Statistical Analysis Plan for Interventional Studies

Sponsor Name: Karuna Pharmaceuticals, Inc.

Protocol Number: KAR-004

Protocol Title: A Phase 2, Randomized, Double-blinded Study to Assess the Safety, Tolerability, and Efficacy of KarXT in Hospitalized Adults with DSM-5 Schizophrenia

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I confirm that I have reviewed this document and agree with the content.

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Table of Contents

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1. Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BLQ	Below the Limit of Quantification
BMI	body mass index
CI	confidence interval
CGI-S	Clinical Global Impression–Severity
CM	concomitant medication
C_{max}	maximum observed plasma concentration
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head/eyes/ears/nose/throat
ICF	informed consent form
ICH	International Conference on Harmonization
ISMC	Independent Safety Monitoring Committee
IWRS	interactive web response system
LLOQ	lower limit of quantification
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MI	multiple imputation
Min	minimum
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
N/A	not applicable
NA	not applicable
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic
PT	preferred term
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	standard international system of units
SOC	System Organ Class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TLF	table, listing and figure
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

CCI will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

The primary objective of the study is to assess 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.

3.2. Secondary Objectives

The secondary objectives of the study are to assess overall safety and tolerability of KarXT in adult inpatients with a DSM-5 diagnosis of schizophrenia:

- To assess spontaneously reported adverse events (AEs) in subjects treated with KarXT versus placebo
- To assess spontaneously reported cholinergic symptoms in subjects treated with KarXT versus placebo
- To assess orthostatic vital signs in subjects treated with KarXT versus placebo
- To assess electrocardiogram (ECG) parameters in subjects treated with KarXT versus placebo
- To assess reduction of PANSS positive score in subjects treated with KarXT versus placebo
- To assess reduction of PANSS negative score in subjects treated with KarXT versus placebo
- To assess reduction of PANSS Marder Factor score in subjects treated with KarXT versus placebo
- To assess the pharmacokinetics (PK) of xanomeline and trospium following administration of KarXT in adult subjects with a DSM-5 diagnosis of schizophrenia
- To assess Clinical Global Impression-Severity (CGI-S) results in subjects with KarXT versus placebo

3.3. Brief Description

The study will be an inpatient study in adult subjects with DSM-5 schizophrenia. Subjects will be randomized to receive either placebo or KarXT (xanomeline 125 mg/trospium 30 mg BID) orally for a treatment period of 5 weeks. Subjects will start on a lead-in dose of xanomeline 50 mg/trospium 20 mg BID for the first 2 days followed by 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 xanomeline 125 mg/trospium 30 mg BID unless the subject is continuing to experience AEs from the previous dose increase of xanomeline 100 mg/trospium 20 mg BID. All subjects who were increased to xanomeline 125 mg/trospium 30 mg BID, depending on clinical response and tolerability, will have the option to return to xanomeline 100 mg/trospium 20 mg BID for the remainder of the treatment period. Dosing must not change in the last 14 days of the study and may be decreased for tolerability reasons no more than once during the study.

3.4. Subject Selection

A total of approximately 180 study subjects and approximately 12 sites in the United States are planned. Subjects who are randomized into the double-blind treatment phase but discontinue or withdraw will not be replaced.

3.4.1. Inclusion Criteria

To be eligible for enrollment, subjects must satisfy all of the following criteria:

1. Subject is aged 18-60 years, inclusive, at screening.
2. 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.
3. Subject is experiencing an acute exacerbation or relapse of symptoms, with onset less than 2 months before screening.
    a. The subject requires hospitalization for this acute exacerbation or relapse of 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.
4. Positive and Negative Syndrome Scale total score between 80 and 120, inclusive, at screening.
    a. Score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale (P) items at screening:
        i. Item 1 (P1; delusions)
        ii. Item 2 (P2; conceptual disorganization)
        iii. Item 3 (P3; hallucinatory behavior)
        iv. Item 6 (P6; suspiciousness/persecution)
5. There should not be a change (improvement) in PANSS total score between screening and baseline of more than 20%.
6. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 2 weeks before baseline.
7. Subjects taking a depot antipsychotic could not have received a dose of medication for at least 1 and a half injection cycles before baseline (eg, 3 or more weeks off for a 2-week cycle).
8. Subject is capable of providing informed consent.
    a. A signed ICF must be provided before any study assessments are performed.
    b. Subject must be fluent (oral and written) in English in order to consent.

9. Subject is willing and able to be confined to an inpatient setting for the study duration, follow instructions, and comply with the protocol requirements.

10. Subject must have CGI-S score of ≥ 4 at screening and baseline visits.

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. Both females of child bearing potential and males with partners of child bearing potential must be willing to use a double-barrier method of birth control (ie, any double combination of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel) during the study and for 7 days after the last dose of study drug.

14. Subject has an identified reliable informant. An informant 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 may not be necessary if the subject has been the patient of the investigator for ≥ 1 year.

3.4.2. Exclusion Criteria

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

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening).

2. 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, to exclude patients with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on the liver function test results.

3. History of or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.

4. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months

5. Has a DSM-5 diagnosis of moderate to severe substance abuse disorder (except tobacco use disorder) within the 12 months before screening (confirmed using MINI version 7.0.2 at screening), or current abuse as determined by urine toxicology screen or alcohol test. 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 he/she can be allowed into the study. 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.

6. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and the 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.

7. Clinically significant abnormal finding on the physical examination, medical history, ECG, or clinical laboratory results at screening.

8. Subjects cannot currently (within 2 weeks of baseline) be receiving oral antipsychotic medications, MAO inhibitors, anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics (eg, lorazepam, chloral hydrate) taken as needed.

9. Pregnant, lactating, or less than 3 months postpartum. Sperm donation is not allowed for 90 days after the final dose of study drug.

10. 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 their ability to adhere to the protocol visit schedule or fulfill visit requirements.

11. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.

12. 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.

13. Risk of violent or destructive behavior.

14. Current involuntary hospitalization or incarceration.

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

3.5. Determination of Sample Size

Assuming a PANSS total score difference of 9 between drug and placebo and standard deviation of 18, a sample size of 180 (90 evaluable subjects per arm) will result in a power of 91% for a 2-sided alpha of 0.05.

3.6. Treatment Assignment & Blinding

Subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo with stratification by site. A randomization number can only be assigned to one subject and cannot be reused once assigned.

An IWRS will allocate treatment based on a prespecified randomization list. Active and placebo study drug will be provided to each site.

Study subjects, informants, investigators, site personnel involved in subject evaluation, and the Sponsor’s medical monitor will be blinded to the subject treatment assignment. 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.

The Sponsor's authorized designee will generate and maintain the security of the randomization code. The blinding code will be broken early only when information is needed to maintain the health and well-being of subjects such as for treatment of an AE.

The reasons for any premature unblinding (either accidental or due to a serious adverse event [SAE] that appears related to the investigational product) will be properly documented in the study file. Unblinding according to the protocol will occur only after completion of the study.

A list of treatment numbers for each treatment group will be generated by the vendor selected by the Sponsor to perform this function, and the treatment prepared in accordance with this list. Numbers will not be reused regardless of the status of the use of the corresponding study drug.

The members of the Independent Safety Monitoring Committee (ISMC) will be unblinded as they review the safety data from the study. There will be an unblinded pharmacist to manage study drug inventory for each site and an unblinded study monitor for drug accountability and review of documentation of drug inventory.

If unblinding is necessary for the welfare of a subject who has experienced an AE, unblinding of study drug may occur for just that subject. 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.

3.7. Administration of Study Medication

Because this is an inpatient study, treatment compliance will be assured. All study drugs will be administered by study staff and recorded in the eCRF.

Study drug accountability will be assessed periodically by the assigned unblinded study monitor.

3.8. Study Procedures and Flowchart

Table 1. Schedule of Assessments

PROCEDURE	SCREENING PHASE	TREATMENT PHASE								
VISIT	1 (Day -7 TO -1)[a]	2 (Day 1)	3 (Day 3 ± 1 day)	4 (Day 7 ± 2 days)	5 (Day 8 ± 2 days)	6 (Day 14 ± 2 days)	7 (Day 21 ± 2 days)	8 (Day 28 ± 2 days)	9/ET (Day 35 ± 2 days)	Unscheduled Visit(s)[b]
WEEKS PAST RANDOMIZATION	NA	0		1		2	3	4	5	
Written informed consent	X									
Collect demographic information (date of birth, gender, race)	X									
Pregnancy test (females of childbearing potential only)[c]	X[c]	X[c]							X[c]	
Urine drugs of abuse test and alcohol testing[d]	X									
Review of inclusion/exclusion criteria	X	X								
Subject eligibility verification process	X									
Medical, psychiatric, and medication history	X									
Complete physical examination[e]	X[e]								X[e]	
Spontaneous AEs and medical status[f]		X	X	X	X	X	X	X	X	X
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X
Height (Screening only) and body weight, BMI, waist circumference	X	X							X	
Orthostatic vital signs: blood pressure and heart rate[g]	X	X	X	X	X	X	X	X	X	X
Resting ECG (12-lead)[h]	X								X	
Blood samples for hematology, coagulation, and serum chemistry and urine sample for urinalysis[i]	X								X	X
CCI [redacted]										
Admission of subject to inpatient unit[k]	X									
Randomization/assignment of subject ID		X								
Determination of dose adjustment					X	X	X			X
Study drug provided (randomized, double-blind) and administered daily BID[l]		X	X	X	X	X	X	X		X

[redacted]

PROCEDURE	SCREENING PHASE	TREATMENT PHASE								
VISIT	1 (Day -7 TO -1)[a]	2 (Day 1)	3 (Day 3 ± 1 day)	4 (Day 7 ± 2 days)	5 (Day 8 ± 2 days)	6 (Day 14 ± 2 days)	7 (Day 21 ± 2 days)	8 (Day 28 ± 2 days)	9/ET (Day 35 ± 2 days)	Unscheduled Visit(s)[b]
WEEKS PAST RANDOMIZATION	NA	0		1		2	3	4	5	
Blood samples for PK analysis[m]					X[m]			X[m]	X[m]	X[m]
MINI version 7.0.2.	X									
Positive and Negative Syndrome Scale (PANSS) for schizophrenia[n]	X	X				X		X	X	
C-SSRS[o]	X	X		X		X	X	X	X	
CGI-S Scale	X	X		X		X	X	X	X	
CCI [redacted]										
Simpson-Angus Rating Scale		X							X	
Barnes Rating Scale for Akathisia		X							X	
Abnormal Involuntary Movement Scale (AIMS)		X							X	

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; 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 If a subject leaves the unit, he/she should have a urine drug screen and test for alcohol (breathalyzer or blood alcohol level) upon returning to the unit.

e A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination. A brief physical examination is performed at Visit 9/Day 35.

f Adverse events as reported by subjects or observed by clinical staff and occurs after dosing. One PK blood sample should be drawn if an AE is reported during a scheduled visit or if there is a dose adjustment or AE reported during an unscheduled visit (no multiple draws).

g Vital signs taken supine and standing after 2 minutes. Blood pressure includes systolic and diastolic blood pressure. Heart rate is beats/minute. During treatment, beginning with Visit 2, vital signs should occur 2 (± 1) hours after dosing. At investigator discretion, additional orthostatic vital signs are allowed to be conducted as needed.

h During the ECG, ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec).

i Refer to Protocol Section 10.1.3.1.4 for individual laboratory tests.

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k If an eligible subject is not already an inpatient, the subject should be admitted to the inpatient unit.

l Starting on Day 1, study drug is administered daily BID by the study staff, with the last dose administered on the evening of Day 34.

m For Visit 5/Day 8 and Visit 8/Day 28, 6 PK blood draws are required: before the morning dose, and at 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. For Visit 9/ET, a single PK blood sample should be drawn prior to discharge (preferably in the morning) for completed (and early termination) subjects. One PK blood sample should also be drawn if an AE is reported during a scheduled visit or if there is a dose adjustment or AE reported during an unscheduled visit (no multiple draws).

n It is recommended, if at all possible, that the PANSS assessment should be performed first of all the other assessments at all visits it is performed. The PANSS assessment includes the Marder Factor.

[redacted]

o C-SSRS first time use lifetime, other times use “since last visit” version.

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4. Endpoints

4.1. Primary Efficacy Endpoint

- Change in PANSS total score at Visit 9

4.2. Secondary Efficacy Endpoints

- Change in PANSS positive score
- Change in CGI-S score
- Change in PANSS negative score
- Change in PANSS Marder Factor score
- Percent of CGI-S responders (with CGI-S scale equal to 1 or 2)

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4.4. Safety Endpoints

- Spontaneous AEs
- Orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate (beats/minute)
- Clinical laboratory evaluations: hematology, clinical chemistry, coagulation, urinalysis, and drug screen
- 12-lead ECG
- Physical examination
- Suicidal ideation with the use of Columbia Suicide Severity Rating Scale (C-SSRS)

4.5. Exploratory Endpoints

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- Simpson-Angus Rating Scale
- Barnes Rating Scale for Akathisia
- Abnormal Involuntary Movement Scale (AIMS)
- Body weight, body mass index (BMI), waist circumference

5. Analysis Populations

5.1. Intent-to-Treat (ITT) Population

The ITT population will include all subjects who are randomized to the study. Subjects will be analyzed according to randomized treatment.

5.2. Safety Population

The Safety population will include all subjects who receive at least one dose of study medication. Subjects will be analyzed according to treatment received. The Safety population will be used for all analyses of safety endpoints.

5.3. Modified Intent-to-Treat (MITT) Population

The MITT population will include all subjects who were randomized, received at least one dose of study medication, and have a baseline and at least one post-baseline PANSS assessment. The MITT population will be used for all analyses of efficacy endpoints.

5.4. PK Population

The PK population will include all subjects who received at least one dose of the study drug and have at least one measurable PK concentration. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or other clinical events potentially interfering with the pharmacokinetic profile, a decision will be made on a case-by-case basis as to their inclusion in the analysis of PK parameters. The PK population will be used for PK analyses.

5.5. Completer Population

The Completer population will include all MITT subjects who have a valid PANSS total score at Visit 9. The Completer population will be used for a sensitivity analysis of the primary efficacy endpoint.

5.6. Per-Protocol (PP) Population

All protocol deviations will be tracked in the clinical study 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.

The PP population will include 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.

6. General Aspects for Statistical Analysis

6.1. General Methods

- Unless otherwise specified, summaries will be presented for each treatment and overall.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- All relevant subject data will be included in listings.

6.2. Key Definitions

6.2.1. First Dose Date

First dose date is defined as the date of first dose of study medication received after randomization.

6.2.2. Last Dose Date

Last dose date is defined as the date of last dose of study medication.

6.2.3. Study Day

The study day is determined relative to the date of first dose of study medication. The day of the first dose of study medication will be defined as study Day 1. The day prior to the first dose of study medication is study Day -1. There is no study Day 0.

6.2.4. Baseline and Change from Baseline

Baseline value is defined as the last value prior to the first dose of study medication administration. This value could be the pre-dose assessment on the first dose date or the assessment at the screening visit. If multiple values are present for the same date, the values from the last assessment will be used as the baseline unless otherwise specified.

Change from baseline = (post-baseline value – baseline value).

For the purpose of tabulations, the unscheduled post-baseline values generally will be excluded from summary tables presented by visit, but will be included in the listings. Unscheduled visits will be considered for analyses of shift from Baseline to worst value (low-normal-high).

6.2.5. Low dose and High dose group

Based on the dosage of KarXT received during the treatment period, subjects will be separated into a low dose group and high dose group. Subjects who never took doses more than Xanomeline 100 mg/Trospium 20 mg BID or who were down-titrated after getting to Xanomeline 125 mg/Trospium 30 mg BID but then remained on 100 mg/20 mg for the rest of the study are categorized as low dose group; subjects who took Xanomeline 125 mg/Trospium 30 mg BID after the first week of “titration” and then throughout the study are categorized as high dose group.

Safety data including adverse events, laboratory tests and vital sign assessments will be summarized by low dose group and high dose group.

6.3. Missing Data

All available data for the subjects who withdraw from the study for any reasons will be analyzed. Missing assessment data will be assumed to be missing at random. There will be no imputation of missing data for analysis purposes unless otherwise specified. Subjects with missing PK data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful PK analysis.

The partial/missing AE or concomitant medication (CM) start/end dates will be imputed for study period and study day determination purpose.

If the date and/or time that an AE is incomplete, the event will be considered a TEAE unless the partial start/end dates/times give sufficient detail in order to prove that the AE started or stopped prior to the first dose in the study. In such cases the event will not be considered a TEAE.

If the date that a medication started is incomplete, the medication will be considered as concomitant unless the partial date(s) give sufficient detail in order to prove that the medication was stopped prior to the day of first dose in the study. In such a case, the medication will be considered as prior medication. A medication started prior to the first dose date and ongoing as of the first dose date will be considered both prior and concomitant.

Incomplete Start Date:

Missing day and month

- If the year is the same as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the same as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is before the year of the first dosing date or the year of the partial date and the first dosing date are the same but the month of partial date is before the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is after the year of the first dosing date or the year of the partial date and the first dose date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, and the corresponding AE will be included as TEAE and the corresponding CM will be included as a concomitant medication.

Incomplete Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is after the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the year of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

6.4. Visit Windows

Unscheduled visits will not be windowed to protocol-specified visits—nominal visits will be used for all by visit summaries. Data collected at unscheduled visits will be included in the data listings but will not be included in the analyses unless otherwise stated.

Early termination visits for efficacy and safety endpoints (PANSS, CGI, C-SSRS scores and vital signs) will be reassigned to the next applicable scheduled visit for each assessment. Otherwise, no visit windowing will be performed.

6.5. Pooling of Centers

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 combined and considered as one 'Other' site in the analysis.

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7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

The number of subjects in each analysis population (ITT population, Safety population, MITT population, PK population, Completer population, and PP population), the number of subjects who completed the study, and the number of subjects who withdrew early from the study and the reasons for discontinuation will be summarized by treatment group and overall.

The reasons for early discontinuation include:

- Adverse Event
- Consent Withdrawn
- Lost to follow-up
- Investigator decision
- Death
- Pregnancy
- Other

Subjects' completion/discontinuation status will be listed, including subject identifier, informed consent date, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation.

7.2. Inclusion/Exclusion Criteria

Inclusion/exclusion criteria definitions and violations will be listed. If no inclusion/exclusion violations are reported, this will be noted in place of the listing.

7.3. Protocol Deviations

All protocol deviations will be tracked in the clinical study management system. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be summarized by the following categories for all subjects in the ITT Population, including the number of subjects with at least one major protocol deviation. All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed.

Protocol deviation category includes:

- Inclusion Criteria
- Exclusion Criteria
- Randomization Error
- ICF
- SAE Not Reported
- Visit Out of Window
- Missed Study Visit
- Procedure Not Per Protocol
- Concomitant Medication
- Lab Sample
- IP Preparation or Dosing Error
- Other

7.4. Demographic and Other Baseline Characteristics

Age (years), height (cm), weight (kg), and BMI (kg/m^2) will be summarized descriptively by treatment group and overall for the ITT Population, Safety Population, MITT Population, Completer Population, and Per-Protocol Population. Sex, race, ethnicity, and child-bearing potential status will be summarized by frequency counts. Body mass index is calculated based on weight and height at baseline.

Demographic data and baseline characteristics (as detailed above) as well as informed consent data will be listed.

The following calculations will be utilized:

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height(m)^2]

7.5. Medical History

The medical or psychiatric history are recorded and coded with Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

A summary of medical history will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall for the ITT Population. A listing of medical history by subject will be provided.

7.6. Other Baseline Characteristics

Baseline MINI test assessment will be listed.

7.7. Prior and Concomitant Medication

Subjects will be asked to report all prior and concomitant medications. Prior medications taken up to 6 months before the study will be recorded. Prior and concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary WHO-DD - B3 Enhanced version March 2018.

7.7.1. Prior Medication

Prior medications are defined as any medications with a start date up to 6 months before the first dose date. The number and percentage of subjects using each medication will be summarized by treatment group and overall using the ITT Population by Anatomical Therapeutic Chemical class level 2 (ATC2) and preferred term together with the number and percentage of subjects using at least one medication within each treatment group.

7.7.2. Concomitant Medication

Concomitant medications are defined as medications either ongoing as of the first dose date or which started on or after the first dose date. A medication may be considered both prior and concomitant. The number and percentage of subjects using each medication will be summarized by treatment group and overall using the ITT Population by ATC2 and preferred term together with the number and percentage of subjects using at least one medication within each treatment group.

8. Efficacy Analyses

8.1. Primary Efficacy Endpoint and Analysis

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.[Kay 1987] 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. If a patient has a PANSS assessment recorded, but any of the 30 items are missing, the last nonmissing score for the respective item from previous assessments will be carried forward. Missing item score at baseline will not be imputed and the total score will be missing. If the total has > 30% of the items missing at a particular visit, the respective total score at the visit will not be calculated and will be treated as missing data in the analysis.

The PANSS assessed prior to the first dose taken will be used as the baseline score. PANSS assessed at Visit 6, Visit 8, and Visit 9 will be used as post-baseline scores.

8.1.1. Primary Analysis

The primary endpoint of the study is the change from baseline in PANSS total score at Visit 9. The difference between KarXT and placebo at Visit 9 will be estimated using a mixed model for repeated measures (MMRM). The model will include the observed change from baseline PANSS total score at Visit 6, Visit 8, and Visit 9 as the response variable. The treatment difference at Visit 9 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. Baseline PANSS total score, site, age, and gender will be used as covariates in the model. Any site with two or fewer subjects in any treatment group will be combined into an “Other” site for analysis.

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

The least square (LS) mean, standard error (SE), and LS mean difference between KarXT and placebo group at Visit 9 along with the 95% confidence interval (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. The SAS code planned for the analysis is outlined below.

```
proc mixed data=&data;
class trtp avisit site usubjid gender;
model chg= trtp avisit trtp*avisit base site age gender / ddfm=kr;
repeated avisit / subject=usubjid type=un;
lsmeans trtp*avisit / cl;
run;
```

The MITT population will be used for the primary efficacy analysis. Observed and change from baseline PANSS total scores will be summarized by visit for the MITT population.

Estimated mean changes (with SE) from baseline PANSS total score will be graphed by treatment group and visit. The x-axis will include the visit (Visit 6, Visit 8, or Visit 9) and the y-axis will represent the change from baseline. LS mean estimates and SEs of these estimates from the primary MMRM will be used for the display.

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8.1.3. Sensitivity Analyses of Primary Endpoint

The following sensitivity analyses will be performed for the primary endpoint:

- 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 previous post-baseline visit assessment values carried forward. The LOCF-imputed values at Visit 9 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:

[redacted]

- MI techniques based on Pattern Mixture Models (PMM) will be applied as a sensitivity analysis in the MITT population. This methodology will structure data based on missing data patterns. The method will be based on a missingness pattern having a monotone structure, i.e. if among the observations over time the PANSS total score at a visit is missing, the PANSS total socre at all the following visits will also be treated as missing. For subjects with intermittent missing values, before performing MI based on the PMM, it will be necessary to create a monotone missingness pattern. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. The MI procedure in SAS will be used for this purpose and this first MI step is planned to be repeated 100 times, creating several different datasets with a monotone missing data structure. A seed value of 201809 will be used in the MI procedure. The imputation is based on the missing at random (MAR) assumption, i.e. the missing data are assumed to follow the same model as the other subjects in their respective treatment group.

- After this, the remaining missing data can be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the created datasets with a monotone missing data pattern, the MI procedure in SAS will be used to impute missing values based on a sequential procedure reflecting the monotone missing data pattern. Subjects with the first missing value occurring at Visit 6 will have their missing Visit 6 value replaced by an imputed value from a regression model with treatment group, site, and the change from baseline PANSS score as explanatory variables. In the next step, subjects with their Visit 8 value missing will have their missing Visit 8 value replaced by an imputed value from a regression model with treatment group, the change from baseline PANSS total score at baseline and the Visit 6 value as explanatory variables. A similar procedure will be used to impute the missing values at Visit 9.

- The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the sensitivity analysis of the primary endpoint. MMRM models similar as described above will thus be run on each of the generated imputed datasets and the difference between the treatment groups at Visit 6, Visit 8, and Visit 9 will be estimated. The MMRM model will be similar to the primary analysis. Finally, the MIANALYZE procedure in SAS will be applied to combine the results from these several datasets to derive an overall estimate of the treatment difference at Visit 9. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated.

- 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. Placebo group based assumption will be used, i.e. the trajectories of the subjects are assumed to follow the placebo group after the discontinuation. 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.

- MI analysis with Missing Not At Random assumption (Tipping point based imputation): If the primary analysis significantly favors KarXT, another MI analysis will 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 an amount of delta. After the MI using the MAR assumption, as defined above has been done, the amount of 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 the 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.

8.1.4. Additional Analyses of Primary Endpoint

- Observed and change from baseline results will be provided by visit
- LS mean (SE), 95% CIs, and p-values of each treatment group and LS differences will be provided for Visit 6 and Visit 8

8.2. Secondary Efficacy Endpoints and Analyses

8.2.1. Hierarchical test for efficacy evaluation

If the primary efficacy endpoint is statistically significant, the secondary efficacy endpoints will be analyzed using hierarchical hypothesis tests in a fixed sequence procedure based on the following order:

a. PANSS Positive Score
b. CGI change from baseline
c. PANSS Negative Score
d. PANSS Marder Factor Score
e. Percentage of CGI responders (defined as a score of 1 or 2)

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

8.2.2. Change from Baseline in PANSS Positive Score

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, but any of the 7 positive symptom scales are missing, the last nonmissing score for the respective item from previous assessments will be carried forward. If > 30% of the 7 positive symptom scale items missing at a particular visit, the respective positive score at the visit will not be calculated and will be treated as missing data in the analysis.

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 Visit 6, Visit 8, and Visit 9 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 by visit for the MITT population.

Estimated mean changes (with SE) from baseline PANSS positive score will be graphed by treatment group and visit. The x-axis will include the visit (Visit 6, Visit 8, or Visit 9) and the y-axis will represent the change from baseline. LS means estimates and SEs of these estimates from the primary MMRM will be used for the display.

8.2.3. Change in CGI-S score

CGI-S will be assessed at screening, baseline (Day 1) and at the end of Visit 4, Visit 6, Visit 7, Visit 8, and Visit 9. The severity of the illness is categorized 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 scores will be summarized by visit using frequency counts for the MITT population.

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

8.2.4. Change from Baseline in PANSS Negative Score

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, but any of the 7 negative symptom scales are missing, the last nonmissing score for the respective item from previous assessments will be carried forward. If > 30% of the 7 negative symptom scale items missing at a particular visit, the respective negative score at the visit will not be calculated and will be treated as missing data in the analysis.

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 Visit 6, Visit 8, and Visit 9 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 by visit for the MITT population.

Estimated mean changes (with SE) from baseline PANSS negative score will be graphed by treatment group and visit. The x-axis will include the visit (Visit 6, Visit 8, or Visit 9) and the y-axis will represent the change from baseline. LS means estimates and SEs of these estimates from the primary MMRM will be used for the display.

8.2.5. Change in PANSS Marder Factor Score

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 item are missing, the last nonmissing score for the respective item from previous assessments will be carried forward. If > 30% of the items missing at a particular visit, the respective positive score at the visit will not be calculated and will be treated as missing data in the analysis.

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

Observed and change from baseline PANSS Marder factor scores will be summarized by visit for the MITT population.

Estimated mean changes (with SE) from baseline PANSS Marder factor score will be graphed by treatment group and visit. The x-axis will include the visit (Visit 6, Visit 8, or Visit 9) and the y-axis will represent the

change from baseline. LS means estimates and SEs of these estimates from the primary MMRM will be used for the display.

8.2.6. CGI-S responders

A CGI-S responder is defined as a subject with CGI-S score equal to 1 or 2. A CGI-S non-responder is defined as a subject with CGI-S scale equal to 3 to 7.

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

Percentage of CGI-S responders at each visit will also be graphed by treatment group. The x-axis will include the visit (Visit 4, Visit 6, Week 3/Day 21, Visit 8, Visit 9) and the y-axis will represent the percentage of subjects.

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9. Pharmacokinetics Analysis

PK analysis will be done for the PK population. PK parameters will be calculated using non-compartmental analysis (NCA) method for xanomeline and trospium using the validated software WinNonlin® (Version 8.0). Actual sample collection times relative to dose administration will be used in the analysis. PK parameters will be estimated for an individual subject only if the subject exhibits measurable concentrations of drug at a minimum of three consecutive time points within a concentration-time profile (at least 50% of the subject concentrations data i.e. 3 out of 6 timepoints are not BLQ).

PK concentrations are listed for all subjects in PK population.

9.1. PK Sampling Schedule

PK samples to evaluate the exposure of xanomeline and trospium will be taken according to the following schedule and acceptable windows in Table 2.

Table 2. Pharmacokinetic Blood Sample Collection and Acceptable Windows

Visit/Day	Timepoints	Window
Visit 5/Day 8	Predose morning	-
Visit 8/Day 28	1 hour post morning dose	± 5 minutes
	2 hour post morning dose	± 10 minutes
	4 hour post morning dose	± 10 minutes
	8 hour post morning dose	± 10 minutes
	12 hour post morning dose	± 10 minutes (prior to evening dose)
Visit 9/ET	Single blood draw	Prior to discharge/ET
Unscheduled Visit/AE	Single blood draw	AE/dose adjustment

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9.3. Presentation of Concentration Data

9.3.1. Handling of missing data

Missing concentration data for all subjects who are administered scheduled study treatments will be considered as non-informative missing data and will not be imputed. No concentration estimates will be provided for missing sample values.

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9.5. Population PK Analysis

In addition to standard non-compartmental analysis, the population PK modelling is planned for xanomeline and trospium, which will be performed as a two-step analysis.

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The details for population PK modelling will be described in a separate population PK SAP, and the results will be presented in a separate population PK modelling report.

10. Safety Analyses

The population used for safety analyses will be the Safety population. Safety will be assessed on the basis of adverse events (AE), adverse events of special interest (AESI), clinical laboratory data, ECG parameters, physical examinations, and orthostatic vital signs.

10.1. Extent of Exposure

The treatment duration (days) and cumulative dose taken (mg) will be summarized. The following calculation will be utilized:

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

The number of subjects experiencing a dose reduction will be summarized.

10.2. Treatment Compliance

The number of doses planned to be taken, the number of doses actually taken, compliance (%), the number of doses missed, and the number of doses missed due to each cause will be summarized.

The number of doses planned to be taken = (Last dose date – first dose date + 1) *2

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

Treatment compliance data will listed based on drug administration data.

10.3. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as AEs that are newly occurring or worsening from the time of the first dose of study medication. Reported AE terms will be coded using MedDRA version 21.0.

The severity of AE is graded as mild, moderate, and severe. If the severity is missing, the TEAE will be considered to be severe for table summary purposes.

The relationship to study medication is evaluated as very likely/certain, probable, possible, unlikely, and unrelated. Events will be classified as related vs non-related. A related AE is an event with a relationship to treatment as very likely/certain, probable, or possible; a non-related AE is an event with relationship to treatment as unlikely, or unrelated. If the relationship to the study treatment is missing, the TEAE will be considered to be treatment-related for table summary purposes.

TEAEs will be summarized by SOC, PT and treatment group. TEAEs with onset after the last dose of the study treatment period are attributed to the treatment received during the treatment period. Both event and subject counts will be summarized. A subject with two or more AEs in an SOC or PT category is counted only once for the subject count. The counts will be complemented by percentages calculated for the subject counts unless otherwise specified.

The following summaries will be provided:

- An overall summary of the number and percentage of subjects reporting TEAEs, serious TEAEs, severe TEAEs, treatment-related TEAEs, TEAEs leading to drug withdrawal, treatment-related TEAEs leading to drug withdrawal, and TEAEs leading to death.

- TEAEs overall and by SOC and PT

- Treatment-related TEAEs overall and by SOC and PT
- TEAEs by maximum severity, overall and by SOC and PT. A subject with two or more AEs in an SOC or PT category is counted only once at the maximum severity for the subject count.
- TEAEs by maximum relationship (related vs. non-related) to study treatment, overall and by SOC and PT. A subject with two or more AEs in an SOC or PT category is counted only once at the maximum relationship to study treatment for the subject count.
- Serious TEAEs, overall and by SOC and PT
- Serious TEAEs by maximum relationship (related vs. non-related) to study treatment, overall and by SOC and PT
- Non-Serious TEAEs, overall and by SOC and PT
- TEAEs leading to study drug withdrawal, overall and by SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as “Study Drug Stopped” is checked.
- TEAEs leading to death, overall and by SOC and PT. This is a subset of the AEs where SAE criteria is checked as “Death”.

The tables will be sorted by descending frequency of SOC according to KarXT column and then, within a SOC, by descending frequency of PT based on the subject count for the KarXT column.

The original (non-imputed) date and time will be shown on all listings of AEs. Listings will be provided for all TEAEs, serious TEAEs, severe TEAE, Treatment-related TEAEs, TEAEs leading to study drug withdrawal, and TEAEs leading to death.Any TEAEs which code to a PT of “Syncope” and/or “Orthostasis” are AEs of special interest (AESI). They are already summarized in TEAEs overall and by SOC and PT table, and will not be summarized seperately. Treatment emergent AESI data will be listed.

10.4. Laboratory Evaluations

Clinical laboratory data are collected at the visits specified in Table 1. The assessments include:

Hematology: hemoglobin, hematocrit, mean cell volume, red blood cell count, white blood cell count with differential, and platelet count.

Serum Chemistry: alkaline phosphatase, gamma-glutamyl transferase, AST, ALT, lactate dehydrogenase, total bilirubin, total protein, cholesterol, triglycerides, urea nitrogen, uric acid, glucose, calcium, chloride, creatinine, inorganic phosphate, potassium, sodium, albumin, and bicarbonate.

Coagulation: prothrombin time, partial thromboplastin time, and fibrinogen.

Urinalysis: color/appearance, pH, glucose, specific gravity, ketones, protein, urobilinogen, occult blood, white blood cells, microscopic.

Other Laboratory Assessments:

A serum pregnancy test for females of childbearing potential will be performed at screening, and urine pregnancy tests will be performed at other visits.

A NIDA-5 urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed at screening only.

Alcohol testing is performed using a breathalyzer or blood alcohol test. If a subject leaves the unit, he/she should have a urine drug screen test and test for alcohol (breathalyzer or blood alcohol test) upon returning to the unit.

The hematology, coagulation, and chemistry laboratory parameters will be summarized with descriptive statistics for the observed values at each visit and change from baseline to post-baseline visits values by treatment group.

The number and percentage of subjects with low, normal, or high values at each visit for each hematology, chemistry, and coagulation parameter will be summarized. These values will be presented as a shift table; ie, the distribution of the 3 response categories at each post-baseline visit will be classified by the baseline category.

Listings will be provided for the hematology, coagulation, chemistry, urinalysis, pregnancy tests, urine drug screen, and alcohol test results.

10.5. Height, Weight, BMI, and Waist Circumference

Observed and change from baseline result for body weight, BMI, and waist circumference will be summarized by visit and treatment.

10.6. Orthostatic Vital Signs

Observed and change from baseline orthostatic vital signs will be summarized by visit and treatment. Box plots will be generated for the observed values of orthostatic vital signs by visit and by high/low dose group and overall for each treatment group.

10.7. ECG

The standard 12-lead ECGs will be performed at the visits specified in Table 1.

A summary of ECG parameters (ventricular rate, PR, QRS, QT, and QTcF interval) and change from baseline will be presented by visit.

In addition, the investigator's interpretation will be summarized by visit.

10.8. Physical Examination

A complete physical examination is performed at Visit 1 and Visit 9 and includes body temperature (°C), general appearance, head/eyes/ears/ nose/throat (HEENT), examination of the thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.

A summary of physical examinations will be presented by visit.

10.9. Other Safety Analyses

10.9.1. A Simpson-Angus Rating 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 visit for the Safety population.

10.9.2. 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 Barnes Rating Scale and the four individual scores will be summarized by visit for the Safety population.

10.9.3. Abnormal Involuntary Movement Scale (AIMS)

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.

Observed and change from baseline AIMS, subscales (AIMS total score for items 1-7, AIMS total score for items 1-10), and individual item scores will be summarized by visit for the Safety population.

10.9.4. C-SSRS

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 treatment group and visit.

All C-SSRS data will be listed.

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11. Interim Analyses

[redacted]

12. Changes from Analysis Planned in Protocol

The following changes were made from the analyses planned in Protocol Version 4.0:

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2. Hierarchical testing procedure for secondary endpoints is specified in section 8.2.1.
3. Secondary endpoint analysis for PANSS negative scores is added in section 8.2.4.
4. Low dose and high dose group definitions are added in section 6.2.5.

13. Reference List

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

Fridericia LS. Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. Acta Med Scand. 1920;53:469–486.

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15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in CCI [redacted]

CCI [redacted] SOPs Developing Statistical Programs CCI [redacted] and Quality Deliveries (SDTM, ADaM, TLF) CCI [redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

CCI [redacted] SOP Pharmacokinetic and Related Data Analyses and Reporting CCI [redacted] describes the procedure for the generation and reporting of PK and pharmacodynamics data.