entry criteria, regardless of treatment discontinuations for any reason?*

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 100mg/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) nor 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 one 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: Hypothetical strategy assuming subjects that discontinue study treatment prior to study discontinuation would follow the same trend as subjects who continued and remained in the study for the full 5 weeks. Data collected up to the point of treatment discontinuation 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 as is customary in trials of acute Schizophrenia.

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 with 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 (e.g. subgroup by use of concomitant medication).

4.3.2. Analysis of the Primary Efficacy Endpoint

The PANSS is a medical scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy. 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. PANSS total score is the sum of all 30 items with a minimum score of 30 and a maximum score of 210. Higher scores indicate more severe symptoms. If a patient has a PANSS assessment recorded, but any of the 30 items are missing, that value will be imputed with the average of the non-missing items with a given domain as follows:

- If no more than 2 items are missing from the PANSS positive scales, then the PANSS Positive Score will be calculated as the average of the non-missing items multiplied by 7.
- Similarly, if no more than 2 items are missing from the PANSS negative scales, then the PANSS Negative Score will be calculated as the average of the non-missing items multiplied by 7.
- If no more than 4 items are missing from the general psychopathology symptom scales, then the score will be calculated as the average of the non-missing items multiplied by 16.

- The PANSS Total Score is then the sum of the positive, negative and general psychopathology symptom scores.

If any of the above thresholds for calculating the PANSS Positive Score, PANSS Negative Score, or the general psychopathology symptom scales (> 30% of the items missing in a given domain at a particular visit), the respective total score at the visit will not be calculated and will be treated as missing data.

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 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. The treatment difference at Week 5 will be estimated using contrasts. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Site, age, gender, and baseline PANSS total score will be used as covariates in the model. Low enrolling sites will be pooled as outlined in Section 3.5.

An unstructured covariance structure will be utilized for the MMRM analysis. The denominator degrees of freedom will be computed using the Kenward-Roger method. In the event that the model does not converge with the unstructured covariance structure, the sandwich variance estimator in combination with the following covariance structures will be attempted in the following, pre-specified order: heterogeneous Toeplitz structure (TOEPH), heterogeneous compound symmetry (CSH).

The least squares (LS) mean, standard error (SE), and LS mean difference between KarXT and placebo group at Week 5 along with the 95% CI will be provided. The p-value for the hypothesis testing will also be provided. Treatment difference will be assessed with a 2-sided alpha level of 0.05.

Observed values and change from baseline in PANSS total score will also be summarized by visit. LS mean, SE, 95% CI, and p-value for LS mean difference from the primary MMRM will also be provided for Week 2, Week 3, and Week 4.

The mITT population will be used for the primary efficacy analysis. Observed and change from baseline PANSS total score will also be summarized by treatment group and visit for the mITT population using descriptive statistics.

Estimated mean change from baseline PANSS total score will be graphed by treatment group and visit. The x-axis will include the week (Week 2, Week 3, Week 4, Week 5) and the y-axis will represent change from baseline. LS means estimates and associated standard error bars from the primary MMRM will be used for the display.

Sensitivity analyses will be performed as outlined in Section 4.3.4.

A by-patient listing will also be provided.

4.3.3. Analysis of Secondary Efficacy Endpoints

Statistical testing will be performed on the secondary efficacy endpoints according to the following hierarchical order:

1) Change from baseline in PANSS positive score at Week 5
2) Change from baseline in PANSS negative score at Week 5
3) Change from baseline in PANSS Negative Marder Factor score at Week 5
4) Change from baseline in CGI-S score at Week 5
5) Percentage of PANSS responders (at least 30% reduction in PANSS total score) at Week 5

The efficacy tests will stop if the previous test shows no statistical significance in favor of KarXT at the alpha level of 0.05.

4.3.3.1. Change from Baseline in PANSS Positive Score at Week 5

PANSS positive score is the sum of all PANSS 7 positive symptom scales with a minimum score of 7 and a maximum score of 49. If a patient has a PANSS assessment recorded and no more than 2 items are missing from the PANSS positive scales, then the PANSS Positive Score will be calculated as the average of the non-missing items multiplied by 7. If 3 or more items are missing (> 30%) at a particular visit, the respective positive score at the visit will not be calculated and will be treated as missing data.

The PANSS positive score will be analyzed using a model similar to the MMRM used for the primary endpoint.

The model will include the observed change from baseline PANSS positive score at Week 2, Week 3, Week 4, and Week 5 as the response. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Baseline PANSS positive score, site, age, and gender will be used as covariates in the model.

Observed and change from baseline PANSS positive scores will be summarized descriptively by treatment group and visit for the mITT population.

Estimated mean change from baseline PANSS positive score will be graphed by treatment group and visit. The x-axis will include the week (Week 2, Week 3, Week 4, Week 5) and the y-axis will represent the change from baseline. LS means estimates from the MMRM will be used for the display.

4.3.3.2. Change from Baseline in PANSS Negative Score at Week 5

PANSS negative score is the sum of all PANSS 7 negative symptom scales with a minimum score of 7 and a maximum score of 49. If a patient has a PANSS assessment recorded, and no more than 2 items are missing from the PANSS negative scales, then the PANSS Negative Score will be calculated as the average of the non-missing items multiplied by 7. If 3 or more items are missing (> 30%) at a particular visit, the respective negative score at the visit will not be calculated and will be treated as missing data.

The PANSS negative score will be analyzed using a model similar to the MMRM used for the primary endpoint.

The model will include the observed change from baseline PANSS negative score at Week 2, Week 3, Week 4, and Week 5 as the response. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Baseline PANSS negative score, site, age, and gender will be used as covariates in the model.

Observed and change from baseline PANSS negative scores will be summarized descriptively by treatment group and visit for the mITT population.

Estimated mean change from baseline PANSS negative score will be graphed by treatment group and visit. The x-axis will include the week (Week 2, Week 3, Week 4, Week 5) and the y-axis will represent the change from baseline. LS means estimates from the MMRM will be used for the display.

4.3.3.3. Change from Baseline in PANSS Negative Marder Factor Score at Week 5

PANSS Marder factor score is the sum of 5 negative scales and 2 general scales (N1. Blunted affect; N2. Emotional withdrawal; N3. Poor rapport; N4. Passive/apathetic social withdrawal; N6. Lack of spontaneity; G7. Motor retardation; and G16. Active social avoidance). If a patient has a PANSS assessment recorded, but any of the 7 items are missing, that value will be imputed with the average of the non-missing items with a given domain as follows:

- If no more than 1 item is missing from the considered PANSS negative scales, then the sum of the considered PANSS negative scales will be calculated as the average of the non-missing items multiplied by 5.

If 2 or more items are missing (> 30%) from the considered PANSS negative scales or 1 or more items are missing (> 30%) from considered general scales at a particular visit, the respective PANSS Negative Marder Factor at the visit will not be calculated and will be treated as missing data.

The PANSS Marder Factor score will be analyzed using a model similar to the MMRM used for the primary endpoint.

The model will include the observed change from baseline PANSS negative marder factor score at Week 2, Week 3, Week 4, and Week 5 as the response. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Baseline PANSS negative marder factor score, site, age, and gender will be used as covariates in the model.

Observed and change from baseline PANSS Marder factor scores will be summarized descriptively by treatment group and visit for the mITT population.

Estimated mean change from baseline PANSS negative marder factor score will be graphed by treatment group and visit. The x-axis will include the week (Week 2, Week 3, Week 4, Week 5) and the y-axis will represent the change from baseline. LS means estimates from the MMRM will be used for the display.

4.3.3.4. Change from Baseline in CGI-S Score at Week 5

The CGI-S categorizes the severity of the illness as: 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = Among the most extremely ill patients.

CGI-S will be analyzed using a model similar to the MMRM used for the primary endpoint.

The model will include the observed change from baseline CGI-S score at Week 1, Week 2, Week 3, Week 4, and Week 5 as the response. The MMRM will include the treatment group (KarXT or placebo), visit, and the interaction between the treatment group and visit as fixed factors. Baseline CGI-S score, site, age, and gender will be used as covariates in the model.

CGI-S scores at Week 5 will also be compared using the Mann-Whitney U (Wilcoxon Rank Sum) Test. The results of the Mann-Whitney U (Wilcoxon Rank Sum) Test will not be considered for hierarchical testing purposes.

Observed and change from baseline CGI-S scores will be summarized descriptively by treatment group and visit for the mITT population.

Estimated mean change from baseline CGI-S score will be graphed by treatment group and visit. The x-axis will include the week (Week 2, Week 3, Week 4, Week 5) and the y-axis will represent the change from baseline. LS means estimates from the MMRM will be used for the display.

CGI-S scores will also be summarized by visit using frequency counts for the mITT population.

In addition, shift tables from Baseline to worst value and at each scheduled post-Baseline visit will be provided by treatment group. A by-patient listing will also be provided.

4.3.3.5. Percentage of PANSS Responders at Week 5

A PANSS responder is defined as a subject with reduction from baseline of at least 30% (at least a 30% improvement) at Week 5 in the PANSS total score.

The percent of PANSS responders at each visit will be compared between the treatment groups (KarXT and placebo) using the Cochran-Mantel-Haenszel test stratified by site.

Percentage of PANSS responders at each visit will also be graphed by treatment group and visit. The x-axis will include the visit and the y-axis will represent the percentage of responders.

Since the minimum baseline PANSS total score is not 0 (30 when PANSS rated as 1-7 for each item), the response rate based on this score tends to be underestimated. Thus, a floor adjusted PANSS total score, defined as the original total score minus 30, will also be used to derive the responders. The PANSS responders based on floor adjusted PANSS total score will be analyzed and presented using the same methods as described above.

4.3.4. Sensitivity Analyses

Completer Analysis:

The primary efficacy analysis will be repeated for the Completer population.

Per Protocol Analysis:

The primary efficacy analysis will be repeated for the PP population.

Last Observation Carried Forward (LOCF):

In this analysis, the missing PANSS total scores will be replaced by the most-recent post-baseline visit assessment values. The values at Week 5 generated via LOCF will be compared using an Analysis of Covariance (ANCOVA) model with treatment group as a fixed factor and baseline PANSS total score and site will be used as a covariate in the model. This analysis will be performed in the mITT population.

Multiple Imputation (MI) Analysis with Missing At Random Assumption:

Multiple Imputation is a broadly applicable technique for handling missing data. Missing data are imputed multiple times using a regression method. Each imputed data set is analyzed by the MMRM model, and the point estimates and standard errors are combined to provide inferences that reflect the uncertainty about the missing values. MI will assume that data are missing at random (MAR).

Primary endpoint data that are missing will be multiply imputed separately for each treatment arm using a regression procedure within SAS PROC MI, with baseline value, Week 2, Week 3, and Week 4 as explanatory variables, and Week 5 as the dependent variable. The regression method assumes monotone missingness, such that if a given visit has a missing value, all subsequent

visits are missing as well. For non-monotone missing data, the Monte Carlo Markov Chain (MCMC) method in PROC MI will be used to impute intermittent missing data so that each imputed dataset has a monotone missing pattern. The proportion of non-monotone missing data is expected to be very small. One hundred imputed datasets (per treatment arm) will be generated from the MCMC method. The regression method is then used to impute missing values having a monotone missingness pattern.

Each of the imputed datasets will then be analyzed via the MMRM and the resulting estimates (LS means and standard errors) combined using SAS PROC MIANALZYE to produce inferential results (difference in LS means, 95% CI for the difference, and the pvalue from the test that the difference is zero). Point estimates (LS means and differences) will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details).

http://support.sas.com/documentation/onlinedoc/stat/143/mianalyze.pdf.

Analyses will be conducted using PROC MI and PROC MIANALYZE in SAS 9.4 (or later).

MI analysis with Missing Not At Random assumption (Placebo group based imputation):

Another MI analysis will be performed with the assumption that the data is not missing at random. Methods similar to the procedure described above will be used in the mITT population. However, the missing values will be imputed using Placebo based imputation. Placebo based imputation assumes that the trajectories of all subjects are assumed to follow the trajectory of those subjects in placebo group.

MI analysis with Missing Not At Random assumption (Tipping point based imputation):

If the primary analysis significantly favors KarXT, another MI analysis may be performed in the mITT population with the assumption that the data in the KarXT group is not missing at random. A tipping point based assumption will be used, i.e. the trajectories of the subjects in the KarXT group after withdrawal are assumed to be worse by a certain amount, delta. After the MI using the MAR assumption, as defined above, has been done, the amount, delta, will be added to each imputed value in the KarXT group. Successively harsher deltas will be imposed on the imputed values in the KarXT group, starting with a PANSS total score increment (worsening) of 0.5 points. The delta is further increased in subsequent steps of 0.5 points (1.0, 1.5, 2.0, …) until the statistical significance is lost, i.e. until the p-value becomes >0.05. For the placebo group, the MI using MAR assumption will be used.

[redacted]

4.5. Pharmacokinetic Evaluations

PK analysis will be conducted by the Sponsor designee and analysis will be specified in another document. However, PK results will be listed for all subjects who received active treatment and the data will be presented graphically via individual plots and mean plots summarized by actual treatment, visit, and timepoint. The profiles or time points obtained with protocol deviations affecting PK results will be flagged and may be excluded from summary figures.

4.6. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.6.1. Study Drug Exposure and Treatment Compliance

Drug exposure and treatment compliance have previously been seen to have an influence on the total PANSS score.

To get a better understanding of drug exposure, treatment duration in days, cumulative dose taken in mg, and the number of subjects experiencing a dose reduction will be summarized by treatment group. By-patient listings will also be provided.

Treatment duration in days will be calculated as the number of days subjects were administered study drug as determined below:

Treatment duration (days) = last treatment date – first treatment date + 1

To get a better understanding of treatment compliance, the number of planned doses, the number of doses actually taken, compliance (%), and the number of doses missed will be summarized by treatment group. By-patient listings will also be provided.

Treatment compliance (%) will be calculated as determined below:

Compliance (%) = (number of doses taken/number of planned doses)*100

4.6.2. Spontaneous Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables by treatment received and in data listings using SOC and PT. AE grade assessment will be based on investigator reporting using NCI-CTCAE, version 5.0.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the administration of study medication through the end of the study (28 days after last dose administered), or any event that was subsequently considered drug-related by the Investigator through the end of the study.

The number and percentage of subjects with any treatment-emergent adverse event (TEAE), with any TEAE event assessed by the Investigator as related to treatment (definite, probable, or possible relationship), with any serious TEAE, with any serious related TEAE, with any TEAE leading to study drug withdrawal with any TEAEs, with a NCI-CTCAE grade of 3 or higher, with a TEAE leading to dose reduction, and with any TEAE leading to death will be summarized by treatment group and overall.

AESIs will be monitored and will include orthostasis and liver function test elevations inclusive of DILI. The number and percentage of subjects with an AESI, with a related AESI, with a serious AESI, and with an AESI of NCI-CTCAE grade 3 or higher will be summarized by treatment group and overall.

Procholinergic symptoms (believed to be associated with xanomeline) and anticholinergic symptoms (believed to be associated with trospium) will also be identified. The number and

percentage of subjects with treatment-emergent procholinergic and anticholinergic symptoms will also be summarized by treatment group and overall.

In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

All AEs occurring on-study will be listed in by-patient listings. Listings will also be provided for the following: drug product related TEAEs, Serious TEAEs, drug product related serious TEAEs, TEAEs leading to study drug withdrawal, events of special interest, procholinergic symptoms, anticholinergic symptoms, and deaths.

4.6.3. Simpson-Angus Scale

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

Observed and change from baseline Simpson-Angus Rating Scale total score, subscale score [Simpson-Angus Rating Scale Total Score (Excluding Item 10)], and individual item scores will be summarized by treatment group and visit for the Safety population. A by-patient listing will be provided.

4.6.4. Barnes Rating Scale for Akathisia

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

Observed and change from baseline BARS and the four individual scores will be summarized by treatment group and visit for the Safety population. A by-patient listing will be provided.

4.6.5. Abnormal Involuntary Movement Scale (AIMS)

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

Observed and change from baseline for AIMS total score (items 1-7, observed movements), Item 8 (overall severity index), Item 9 (incapacitation), and Item 10 (awareness) will be summarized by treatment group and visit for the Safety population. A by-patient listing for all items will be provided.

4.6.6. Body Weight, Body Mass Index, Waist Circumference

Observed, change from baseline, and percentage change from baseline in body weight as well as the percentage of subjects who have gained or lost weight (+/- 7 percent from baseline body weight) will be summarized by treatment group and visit.

BMI, and waist circumference will be summarized by treatment group and visit. Male subjects with a waist circumference of greater than 102 cm and female subjects with a waist circumference of greater than 88 cm will also be summarized by treatment group and visit.

By-subject listings will be provided.

4.6.7. Orthostatic Vital Signs

Observed and change from baseline in orthostatic vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) will be summarized by treatment group, position (supine, standing) and visit. The difference between supine and standing measurements will also be summarized. A by-subject listing will be provided.

4.6.8. Laboratory Data

Clinical laboratory values will be presented using the International System of Units (SI). Values will be normalized against normal ranges from a common source (US National Library of Medicine [NLM], MedlinePlus) as outlined in Section 6 according to the following Scale Model formula (Karvanen):

$$s = x \frac{Us}{Ux}$$

where s = the individual laboratory value normalized against the laboratory normal range from the common source; x = the original individual laboratory value; Ux is the upper limit of the normal range for an individual laboratory parameter; Us is the upper limit of the laboratory normal range for that laboratory parameter from the common source. If NLM ranges are unavailable as a common source for a given parameter, official [redacted] reference ranges will be utilized.

Clinical laboratory parameters include:

Hematology

Full and differential blood count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, white blood cell (WBC) count with differential

Serum Chemistry

Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, uric acid, blood urea nitrogen or urea, carbon dioxide, creatinine, creatine kinase and subtypes, electrolytes (sodium, potassium, chloride, calcium, phosphorous), gamma-glutamyl transferase, glucose, lactate dehydrogenase, total bilirubin, direct bilirubin, total cholesterol, triglycerides, total protein

Coagulation

Prothrombin time, activated partial thromboplastin time, fibrinogen

Urine Analysis (Dipstick)

Appearance, pH, protein, glucose, ketone bodies, indicators of blood and WBCs, specific gravity, urobilinogen, occult blood, WBCs

Serology

HBV, HCV, HIV

Other

COVID-19

The observed and change from baseline to each visit will be summarized for each clinical laboratory parameter by treatment received, if applicable. In the event of repeat values, the last non-missing value will be used.

The frequency of patients with abnormal safety laboratory parameters (Hematology, Chemistry, Coagulation) will be tabulated by treatment received.

Shift tables of change in NCI-CTCAE grade of laboratory parameters from baseline to worst on-study values will be presented for hematology, chemistry, and coagulation by treatment received, if applicable. If multiple values are equal and qualify for the worst on-study value for a given laboratory parameter, the earliest of the values will be considered. Shift tables of urinalysis results will be provided.

The number and percentage of subjects in each treatment group with an elevated alanine aminotransferase level (>3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN), an elevated aspartate aminotransferase (>3 x ULN, >5 x ULN, >8 x ULN, >10 x ULN, >20 x ULN), an elevated alkaline phosphatase (>1.5 x ULN, > 2 x ULN), an elevated total bilirubin (>1.5 x ULN, >2 x ULN), or an elevated gamma-glutamyl transferase (>2 x ULN) will be presented by study visit and treatment received. A listing of subjects who meet the criteria for Hy's law will also be provided where Hy's law is defined as an elevated alanine aminotransferase level (>3 x ULN) or an elevated aspartate aminotransferase (>3 x ULN) in combination with alkaline phosphatase <2 x ULN and elevated total bilirubin (>2 x ULN).

The number and percentage of subjects in each treatment group with an elevated glucose level ($\geq$ 100 mg/dL), an abnormal shift in glucose level (thresholds of 10.0%, 25.0%, and 50.0% in either direction), an elevated total cholesterol ($\geq$ 200 mg/dL), an abnormal shift in total cholesterol (thresholds of 10.0%, 25.0%, and 50.0% in either direction), an elevated triglycerides ($\geq$ 150 mg/dL), or an abnormal shift in triglycerides (thresholds of 10.0%, 25.0%, and 50.0% in either direction) will be presented by study visit and treatment received. A listing presenting the all of the laboratory values for aforementioned parameters for all subjects meeting at least one of the aforementioned criteria will be provided.

In the event of lab disruptions due to COVID-19, additional analyses may be conducted to investigate any impact in an ad-hoc fashion if deemed appropriate.

All laboratory data, including pregnancy tests, urine drug screens, and alcohol test results, will be provided in by-patient listings.

4.6.9. Electrocardiograms

ECG results for ventricular rate, PR, QRS, QT, and QTcF will be summarized descriptively by visit and treatment received and the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results will be provided. The overall interpretation will also be summarized by visit and treatment received. A by-patient listing will be provided.

4.6.10. Physical Examination

Results of the physical examination will be presented by visit and treatment received. A by-patient listing will also be provided.

4.6.11. Columbia-Suicide Severity Rating Scale

The C-SSRS is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. The frequency and percentage of subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized as appropriate by visit and treatment received. A by-patient listing will also be provided.

4.6.12. Prior and Concomitant Medications

Prior medications are defined as any medications with a start date prior to first dose date.

Prior medication use will be summarized using the Anatomical Therapeutic Chemical Class level 2 (ATC2) and preferred term by treatment received.

Concomitant medications are defined as medications either ongoing at the time of first dose date or which start on or after the first dose date but before drug discontinuation. A medication may be considered both prior and concomitant.

Concomitant medication use will be summarized using ATC2 and preferred term by treatment received.

The use of prior and concomitant medications will be presented in a by-patient listing.

[redacted].

4.6.14. Mini International Neuropsychiatric Interview (MINI) 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.

Available results from the MINI will be presented in by-patient listings.

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