Official Title of Study:

A Phase 3, Multicenter, Two-part Study with a 5-week Double-blind Part (Randomized, Parallel-group, Placebo-controlled) followed by a 12-week Open-label Extension Part, to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects with DSM-5 Schizophrenia

NCT Number: NCT05919823

Document Date (Date in which document was last revised): 26 Apr 2024

Clinical Trial Protocol

Protocol Title:	A Phase 3, Multicenter, Two-part Study with a 5-week Double-blind Part (Randomized, Parallel-group, Placebo-controlled) followed by a 12-week Open-label Extension Part, to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects with DSM-5 Schizophrenia
Protocol No.:	ZL-2701-001
Version No.:	3.0
Version Date:	26 April 2024
Investigational Product(s) Name:	KarXT
Study Phase:	Phase 3
Sponsor(s):	Karuna Therapeutics, Inc. (Zai Lab (Shanghai) Co., Ltd. as territory representative) Karuna Therapeutics, Inc.: 99 High Street, 26th Floor, Boston, Massachusetts, 02110, United States of America Zai Lab (Shanghai) Co., Ltd.: 4/F, No.1 South Tower, 4560 Jinke Rd. Pilot Free Trade Zone (Shanghai), China

SPONSOR SIGNATURE PAGE

Signature **Date**

Karuna Therapeutics, Inc.

ZAI LAB SIGNATURE PAGE

[redacted]

[redacted]

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Signature **Date**

Zai Lab (Shanghai), Co. Ltd.

VERSION HISTORY

Document	Version No.	Date	Summary of Changes and Brief Rationale
Protocol Amendment 2	3.0	26 April 2024	• [redacted] • To clarify the time requirement for signing the ICF for the open-label part for subjects who will participate in this part. • To clarify in Section 6.2.1 that PK samples on Visit 5/Day 8 in the double-blind part should also be drawn from the subject whose dose is not escalated as confirmed by the investigator. • To clarify permitted and prohibited concomitant therapies in Section 6.7.2.
Protocol Amendment 1	2.0	27 April 2023	• To reconcile the inconsistency between secondary endpoints and secondary objectives in the double-blind part, the percentage of PANSS responders included as one of the secondary endpoints was added to secondary objectives; • To reconcile the inconsistency between Sections 9.2.3 and 7.1, the NCI CTCAE v5.0 criteria for AE severity was added to Section 9.2.3, modified "intensity" to "severity" in Section 11.1 to be consistent with Section 9.2.3; • To refine the requirement for subjects who show violent or destructive behavior to be more rigorous and practical; • To reconcile the inconsistency between Visits and Note for "urine test for drugs of abuse and alcohol testing" in Table 1 (schedule of activities), relevant requirements of test were revised in the Note. Note b in table 3 (laboratory assessment) was revised accordingly; • For laboratory assessment, ➢ "COVID-19 Nucleic acid test" was removed from laboratory assessment based on the current situation of COVID-19 pandemic prevention. The relevant requirements were deleted from the exclusion criteria accordingly; ➢ Revised the test name of "HIV-1 antibody and HIV-2 antibody" to "HIV antibody" to be consistent with clinical practice in China;

			➢ Clarified that either “indicators of WBCs” or “WBCs” test is sufficient; • [redacted] • Modified the test name of “ventricular rate” to “heart rate” in accordance with the ECG result; • There were no unblinded individuals at the study site, and the requirements related to unblinded individual were removed; • Corrected contact information of sponsor’s medical expert and removed department information for the leading site which was not applicable.
Original Protocol	1.0	08 October 2022	NA

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ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APD	Antipsychotic drug
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
[redacted]	
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	Electrocardiogram
EOS	End-of-Study
EOT	End-of-Treatment
EPS	Extrapyramidal symptoms
ET	Early termination
eCRF	Electronic case report form
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IRB	Institutional Review Board
IRT	Interactive response technology (system)
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MCC	Microcrystalline cellulose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview (for Schizophrenia and Psychotic Disorder Studies)
mITT	modified intent-to-treat
MMRM	Mixed model repeated measures
NCI	National Cancer Institute
[redacted]	[redacted]
NF	National Formulary
OATP	Organic anion transport protein
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic(s)
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcF	QT interval corrected by Fridericia
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TID	Three times daily
T_{max}	Time to C_{max}
$t_{1/2}$	Elimination half-life
[redacted]	[redacted]

Abbreviation or special term	Explanation
[redacted]	[redacted]
UNS	Unscheduled
US	United States
USP	United States Pharmacopeia
WBC	White blood cell
WOCBP	Women of childbearing potential
YLD	Years lived with disability

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Two-part Study with a 5-week Double-blind Part (Randomized, Parallel-group, Placebo-controlled) followed by a 12-week Open-label Extension Part, to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects with DSM-5 Schizophrenia
Protocol No.: ZL-2701-001
Study Phase: Phase 3
Sponsor(s): Karuna Therapeutics, Inc. (Zai Lab (Shanghai) Co., Ltd. as territory representative) Karuna Therapeutics, Inc.: 99 High Street, 26th Floor, Boston, Massachusetts, 02110, United States of America Zai Lab (Shanghai) Co., Ltd.: 4/F, No.1 South Tower, 4560 Jinke Rd. Pilot Free Trade Zone (Shanghai), China
National co-ordinating investigator: [redacted]
Investigational Product(s) Name: KarXT
Rationale: This study will provide efficacy, safety, and pharmacokinetic (PK) data for KarXT in Chinese adult schizophrenia patients [redacted].
Objectives: **<u>Double-blind Part</u>** The primary objective of the double-blind part is to evaluate the efficacy of KarXT (a combination of xanomeline tartrate and trospium chloride) administered twice daily (BID) versus placebo in reducing Positive and Negative Syndrome Scale (PANSS) total scores in

Chinese adult subjects with acute schizophrenia (by Diagnostic and Statistical Manual-Fifth Edition [DSM-5] criteria).

The secondary objectives of the double-blind part are:

- To evaluate the reduction of PANSS positive symptom score in subjects treated with KarXT versus placebo;
- To evaluate the reduction of PANSS negative symptom 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 PANSS responders in subjects treated with KarXT versus placebo;
- To evaluate the safety and tolerability of KarXT;
- To assess the PK of xanomeline and trospium.

[redacted]

Open-label Part

- To evaluate the safety and tolerability of KarXT;
- To assess the open-label KarXT efficacy.

Endpoints:

Double-blind Part

Primary endpoint:

- Change from baseline in PANSS total score at Week 5.

Secondary endpoints:

Efficacy endpoints:

- Change from baseline in PANSS positive symptom score at Week 5;
- Change from baseline in PANSS negative symptom 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 (defined as a ≥30% change in PANSS total score from baseline) at Week 5.

Safety endpoints:

- Proportion (%) of subjects with any treatment-emergent adverse event (TEAE) during the double-blind part;
- Proportion (%) of subjects with any serious TEAE during the double-blind part;
- Proportion (%) of subjects with any TEAE leading to study drug withdrawal during the double-blind part;
- Orthostatic vital signs, physical examinations, clinical laboratory values and electrocardiogram (ECG) parameters;
- Columbia-Suicide Severity Rating Scale (C-SSRS), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS);
- Body weight, body mass index (BMI), and waist circumference.

PK endpoints:

- Area under the plasma concentration-time curve (AUC) of xanomeline and trospium;
- Maximum observed plasma concentration (C_{max}) of xanomeline and trospium;
- Time to C_{max} (T_{max}) of xanomeline and trospium.

[redacted]

Open-label Part

Safety endpoints:

- Proportion (%) of subjects with any TEAE during the open-label part;
- Proportion (%) of subjects with any serious TEAE during the open-label part;
- Proportion (%) of subjects with any TEAE leading to study drug withdrawal during the open-label part;
- Orthostatic vital signs, physical examinations, clinical laboratory values and ECG parameters;
- C-SSRS, SAS, BARS, AIMS;

- Body weight, BMI, and waist circumference.

Efficacy endpoints:

- Change from baseline in PANSS total score at Week 12;
- Change from baseline in PANSS positive symptom score at Week 12;
- Change from baseline in PANSS negative symptom score at Week 12;
- Change from baseline in PANSS Negative Marder Factor score at Week 12;
- Change from baseline in CGI-S score at Week 12;
- Percentage of PANSS responders (defined as a ≥30% change in PANSS total score from baseline) at Week 12.

Study Design:

This is a Phase 3, multicenter, two-part study, including a 5-week randomized, parallel-group, double-blind, placebo-controlled part, followed by a 12-week open-label extension part in Chinese adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia.

In the double-blind part, subjects will be in an inpatient setting. Subjects will be randomized in a 1:1 ratio to receive either KarXT or placebo for a treatment period of 5 weeks. The randomization will be stratified by study site. Subjects will start on a lead-in dose of KarXT 50/20 (xanomeline 50 mg/ trospium chloride 20 mg) BID for the first 2 days (Days 1 and 2) followed by KarXT 100/20 (xanomeline 100 mg/ trospium chloride 20 mg) BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be increased to KarXT 125/30 (xanomeline 125 mg/ trospium chloride 30 mg) BID unless the subject is experiencing intolerant adverse events (AEs) from the previous dose increase of KarXT 100/20 BID, based on investigator's judgement. All subjects who were increased to KarXT 125/30 BID, depending on clinical response and tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period; such dose reduction is permitted only once during the double-blind part. However, dosing must not change after Visit 7 (Day 21) to Visit 9 (Day 35). In addition, dose escalation to KarXT 125/30 BID may not occur outside of the permitted window for Visit 5 (Day 8). Subjects in the placebo group will follow the same rules receiving matching placebo.

For subjects who complete the 5-week double-blind part and are willing to continue participation, and if investigator judges the subject is suitable to continue, they will continue treatment in the 12-week open-label part of the study in an outpatient/inpatient setting during which the long-term safety and effectiveness of KarXT will be evaluated.

For subjects who will not participate in the open-label part, they will undergo End-of-Treatment assessment on Visit 9 (Day 35) and an End-of-Study visit (i.e., safety follow-up, 7 [±3] days after the last dose of study drug).

In the open-label part, all subjects will receive KarXT for up to 12 weeks. Regardless of treatment assignment in the preceding double-blind part, all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2 of the open-label part), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7 of the open-label part). At Visit 11 (Day 8 of the open-label part), dosing will be increased to KarXT 125/30 BID unless the subject is experiencing intolerant AEs from the previous dose of KarXT 100/20 BID, based on investigator's judgement. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for at least a week is allowed and will require a discussion between the principal investigator and the sponsor's medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the sponsor's medical monitor.

An End-of-Study visit (i.e., safety follow-up, Visit 16/ Day 91 ±3 days of the open-label part) will occur for all subjects after the last dose of KarXT.

This is a China single-country study, and about 20 sites will be included.

Study Period:

Total study duration for an individual subject is up to 20 weeks, including a maximum 7-day screening phase (up to a 7-day extension of the screening phase is allowed, if necessary), a 5-week double-blind treatment period, a 12-week open-label extension part, and a 7-day End-of-Study visit (i.e., safety follow-up).

The overall study duration is expected to be approximately 20 months from when the study opens to enrollment until end of study.

Patient Number:

Approximately 200 Chinese adults (aged 18 to 65 years, inclusive) are planned to be randomized in a 1:1 ratio to 2 treatment groups, either KarXT or placebo, to achieve approximately 150 completers in the double-blind part.

Only subjects who complete the 5-week double-blind part and are willing to continue participation will enter open-label part of the study. It is assumed that approximately 100 subjects will enter the open-label extension part.

Study Population:

Inclusion Criteria:

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

1. Subject is Chinese national, aged 18 to 65 years, inclusive, at screening.
2. Subject is capable of providing written informed consent.
3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2.
4. Subject is experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 2 months before screening.
   a. The subject requires hospitalization for this acute exacerbation or relapse of psychotic symptoms at screen.
   b. If already an inpatient at screening, hospitalization has to be ≤2 weeks for the current exacerbation at the time of screening.
5. PANSS total score between 80 and 120, inclusive, with a

   scores of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items:

   i. Item 1 (P1; delusions)

   ii. Item 2 (P2; conceptual disorganization)

   iii. Item 3 (P3; hallucinatory behavior)

   iv. Item 6 (P6; suspiciousness/persecution)
6. Subjects with no change (improvement) in PANSS total score between screening and baseline (Day -1) of more than 20%.
7. Subject has a CGI-S score of ≥4 at screening and baseline (Day -1) visits.
8. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 5 half-lives or 1 week, whichever is longer, before baseline (Day -1).
9. Subjects taking a long-acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®) before baseline visit (Day -1).
10. Subject is able to be confined to an inpatient setting for the duration of the 5-week double-blind part of the study, follow instructions, and comply with the protocol requirements.

11. Body mass index of 18 to 40 kg/m^2, inclusive.
12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator.
13. Subject has an identified reliable informant. 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 a patient of the investigator for ≥1 year.
14. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 5.3.

Exclusion criteria

Subjects who meet any of the following criteria are excluded from the study:

1. Any primary DSM-5 disorder other than schizophrenia within 12 months before screening (confirmed using MINI version 7.0.2 at screening).
2. Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia.
3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
4. Subjects with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test results.
5. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:

   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. Non-suicidal, self-injurious behavior is not exclusionary.
8. Clinically significant abnormal findings on the physical examination, medical history, electrocardiogram, or clinical laboratory results at screening that, in the opinion of the

investigator, would jeopardize the safety of the subject or the validity of the study results.

9. Subjects are receiving or have recently received (within 5 half-lives or 1 week, whichever is longer, before baseline [Day -1]) oral antipsychotic medications; monoamine oxidase inhibitors; anticonvulsants (e.g., lamotrigine, valproate); tricyclic antidepressants (e.g., imipramine, desipramine); selective serotonin reuptake inhibitors; or any other psychoactive medications except for as-needed anxiolytics (e.g., lorazepam, chloral hydrate).
10. Subjects are receiving or have recently received (within 1 week before baseline [Day -1]) metformin.
11. Pregnant, lactating, or less than 3 months postpartum.
12. In the opinion of the investigator and/or Sponsor, subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator and/or Sponsor, may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
13. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.
14. 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 has required clozapine within the last 12 months.
15. Subjects with prior exposure to KarXT.
16. Subjects who experienced any significant adverse effects due to trospium chloride.
17. Participation in another clinical study within 3 months before screening in which the subject received an experimental or investigational drug agent.
18. Significant risk of violent or destructive behavior.

Treatment Groups and Duration:

Double-Blind Part:

Subject in the KarXT group will receive three dosing regimens of KarXT sequentially:

- 50/20 mg BID (total daily dose [TDD]: 100 mg of xanomeline as the tartrate salt and 40 mg of trospium chloride)
- 100/20 mg BID (TDD: 200 mg xanomeline as the tartrate salt and 40 mg trospium chloride)

- 125/30 mg BID (TDD: 250 mg xanomeline as the tartrate salt and 60 mg trospium chloride)

Subject in placebo group will receive matching placebo.

Dosing Schedule:

Treatment Day	Dosing Regimen	Number of Doses
Day 1-Day 2	KarXT 50/20 mg or placebo BID	4
Day 3-Day 7	KarXT 100/20 mg or placebo BID	at least 8
From Day 8-Day 35*	KarXT 125/30 mg or placebo BID	56

BID= twice daily.
* 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; such dose reduction is permitted only once during the double-blind part. No dose adjustment will be allowed after Visit 7 (Day 21 ± 2 days) to Visit 9 (Day 35 – 2 days). All subjects will continue taking the doses chosen for KarXT at Visit 7 (Day 21 ± 2 days).

Open-Label Part:

All subjects will receive three dosing regimens of KarXT sequentially:

- 50/20 mg BID (TDD: 100 mg of xanomeline as the tartrate salt and 40 mg of trospium chloride)
- 100/20 mg BID (TDD: 200 mg xanomeline as the tartrate salt and 40 mg trospium chloride)
- 125/30 mg BID (TDD: 250 mg xanomeline as the tartrate salt and 60 mg trospium chloride)

Dosing Schedule:

Treatment Day	Dosing Regimen	Number of Doses
Day 1-Day 2	KarXT 50/20 mg BID	4
Day 3-Day 7	KarXT 100/20 mg BID	at least 8
From Day 8-Day 84*	KarXT 125/30 mg BID	153

BID=twice daily.
* All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for at least a week is allowed and will require a discussion between the principal investigator

and the sponsor's medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the sponsor's medical monitor. All subjects will receive their final dose of KarXT on the morning of Visit 15/Day 84.

Statistical methods

The primary efficacy endpoint of the study is the change from baseline in PANSS total score at Week 5 in the double-blind part. The difference between KarXT and placebo will be estimated using a mixed model for repeated measures.

[redacted]

The secondary efficacy endpoints are the change from baseline to Week 5 of the double-blind part in PANSS positive score, PANSS negative score, PANSS Negative Marder Factor Score, and CGI-S score, and percentage of PANSS responders at Week 5 of the double-blind part.

Statistical analysis of the primary and secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure to control the overall Type I error rate.

Safety endpoints will be summarized using descriptive statistics.

1.2 Schedule of Activities

Table 1 Schedule of Activities

Procedure	SC	Double-blind part (inpatient)									Open-label part					EOT/ ET[t]	EOS[t]/ UNS[u]
Days	**-8 to -2[a]**	**D-1**	**D1**	**D3**	**D7**	**D8**	**D14**	**D21**	**D28**	**D35[s]**	**D3**	**D8**	**D14**	**D28**	**D56**	**D84**	**D91**
Windows (day)					**±2**	**-1/+2**	**±2**	**±2**	**±2**	**-2**		**-1/+2**	**±2**	**±3**	**±3**	**±3**	**±3**
Visit	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Informed consent	X	X[v]															
Demography	X																
Pregnancy test (females of childbearing potential only)[b]	X									X		X	X	X	X	X	X
Urine test for drugs of abuse and alcohol testing[c]	X										X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X															
Subject eligibility verification by Sponsor	X																
Medical, psychiatric, and medication history	X																
Complete physical examination[d]	X									X						X	X
AEs[e]	X															X	X

Procedure	SC	Double-blind part (inpatient)									Open-label part					EOT/ ET[t]	EOS[t]/ UNS[u]
Days	**-8 to -2[a]**	**D-1**	**D1**	**D3**	**D7**	**D8**	**D14**	**D21**	**D28**	**D35[s]**	**D3**	**D8**	**D14**	**D28**	**D56**	**D84**	**D91**
Windows (day)					**±2**	**-1/+2**	**±2**	**±2**	**±2**	**-2**		**-1/+2**	**±2**	**±3**	**±3**	**±3**	**±3**
Visit	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Concomitant medications								X								X	X
Height (Screening only) and body weight, BMI, waist circumference	X	X								X						X	X
Orthostatic vital signs: BP and heart rate[f]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Resting 12-lead ECG[g]	X		X						X	X			X			X	X
Hematology, coagulation, and serum chemistry and urinalysis[h]	X							X		X			X			X	X
[redacted]																	
Blood sample for viral serology[j]	X																
[redacted]																	
Admission of subject to inpatient unit[l]	X																
Discharge from unit[m]										X							

Procedure	SC	Double-blind part (inpatient)									Open-label part					EOT/ ET[t]	EOS[t]/ UNS[u]
Days	**-8 to -2[a]**	**D-1**	**D1**	**D3**	**D7**	**D8**	**D14**	**D21**	**D28**	**D35[s]**	**D3**	**D8**	**D14**	**D28**	**D56**	**D84**	**D91**
Windows (day)					**±2**	**-1/+2**	**±2**	**±2**	**±2**	**-2**		**-1/+2**	**±2**	**±3**	**±3**	**±3**	**±3**
Visit	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Randomization/assignment of subject randomization number		X															
Determination of dose adjustment						X	X	X				X	X	X	X		
Study drug administration BID			X														
Blood samples for PK analysis[n]						X			X	X			X			X	
[redacted]																	
MINI version 7.0.2[p]	X																
PANSS for schizophrenia[q]	X	X					X	X	X	X			X	X	X	X	X
C-SSRS[r]	X	X			X		X	X	X	X	X	X	X	X	X	X	X
CGI-S Scale	X	X			X		X	X	X	X			X	X	X	X	X
SAS		X			X		X	X	X	X				X	X	X	X
BARS		X			X		X	X	X	X				X	X	X	X
AIMS		X			X		X	X	X	X				X	X	X	X

Abbreviations: AE = adverse event; AIMS= Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BID = twice daily; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS= End-of-Study; EOT= End-of-Treatment; ET = early termination; HBV=hepatitis B virus; HCV= hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; MINI = Mini International Neuropsychiatric Interview (for Schizophrenia and Psychotic Disorder Studies); PANSS= Positive and Negative Syndrome Scale; PK = pharmacokinetic(s); QTcF = QT interval corrected by Fridericia; SAS= Simpson-Angus Scale; SC=Screening; UNS=unscheduled.

Note:

a. Up to a 7-day extension of the screening phase is allowed, in case extension happens due to administration issues. For example, the test has been done within 7 days after informed consent, but the result is received after 7-day window.
b. A serum pregnancy test for females of childbearing potential should be done at screening, and urine pregnancy tests are acceptable at other visits. But if the urine pregnancy test result is positive, serum pregnancy test is required to confirm. In the open-label part, if a subject is still inpatient, pregnancy test is optional.
c. A National Institute on Drug Abuse-5 urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or urine alcohol level) will be performed at scheduled visits.
d. 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.
e. AEs as reported by subjects or observed by clinical staff occur from when the ICF is signed. 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.
f. Vital signs taken in supine and standing (after standing for 2 minutes) position. BP includes systolic and diastolic BP. For consistency, it is recommended that BP is taken in the same arm throughout 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.
g. 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, heart rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements should be obtained.
h. Refer to Table 3 for individual laboratory tests.
[redacted]
j. All subjects must have the following viral serology tests completed at Screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, and HIV antibody.
[redacted]
l. If an eligible subject is not already an inpatient, the subject should be admitted to the inpatient unit.
m. In the open-label part it is not mandatory to stay in study site and the time of discharge from study site could be at the investigator's and/or subject's decision.

n. PK Sampling Schedule see Table 2.

[redacted]

p. MINI should be performed before PANSS assessment.

q. 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.

r. C-SSRS first time use “lifetime” version, other times use “Since Last Visit” version. At the unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.

s. D35 in the double-blind part is the D-1 for open-label part.

t. For subjects who have received at least one dose of study drug, if they early discontinue from study treatment or will not participate in the open-label part, they should undergo ET/EOT visit on the day of treatment discontinuation and EOS visit 7 (±3) days after the last dose of study drug.

u. The assessments on UNS visit could be at the investigator’s discretion.

v. For subjects who will participate in the open-label part, the investigator (or designee) will obtain written informed consent for open-label part from the subject before the start of this part.

Table 2 Pharmacokinetic Sampling Schedule

Part	Visit/Study Day	Timing of Collection	Collection Window
Double-blind part (inpatient)	Visit 5/Day 8	Before morning dose	within 1 hour
		0.5 hours	± 5 min
		1 hour	± 5 min
		2 hours	± 10 min
		4 hours	± 10 min
		8 hours	± 10 min
		12 hours (before the evening dose)	± 10 min
	Visit 8/Day 28	Before morning dose	within 1 hour
		0.5 hours	± 5 min
		1 hour	± 5 min
		2 hours	± 10 min
		4 hours	± 10 min
		8 hours	± 10 min
		12 hours (before the evening dose)	± 10 min
	Visit 9/Day 35	Before morning dose	within 1 hour
Open-label part	Visit 12/Day 14	Before morning dose	within 1 hour
	Visit 15/Day 84	Before morning dose	within 1 hour
ET/UNS[a]	-	-	-

Abbreviations: AE= adverse event; ET = early termination; PK=pharmacokinetic(s); UNS=unscheduled.

a. 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. 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.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design

	SC	Double-blind part (inpatient)									Open-label part							EOT/ET	EOS/UNS
Days	**-8 to -2**	**D-1**	**D1**	**D3**	**D7**	**D8**	**D14**	**D21**	**D28**	**D35**	**D1**	**D3**	**D8**	**D14**	**D28**	**D56**	**D84**	**D91**
Windows(day)					**±2**	**-1/+2**	**±2**	**±2**	**±2**	**-2**			**-1/+2**	**±2**	**±3**	**±3**	**±3**	**±3**
Visit	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	N/A	**10**	**11**	**12**	**13**	**14**	**15**	**16**
KarXT*			50/20 BID	100/20 BID	100/20 BID	125/30 BID [a]	125/30 BID [a]	125/30 BID [a]	125/30 BID [b]	125/30 BID [b]	50/20 BID	100/20 BID [c]	125/30 BID [d]	125/30 BID [d,e]	125/30 BID [d,e]	125/30 BID [d,e]	125/30 BID	N/A
Placebo			#	#	#	#	#	#	#	#	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Comments		baseline	2-day lead-in dose	Upward titration of dose		Upward titration of dose					2-day lead-in dose	Upward titration of dose	Upward titration of dose					

Abbreviations: BID = twice daily; EOS = End-of-Study; EOT = End-of-Treatment; ET = early termination; N/A = not applicable; PI = principal investigator; SC=Screening; UNS = unscheduled visit.

* All the KarXT doses are in mg.

Placebo group will receive matching capsules.

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; such dose reduction is permitted only once during the double-blind part. The dose escalation to KarXT 125/30 BID may not occur outside of the permitted window for Visit 5 (Day 8).

b. No dose adjustment will be allowed after Visit 7 to Visit 9. All subjects will continue taking the doses chosen for KarXT at Visit 7.

c. On open-label extension treatment, all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7).

d. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID.

e. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

2 INTRODUCTION

2.1 Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] There is a lack of large-scale epidemiological data on schizophrenia in China. A meta–analysis conducted in 2013 demonstrated that the lifetime prevalence of schizophrenia in China was 5.44 per 1000 (overall).[2] In China, schizophrenia contributed about 4.6 million years lived with disability (YLD) to burden of disease in 2016 and the YLD rate was significantly higher than the global average.[3]

Antipsychotic drugs (APDs) are the mainstay of treatment for schizophrenia.[4] All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, which include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[5, 6, 7] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[8, 9] Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence from animal and human studies.[10, 11] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[12] However, compounds that agonize M1 and M4 receptors are often not specific enough to avoid binding to M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share. This leads to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects such as nausea, vomiting, diarrhea, sweating, and excess salivation.

2.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline is a muscarinic-cholinergic receptor agonist. It preferentially stimulates M1 and M4 receptors and this binding in the CNS is thought to be responsible for the drug's therapeutic effects. However, xanomeline also stimulates M2 and M3 receptors, which, when activated in the periphery, are likely responsible for the AEs. In preliminary studies in patients, xanomeline has been shown to have robust positive effects on symptoms of psychosis and cognition in both Alzheimer's and schizophrenic patients.[13, 14] Xanomeline was initially developed during the 1990's and early 2000's by Eli Lilly (Lilly) as compound LY246708 to treat Alzheimer's disease. Two Investigational New Drug applications were opened, one for an oral formulation and one for a transdermal formulation. However, gastrointestinal side effects and skin irritation reactions led Lilly to terminate the project.

Trospium is a muscarinic antagonist that binds to and antagonizes all 5 muscarinic receptor subtypes with near-equal affinity. It is approved by the United States Food and Drug Administration and by European authorities for the treatment of overactive bladder. Trospium is a quaternary ammonium compound with a permanent cationic charge that limits its ability to cross the blood-brain barrier. It is well tolerated, with side effects limited to peripheral anticholinergic effects (e.g., constipation, dry mouth).

KarXT is a combined formulation of xanomeline tartrate and trospium chloride and is being developed to mitigate the peripheral side effects of xanomeline. Trospium doesn't cross the blood brain barrier, so it is expected to compete with xanomeline for binding at peripheral receptors to reduce the negative muscarinic side effects of xanomeline tartrate without reducing the intended therapeutic effects of xanomeline in the brain.

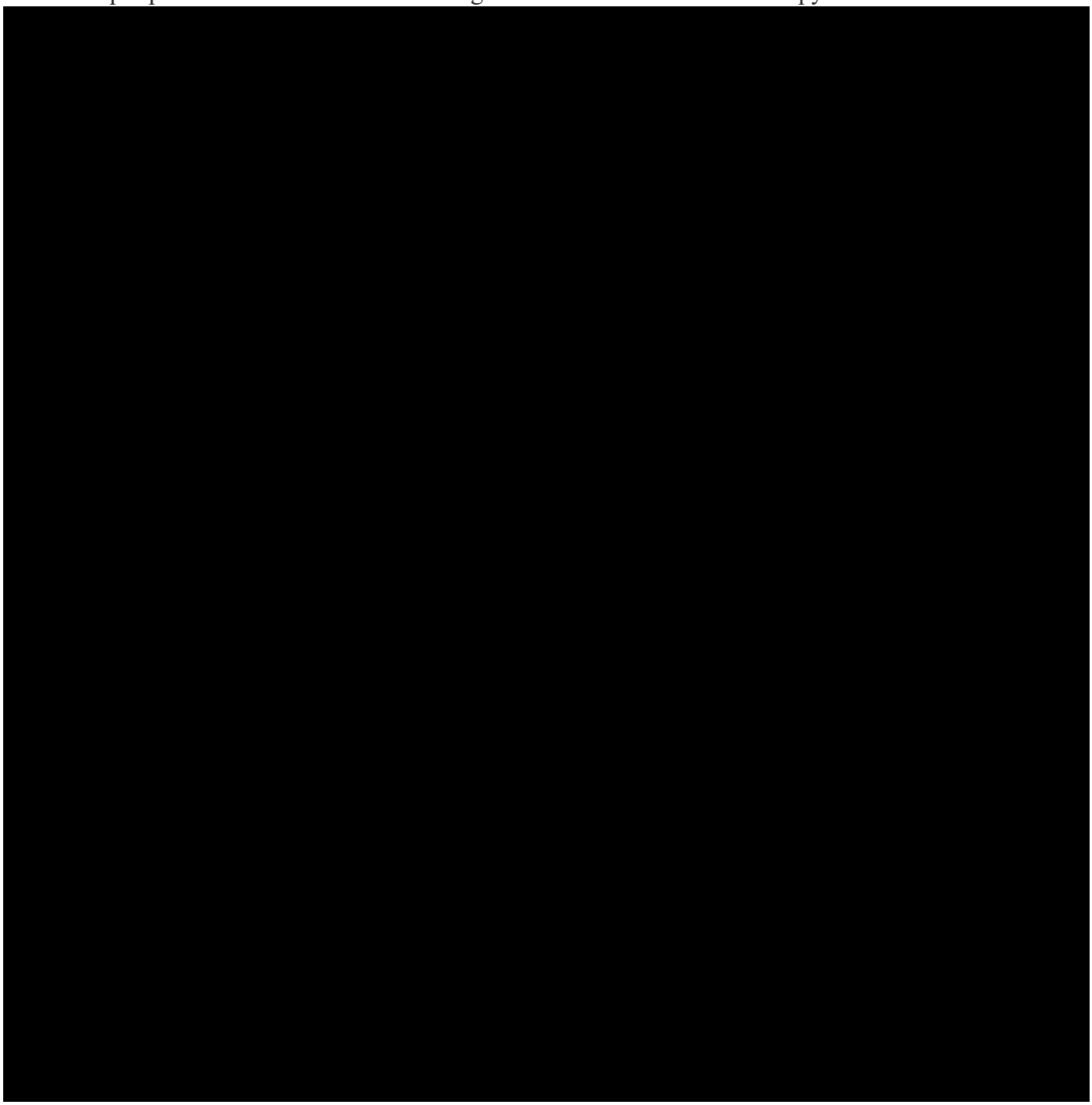
2.2.1 Nonclinical studies

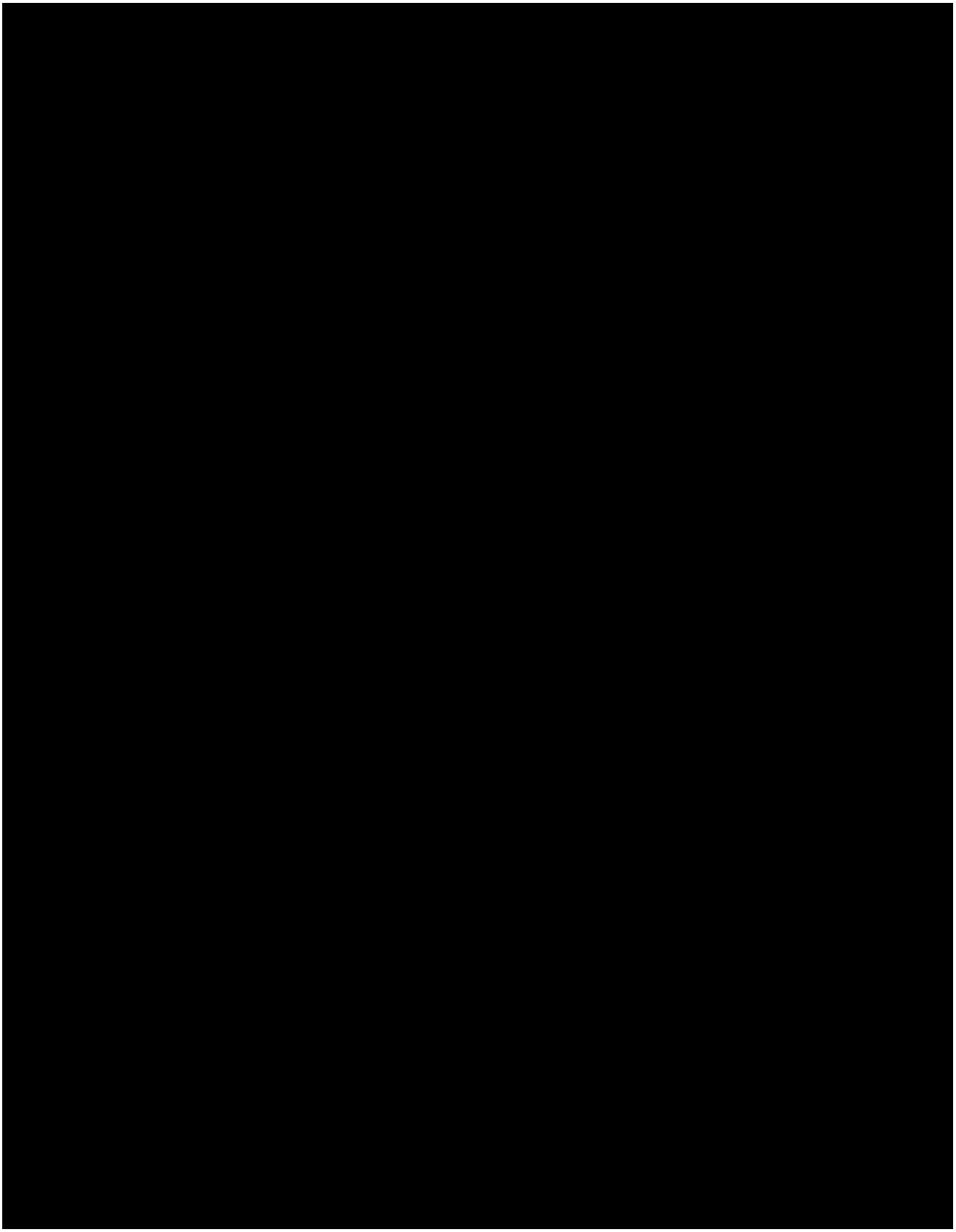
A number of nonclinical studies across species have been conducted to demonstrate the pharmacology, pharmacokinetics (PK), and toxicology of KarXT. The full discussion of these studies may be found in the Investigator's Brochure (IB).

2.2.1.1 Nonclinical pharmacology

Pharmacodynamic studies have confirmed that xanomeline is a potent, orally bioavailable (as the tartrate salt), and brain-penetrant muscarinic agonist with M1 and M4 receptor selectivity. All findings in cell culture, *ex vivo*, and *in vivo* studies can be ascribed to this selective muscarinic effect of the drug, confirming both peripheral and CNS target activation. Secondary pharmacology studies revealed no other significant activity at multiples of clinically relevant concentrations, and findings in safety pharmacology studies were all consistent with the anticipated effects of a muscarinic agonist. It is reasonable to conclude

that, with a co-administered dose of the non-CNS-penetrating muscarinic antagonist trospium chloride, clinically beneficial CNS actions of xanomeline can be achieved with significantly less peripheral intolerance than following xanomeline tartrate monotherapy.





2.2.2 Clinical experience

2.2.2.1 Xanomeline tartrate

An oral formulation of xanomeline tartrate has been studied in 15 clinical trials and was administered to >600 patients, some for as long as 3 years. Those double-blind, placebo-controlled trials have provided strong evidence for the antipsychotic efficacy of xanomeline. In the multicenter outpatient trial in Alzheimer's disease (H2Q-MC-LZZA [LZZA]), three doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks. Significant dose-dependent improvement in psychotic symptoms was observed. Results showed a resolution of psychotic symptoms in patients who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo. In a completer analysis, cognitive improvement was also found, suggesting that longer treatment intervals may be necessary for cognitive enhancement. In a subsequent small, independent, double-blind, placebo-controlled inpatient trial in treatment-resistant patients with schizophrenia[14], xanomeline at 225 mg/day demonstrated robust and relatively rapid improvement in psychosis compared to placebo. Improvement in both negative symptoms and cognitive impairment was observed.

In both Alzheimer's disease and schizophrenia trials, as well as in healthy subject studies with xanomeline, dose-dependent "pro-cholinergic" AEs were reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. Stimulation of peripheral muscarinic-cholinergic receptors likely mediated these effects. These side effects were frequent, and at the higher

doses of xanomeline they led to significant rates of discontinuation in the Alzheimer's disease studies. This "pro-cholinergic" AE profile contributed to Lilly's discontinuation of xanomeline development as a single agent.

2.2.2.2 Trospium chloride

Trospium chloride, per the Sanctura® product label, antagonizes the effect of acetylcholine on cholinergically innervated organs and exhibits parasympatholytic action by reducing tone of smooth muscles, including relaxation of the detrusor muscle to inhibit urinary bladder evacuation. Trospium dosed as Sanctura® is poorly absorbed orally with maximum observed plasma concentration (C_{max}) seen at about 5 hours. Mean absolute bioavailability is about 10%, area under the plasma concentration-time curve (AUC) and C_{max} being reduced by 70-80% when trospium chloride is dosed with a high-fat meal. The reported AEs are primarily those related to known side effects of other anti-cholinergic drugs. The most frequently reported AEs in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. The majority of these findings were mild to moderate in severity and resolved without serious intervention. No significant cardiovascular, hepatic, hematologic, or renal toxicity was identified. Active renal secretion is an important elimination pathway for trospium, such that a dose reduction in severe renal insufficiency is appropriate. Sanctura® was assigned a pregnancy Category C and was found to be excreted to a limited extent in the milk of lactating rats, indicating that it should not be used during pregnancy or lactation unless the potential benefit justified potential risk to the fetus.

2.2.2.3 KarXT

[redacted]

2.2.2.3.1 Pharmacokinetics

The PK of xanomeline and trospium have been evaluated following administration of separate formulations of xanomeline tartrate and trospium chloride in healthy subjects, as well as after administration of the co-formulated product KarXT in both healthy subjects and subjects with schizophrenia. [redacted]

Results from the PK analyses of these clinical studies showed the following:

- Xanomeline and trospium are both quickly and extensively absorbed into the systemic circulation after oral administration. Peak concentrations of xanomeline and trospium typically occur at a median time of about 2 hours and 1 hour, respectively.
- The PK of xanomeline is similar following administration of xanomeline alone and xanomeline plus trospium chloride.
- Plasma concentrations of xanomeline and trospium are highly variable between subjects, with considerable overlap in exposures occurring between subjects receiving various KarXT dosing regimens. Geometric coefficients of variation of 80% to 120% have been typical for C_{max} and AUC in healthy subjects (study KAR-003) and subjects with schizophrenia (study KAR-004).
- Plasma concentrations of xanomeline and trospium during KarXT treatment appear to be dose-proportional, although the high variability in these concentrations and sizes and designs of the studies have not permitted a conclusive determination of that relationship.
- Median elimination half-life ($t_{1/2}$) estimates for xanomeline during a dosing interval ranged from 3.35 to 5.76 hours. Median $t_{1/2}$ estimates for trospium ranged from 4.11 to 7.10 hours. [redacted] No significant accumulation of xanomeline or trospium is expected during treatment.
- There have been no reports of CYP inhibition attributable to xanomeline. The potential for xanomeline to inhibit various transporters has also been evaluated and the results indicate that P-glycoprotein, breast cancer resistance protein, organic anion transporting protein (OATP) 1B1, OAT1, and OAT3 (but not OATP1B3) may be inhibited, but not at clinically relevant xanomeline plasma concentrations.
- Available historical data for trospium indicate that it is unlikely for trospium to have PK interactions with drugs metabolized by CYPs or with drugs that induce or inhibit CYPs.

2.2.2.3.2 Efficacy

In a Phase 2 study (KAR-004, also known as EMERGENT-1) conducted in the United States (US), 28 days of KarXT (100/20 and 125/30) treatment significantly reduced the symptoms of schizophrenia in subjects with acute psychosis. This study met the primary endpoint with the Positive and Negative Syndrome Scale (PANSS) total score showing a 11.6-point mean improvement compared to placebo with a highly significant ($P < 0.0001$) separation from placebo (-17.4 KarXT vs -5.9 placebo) at Week 5. KarXT, as compared with placebo, demonstrated highly significant ($P < 0.0001$) reduction in PANSS total scores at all post-randomization time points (Weeks 2, 4, and 5). KarXT, as compared to placebo, demonstrated significant improvement at all post-randomization time points for PANSS positive symptom

subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and Clinical Global Impression-Severity (CGI-S) scores. These results demonstrate the potential benefit of KarXT for acute psychosis.

Karuna has initiated another four Phase 3 KarXT studies (KAR-007 [in the US], KAR-008 [in the US and Ukraine], KAR-009 [in the US and Ukraine], and KAR-011 [in the US]) for the targeted indication of "treatment of adults with schizophrenia." At the time of publishing this protocol, the KAR-007 study has completed and reported its topline results, and the other three studies are still ongoing. The development goal is to assess KarXT for improving positive and negative symptoms and cognition in schizophrenia.

On August 8, 2022, Karuna reported positive topline results from the Phase 3 KAR-007 study (also known as EMERGENT-2) evaluating the efficacy, safety, and tolerability of KarXT in adults with schizophrenia. The study met its primary endpoint with KarXT demonstrating a statistically significant and clinically meaningful 9.6-point reduction in the PANSS total score change from baseline compared to placebo (-21.2 KarXT vs. -11.6 placebo, $p<0.0001$) at Week 5 (Cohen's d effect size of 0.61). KarXT also demonstrated an early and sustained statistically significant reduction of symptoms, as assessed by PANSS total score, starting at Week 2 and maintained such reduction through all timepoints in the trial. [15]

2.2.2.3.3 Safety

The safety of multiple doses of xanomeline 75 mg three times daily (TID) alone compared to multiple doses of xanomeline 75 mg TID with trospium chloride 20 mg BID was evaluated in healthy subjects in Study KAR-001. The safety of multiple BID dosing regimens of KarXT was evaluated in healthy subjects (Studies KAR-002 [discontinued early], KAR-003, and KAR-020) and subjects with schizophrenia (Study KAR-004).

The KAR-001 study in healthy subjects demonstrated that adding trospium chloride to a treatment regimen of xanomeline tartrate reduced the "cholinergic" side effects by 46% compared to xanomeline alone. Moreover, the remaining cholinergic AEs (nausea, vomiting, sweating, excessive salivation, and diarrhea) were generally mild to moderate in severity and transient in nature, often lasting a few hours without recurrence.

The KAR-003 study reported no new safety issues with KarXT. For the treatment groups that completed dosing, overall subject incidence of treatment-emergent adverse events (TEAEs) was lower in the KarXT 100/20 BID group (12 [66.7%] subjects) compared to the KarXT 125/40 BID group (16 [88.9%] subjects). The most commonly reported TEAEs (≥20% of subjects) in the KarXT 100/20 BID group or the KarXT 125/40 BID group were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. The majority of TEAEs in both of these groups were considered mild in severity. For the treatment groups that did not complete dosing, TEAEs occurred in 4 (80.0%) subjects in the

KarXT 150/20 BID group and 10 (83.3%) subjects in the KarXT 150/40 BID group. The most commonly reported TEAEs were similar to those reported for the treatment groups that completed dosing.

In the KAR-004 study, 179 subjects received at least 1 dose of study drug (90 placebo and 89 KarXT). Treatment-emergent AEs were reported in 43.3% of subjects in the placebo group and 53.9% of subjects in the KarXT group. The most commonly reported TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group.

In the KAR-020 study, 24 subjects were randomized in a 1:1:1:1 ratio to 1 of 4 treatment sequences, each consisted of four, 4-day treatment periods during which a subject received either placebo, KarXT 50/20 BID, KarXT 100/20 BID, or KarXT 125/30 BID. The most commonly reported individual TEAEs with KarXT were tachycardia, fatigue, dry mouth, nausea, vertigo, vomiting, chills, headache, dizziness, dyspepsia, dysphagia, and somnolence.

2.3 Benefit/Risk Assessment

KarXT is a fixed-dose combination of xanomeline tartrate and trospium chloride. More detailed information about the known and expected benefits and risks and reasonably expected AEs of KarXT may be found in the IB.

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared with all available APDs. Most of these clinical data were generated by subjects who were either “institutionalized” or studied in an “inpatient” hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity.

In subjects with schizophrenia in study KAR-004, KarXT showed a statistically significant and clinically meaningful mean reduction in total PANSS at 5 weeks compared to placebo ($p<0.0001$), with statistical separation at each time point assessed (2, 4, and 5 weeks).

Over 867 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium chloride, or as the fixed-dose combination product KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic-related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium chloride decreases the peripheral cholinergic effect of xanomeline

creating a better-tolerated therapy. In addition, a titration phase increases the tolerability of KarXT. Trospium chloride has been marketed in the US for 18 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation.

Subjects assigned to active study drug may benefit by improvement in schizophrenia symptoms. The open-label part will allow subjects who receive placebo in the double-blind part to receive KarXT therapy.

2.4 Study Rationale

KarXT represents a novel approach to the treatment of patients with schizophrenia that has the potential to provide an important and meaningful alternative to current therapies. [redacted] This Phase 3 study, conducted in China, plans to evaluate the efficacy, safety, and PK of KarXT in the Chinese schizophrenia population [redacted]

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Double-blind part

The primary objective of the double-blind part is to evaluate the efficacy of KarXT (a combination of xanomeline tartrate and trospium chloride) administered BID versus placebo in reducing PANSS total scores in Chinese adult subjects with acute schizophrenia (by Diagnostic and Statistical Manual-Fifth Edition [DSM-5] criteria).

The secondary objectives of the double-blind part are:

- To evaluate the reduction of PANSS positive symptom score in subjects treated with KarXT versus placebo;
- To evaluate the reduction of PANSS negative symptom 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 CGI-S results in subjects treated with KarXT versus placebo;
- To evaluate the percentage of PANSS responders in subjects treated with KarXT versus placebo;
- To evaluate the safety and tolerability of KarXT;

- To assess the PK of xanomeline and trospium.

[redacted]

3.1.2 Open-label part

- To evaluate the safety and tolerability of KarXT;
- To assess the open-label KarXT efficacy.

3.2 Endpoints

3.2.1 Double-blind part

Primary endpoint:

- Change from baseline in PANSS total score at Week 5.

Secondary endpoints:

Efficacy endpoints:

- Change from baseline in PANSS positive symptom score at Week 5;
- Change from baseline in PANSS negative symptom 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 (defined as a ≥30% change in PANSS total score from baseline) at Week 5.

Safety endpoints:

- Proportion (%) of subjects with any TEAE during the double-blind part;
- Proportion (%) of subjects with any serious TEAE during the double-blind part;
- Proportion (%) of subjects with any TEAE leading to study drug withdrawal during the double-blind part;
- Orthostatic vital signs, physical examinations, clinical laboratory values and electrocardiogram (ECG) parameters;
- Columbia-Suicide Severity Rating Scale (C-SSRS), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS);
- Body weight, body mass index (BMI), and waist circumference.

PK endpoints:

- AUC of xanomeline and trospium;

- C_{max} of xanomeline and trospium;
- T_{max} of xanomeline and trospium;

[redacted]

3.2.2 Open-label part

Safety endpoints:

- Proportion (%) of subjects with any TEAE during the open-label part;
- Proportion (%) of subjects with any serious TEAE during the open-label part;
- Proportion (%) of subjects with any TEAE leading to study drug withdrawal during the open-label part;
- Orthostatic vital signs, physical examinations, clinical laboratory values and ECG parameters;
- C-SSRS, SAS, BARS, AIMS;
- Body weight, BMI, and waist circumference.

Efficacy endpoints:

- Change from baseline in PANSS total score at Week 12;
- Change from baseline in PANSS positive symptom score at Week 12;
- Change from baseline in PANSS negative symptom score at Week 12;
- Change from baseline in PANSS Negative Marder Factor score at Week 12;
- Change from baseline in CGI-S score at Week 12;
- Percentage of PANSS responders (defined as a ≥30% change in PANSS total score from baseline) at Week 12.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, multicenter, two-part study, including a 5-week randomized, parallel-group, double-blind, placebo-controlled part, followed by a 12-week open-label extension part in Chinese adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia.

In the double-blind part, subjects will be in an inpatient setting. Approximately 200 Chinese adult subjects will be randomized in a 1:1 ratio stratified by study site to receive either KarXT or placebo for a treatment period of 5 weeks. Subjects will start on a lead-in dose of KarXT 50/20 (xanomeline 50 mg/ trospium chloride 20 mg) BID for the first 2 days (Days 1 and 2) followed by KarXT 100/20 (xanomeline 100 mg/ trospium chloride 20 mg) BID for the

remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be increased to KarXT 125/30 (xanomeline 125 mg/ trospium chloride 30 mg) BID unless the subject is experiencing intolerant AEs from the previous dose increase of KarXT 100/20 BID, based on investigator's judgement. All subjects who were increased to KarXT 125/30 BID, depending on clinical response and tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period; such dose reduction is permitted only once during the double-blind part. However, dosing must not change after Visit 7 (Day 21) to Visit 9 (Day 35). In addition, dose escalation to KarXT 125/30 BID may not occur outside of the permitted window for Visit 5 (Day 8). Subjects in the placebo group will follow the same rules receiving matching placebo.

For subjects who complete the 5-week double-blind part and are willing to continue participation, and if investigator judges the subject is suitable to continue, they will continue treatment in the 12-week open-label part of the study in an outpatient/inpatient setting during which the long-term safety and effectiveness of KarXT will be evaluated.

For subjects who will not participate in the open-label part, they will undergo End-of-Treatment assessment on Visit 9 (Day 35) and an End-of-Study (EOS) visit (i.e., safety follow-up, 7 [±3] days after the last dose of study drug).

In the open-label part, all subjects will receive KarXT for up to 12 weeks. Regardless of treatment assignment in the preceding double-blind part, all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2 of the open-label part), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7 of the open-label part). At Visit 11 (Day 8 of the open-label part), dosing will be increased to KarXT 125/30 BID unless the subject is experiencing intolerant AEs from the previous dose of KarXT 100/20 BID, based on investigator's judgement. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for at least a week is allowed and will require a discussion between the principal investigator and the sponsor's medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the sponsor's medical monitor.

An EOS visit (i.e., safety follow-up, Visit 16/ Day 91 ±3 days of the open-label part) will occur for all subjects after the last dose of KarXT.

This is a China single-country study, and about 20 sites will be included.

4.2 Scientific Rationale for Study Design

This Phase 3 study in China is designed to evaluate the efficacy, safety, and PK of KarXT in the Chinese schizophrenia population [redacted]

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

Schizophrenia is a long-term mental disorder which requires a chronic therapy. A 5-week treatment duration in the double-blind part is considered an acceptable treatment duration to observe clinically significant response (i.e., primary endpoint can be achieved). The 5-week treatment duration is substantiated by the statistically significant outcome of the KAR-004 study and being used in KAR-007, and/or KAR-009 studies.

Subjects will be hospitalized during the 5-week double-blind part, where the clinical staff is available to help them 24 hours a day. The inpatient setting represents an important venue for research, examining the effects of KarXT and helping to eliminate or reduce the extent of possible subjectivity and bias. This inpatient setting will also enhance measurable quality standards and increase adherence.

The open-label part of the study will allow subjects to reinstitute (or initiate treatment if a placebo subject) KarXT therapy. Thus, subjects who were randomized to receive placebo in the 5-week inpatient portion of the study and may not have demonstrated clinical benefit, will also have the opportunity to receive KarXT in the 12-week open-label part.

4.3 Justification for Dose

The current dose-titration plan and flexible-dose design were used in a completed [redacted]. The dosing regimen for this study is similar to the regimen in those studies.

4.4 End-of-Study Definition

A subject will have fulfilled the requirements for study completion when the subject has completed all their consented study periods (i.e., double-blind part only, or double-blind part and open-label part), including the EOS Visit as indicated in the Schedule of Activities (SoA, Table 1) in accordance with the protocol.

The study will be completed when the last subject completes his/her last visit.

4.5 Study Early Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Independent Ethics Committee (IEC)/Institutional Review Board (IRB) may take such an action. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if Sponsor terminates the study, it will inform the investigators, the IEC/IRB, Regulatory Authority(ies), and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to a study treatment. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria apply:

1. Subject is Chinese national, aged 18 to 65 years, inclusive, at screening.
2. Subject is capable of providing written informed consent.
3. Subject has a primary diagnosis of schizophrenia established by a comprehensive psychiatric evaluation based on the DSM-5 (American Psychiatric Association 2013) criteria and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI) version 7.0.2.
4. Subject is experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 2 months before screening.
    a. The subject requires hospitalization for this acute exacerbation or relapse of psychotic symptoms at screen.
    b. If already an inpatient at screening, hospitalization has to be ≤2 weeks for the current exacerbation at the time of screening.

5. PANSS total score between 80 and 120, inclusive, with a

   scores of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items:

   i. Item 1 (P1; delusions)

   ii. Item 2 (P2; conceptual disorganization)

   iii. Item 3 (P3; hallucinatory behavior)

   iv. Item 6 (P6; suspiciousness/persecution)

6. Subjects with no change (improvement) in PANSS total score between screening and baseline (Day -1) of more than 20%.
7. Subject has a CGI-S score of ≥4 at screening and baseline (Day -1) visits.
8. Subject will have been off lithium therapy for at least 2 weeks before baseline and free of all oral antipsychotic medications for at least 5 half-lives or 1 week, whichever is longer, before baseline (Day -1).
9. Subjects taking a long-acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®) before baseline visit (Day -1).
10. Subject is able to be confined to an inpatient setting for the duration of the 5-week double-blind part of the study, follow instructions, and comply with the protocol requirements.
11. Body mass index of 18 to 40 kg/m^2, inclusive.
12. Subject resides in a stable living situation and is anticipated to return to that same stable living situation after discharge, in the opinion of the investigator.
13. Subject has an identified reliable informant. 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 a patient of the investigator for ≥1 year.
14. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 5.3.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria are excluded from the study:

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

2. Subjects who are newly diagnosed or are experiencing their first treated episode of schizophrenia.
3. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
4. Subjects with human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary carcinoma, and/or active hepatic viral infections based on either medical history or liver function test results.
5. History or high risk of urinary retention, gastric retention, or narrow-angle glaucoma.
6. History of irritable bowel syndrome (with or without constipation) or serious constipation requiring treatment within the last 6 months.
7. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:

   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. Non-suicidal, self-injurious behavior is not exclusionary.
8. Clinically significant abnormal findings on the physical examination, medical history, ECG, or clinical laboratory results at screening that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
9. Subjects are receiving or have recently received (within 5 half-lives or 1 week, whichever is longer, before baseline [Day -1]) oral antipsychotic medications; monoamine oxidase inhibitors; anticonvulsants (e.g., lamotrigine, valproate); tricyclic antidepressants (e.g., imipramine, desipramine); selective serotonin reuptake inhibitors; or any other psychoactive medications except for as-needed anxiolytics (e.g., lorazepam, chloral hydrate).
10. Subjects are receiving or have recently received (within 1 week before baseline [Day -1]) metformin.
11. Pregnant, lactating, or less than 3 months postpartum.
12. In the opinion of the investigator and/or Sponsor, subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator and/or Sponsor, may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.

13. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening.
14. 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 has required clozapine within the last 12 months.
15. Subjects with prior exposure to KarXT.
16. Subjects who experienced any significant adverse effects due to trospium chloride.
17. Participation in another clinical study within 3 months before screening in which the subject received an experimental or investigational drug agent.
18. Significant risk of violent or destructive behavior.

5.3 Contraception

5.3.1 Male subjects

Male subjects with female partners of childbearing potential are eligible to participate if they have a vasectomy, or have a female partner of non-childbearing potential, or agree to ONE of the following from the time of screening until 30 days after the last dose of study drug:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom (not made of natural [animal] membrane [e.g., latex or polyurethane condoms]) plus WOCBP partner use of an acceptable contraceptive method (injected, implanted or oral hormonal methods of contraception; intrauterine device; diaphragm combined with spermicidal foam/gel/film/cream/suppository) when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male subjects must refrain from donating sperm for the duration of the study and for 30 days after the last administration of study drug.

5.3.2 Female subjects

Female subjects must have been postmenopausal (at least 2 years prior to dosing), or surgically sterile, or agreed to use an acceptable form of birth control from screening until 30 days after the last dose of study drug.

Females must be of non-childbearing potential, defined as:

- Surgically sterile (i.e., hysteroscopic sterilization, hysterectomy, bilateral tubal ligation or bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the first dose of study drug) or;

- Postmenopausal with amenorrhea for at least 2 years before the first dose of study drug.

Or

Females of childbearing potential must agree to use an allowable form of highly effective birth control from screening until at least 30 days after the last dose of study drug. The following are allowed birth control methods for this study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose of study drug and with either a physical (e.g., condom, diaphragm) or a chemical (e.g., spermicide) barrier method from the time of screening until 30 days following the last dose of study drug.
- Surgical sterilization of the male partner (vasectomy for 4 months minimum) and be using a physical (e.g., condom, diaphragm) and a chemical barrier (e.g., spermicide) from screening until 30 days following last dose of study drug.

5.4 Screen Failures and Rescreening

Screen failures are defined as subjects who signed the informed consent form (ICF) to participate in the clinical study but are not subsequently randomly assigned to study treatment.

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements for eligibility assessments and therefore do not enroll (that is, screen failures) may be rescreened, upon approval of the medical monitor on a case-by-case basis. Such individuals may be allowed to rescreen 1 time. Subjects who are rescreened are required to sign a new ICF.

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

6 STUDY TREATMENTS

6.1 Details of Study Treatments

6.1.1 Identity of study treatments

KarXT is formulated as hard hydroxypropyl methylcellulose capsules containing two distinct populations of drug beads, one of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. The drug beads also contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

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

[redacted]

Excipients in KarXT capsules are MCC (National Formulary [NF]); lactose monohydrate (NF); talc (United States Pharmacopeia [USP]), ascorbic acid (USP/NF); and colored opaque, hard hydroxypropyl methylcellulose capsule shells as described below:

[redacted]

Placebo will be prepared in matching capsules as described below:

[redacted]

6.1.2 Packaging

[redacted] All packaging and labeling operations will comply with Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Blisters in wallets or Bottles with KarXT and matching placebo will be labeled with unique drug numbers and with recommended storage conditions, the name of the manufacturer, and the Investigational Use Statement ("for clinical trial use only").

6.2 Administration of KarXT and Matching Placebo

6.2.1 Double-blind part

The study drug should be administered BID on an empty stomach, i.e., at least 1 hour before a meal or 2 to 3 hours after a meal, and the evening dose will be administered 12 ± 0.5 hours after the morning dose. Some considerations for dosing and PK blood withdrawals are provided in the subsections below.

Visit 2b/Day 1 to Day 2 Dosing:

- The first dose of the KarXT 50/20 will be administered in the morning.
- All subjects must be administered 4 doses of the KarXT 50/20 or matching placebo before dose escalation to KarXT 100/20 or matching placebo BID.

Visit 3/Day 3 to Day 7 Dosing:

- If dose escalation to the KarXT 100/20 level or matching placebo is confirmed by investigator order on Visit 3/Day 3, that dose is to be administered in the morning.
- All subjects must be administered at least 8 doses of the KarXT 100/20 or matching placebo before dose escalation to KarXT 125/30 or matching placebo BID.

Visit 5/Day 8 to Visit 8/Day 28 Dosing and PK Considerations:

- If dose escalation to the KarXT 125/30 level or matching placebo is confirmed by investigator order on Visit 5/Day 8, that dose is to be administered in the morning (after the predose PK blood draw) to allow for serial postdose PK blood draws per protocol (Table 2). In the event that the subject's dose is not escalated to KarXT 125/30 or matching placebo, as confirmed by the investigator, the PK samples on Visit 5/Day 8 should also be drawn per Table 2.
- In case where visit windows are used, serial PK sampling must be done on the actual day of dose escalation for Visit 5.
- All subjects, depending on clinical response and tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period; such dose reduction is permitted only once during the double-blind part.
- For Visit 8, serial PK sampling is meant to capture the PK profile of the subject's final KarXT dose level (125/30 or 100/20) after multiple doses; therefore, there must be no changes in dose for at least 7 days prior to Visit 8. PK sampling must be done on the actual day of Visit 8 if a window is used.

Visit 9/Day 35 Dosing and PK Considerations:

- All subjects will receive their final dose level (125/30 or 100/20) until Visit 9/Day 35.
- A single PK sample should be drawn at Visit 9/Day 35 before the morning dose (Table 2).

6.2.2 Open-label part

In the open-label part it is not mandatory to stay in the study site, and the time of discharge from the study site could be at the investigator's and/or subject's decision. On the day of discharge and subsequent visits, the site pharmacist will dispense sufficient quantities of KarXT for the dosing until next visit. Site staff will provide the subject's caregiver(s) with instruction to self-administrate KarXT BID and record the dosing.

KarXT should be administered BID on an empty stomach (i.e., at least 1 hour before a meal or 2 to 3 hours after a meal). For all KarXT doses, the first dose is to be in the morning and the evening dose will be administered at 12 (±4.5) hours after the morning dose. Some considerations for dosing and PK blood withdrawals are provided in the subsections below.

Day 1 to Day 2 Dosing

- Initiate BID dosing with KarXT 50/20 × 4 doses.
- All subjects must have taken 4 doses of the KarXT 50/20 before dose escalation to KarXT 100/20 BID. Subjects who discharge from the study site should be instructed to contact the investigator in the event they did not take all 4 doses of KarXT 50/20 prior to Visit 10/Day 3.

Visit 10/Day 3-D7 Dosing:

- If dose escalation to the KarXT 100/20 level is confirmed by investigator order, initiate BID dosing with KarXT 100/20.
- All subjects must have taken at least 8 doses of the KarXT 100/20 before dose escalation to KarXT 125/30 BID. Subjects who discharge from the study site should be instructed to contact the investigator in the event they did not take at least 8 doses of KarXT 100/20 prior to Visit 11/Day 8.
- Remind subjects who discharge from the study site and subjects' caregiver(s) to bring their used packs of study drug to the next clinic visit.

Visit 11/Day 8 to Day 13 Dosing:

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order, initiate BID dosing with KarXT 125/30. In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, the subject will continue BID dosing of KarXT at the 100/20 level. Subjects who discharge from the study site will not adjust the dose level of KarXT until the next clinic visit.
- Remind subjects who discharge from the study site and subjects' caregiver(s) to bring their used packs of the study drug to the next clinic visit.

Visit 12/Day 14 to Visit 15/Day 84 Dosing and PK Considerations

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order, initiate BID dosing with KarXT 125/30. In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, the subject will continue BID dosing of KarXT at the 100/20 level. Subjects who discharge from the study site will not adjust the dose level of KarXT until the next clinic visit.
- A single PK sample should be drawn at Visit 12/Day 14 and Visit 15/Day 84 before the morning dose (Table 2), and the dose of KarXT and time of most recent dosing should be recorded.
- Remind subjects who discharge from the study site and subjects' caregiver(s) to bring their used packs of the study drug to the next clinic visit.
- All subjects will receive their final dose of KarXT on the morning of Visit 15/Day 84.

6.3 Measures to Minimise Bias: Randomization and Blinding

6.3.1 Treatment assignment and randomization

At screening, the interactive response technology (IRT) system will assign a unique subject identification number to the subject known as the Subject Number. This number will be associated with the subject throughout the study. Every subject who signs an ICF must be entered into the IRT system regardless of eligibility in order to obtain a Subject Number.

On Day -1, all eligible subjects will be randomly assigned in a 1:1 ratio to either KarXT or placebo groups stratified by study site. Subjects will be assigned a randomization number through the IRT, in accordance with the randomization code generated by the authorized personnel. Once a randomization number is allocated to one subject, it may not be assigned to another subject even if the former discontinued the study.

Completers from the double-blind part who are willing to enter the open-label part will all receive KarXT regardless of what they have been assigned in the double-blind part. Randomization is not applicable for the open-label part.

6.3.2 Blinding and unblinding

Except for designated unblinded individual(s), no study site personnel, subjects, caregivers, sponsor personnel, or sponsor designees will be unblinded to the treatment assignment before the protocol specified time point for unblinding unless unblinding is required. This prevents bias on the part of the study staff and prevents the subject from influencing the results of the study.

Study drug and packaging will be identical in size, shape, color, and appearance to maintain blinding. An IRT system will allocate treatment based on a prespecified randomization list. The randomization code will be maintained by the designated unblinded personnel. IRT

system will be programmed with blind-breaking instructions. At study initiation, the study site will be instructed on the method for breaking the blind if it becomes necessary.

Unblinding according to the protocol will occur only after the last subject completes the double-blind part.

If an investigator becomes unblinded to a given subject's study treatment before protocol specified unblinding timepoint, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued. 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 IRT system. The site is expected to notify the study medical monitor/Sponsor before breaking the study blind unless it is in the subject's best interest if the blind is broken immediately. The unblinding and its cause will be documented in the electronic case report form (eCRF). Note: In most circumstances, it is not necessary to unblind a subject, even if a serious adverse event (SAE) has occurred. If an AE is thought to be related to the study drug and poses a safety risk, the investigator must decide whether to stop study treatment and/or treat the subject.

6.4 Storage and Accountability

The investigator or an approved representative (e.g., pharmacist) will ensure that all study treatments (KarXT and matching placebo) are stored in a secured area with controlled access under controlled room-temperature conditions and in accordance with applicable regulatory requirements. Study treatments should be stored in their original containers and in accordance with the labels.

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

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Study drugs will not be returned to Sponsor or designee or destroyed until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

6.5 KarXT Retention

All unused and used KarXT must be returned or destroyed at the site, as specified by Sponsor. It is the investigator's responsibility to ensure that Sponsor has provided written authorization prior to destruction on site, and that appropriate records of the disposal are documented and

maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

6.6 Treatment Compliance

For inpatient subjects, the study drug will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to ensure the study drug was swallowed.

For outpatient subjects, administration of KarXT will be supervised by study site personnel (during in-clinic visits). The investigator site personnel will review subject's study drug administration record at each visit and remind subjects and his/her caregiver(s) of treatment compliance.

6.7 Prior and Concomitant therapy

6.7.1 Prior medications

Subjects will be asked for all prior medications they were taking up to 6 months before signing ICF. All prior medications will be recorded on the medical records and the eCRF.

Restricted prior therapies are provided in Exclusion Criteria (Section 5.2).

6.7.2 Concomitant therapies

All medications and therapies taken after signing the ICF must be recorded on the medical records and eCRF.

During the study (i.e., from the time of enrollment at baseline visit [Day -1] until study completion [EOS Visit]), subjects should refrain from the use of any new concomitant medications without the prior approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without prior approval of the investigator unless its use is deemed necessary in a medical emergency.

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

- Within 5 half-lives or 1 week, whichever is longer, before baseline (Day -1), subjects could not have taken oral antipsychotic medications, monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine, valproate), tricyclic antidepressants (e.g., imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (e.g., lorazepam, chloral hydrate).

- Within 2 weeks before baseline (Day -1), subjects could not have taken mood stabilizers (e.g., lithium).
- Subjects taking a long-acting injectable antipsychotic could not have received a dose of medication for at least 12 weeks (24 weeks for INVEGA TRINZA®).

Additional requirements related to concomitant therapies in this study are as follows:

- Within 3 months before baseline (Day -1), subjects could not have received electroconvulsive therapy.
- In the double-blind part, subjects could not receive electroconvulsive therapy, biofeedback therapy, transcranial magnetic stimulation, psychotherapy (including long-term medical order that contains the word "therapy", e.g., behavioral therapy, music therapy, behavioral intervention therapy on impulsivity, behavioral modification therapy). The above therapies are permitted to be used in the open-label part with the exception of electroconvulsive therapy and transcranial magnetic stimulation. Behavioral intervention on impulsivity is permitted to treat AE. Additional therapies may be permitted upon approval by the sponsor's medical monitor.
- Partial observation, training, and nursing operations are permitted, e.g., behavioral observation, occupational therapy training for mental disorders, activities of daily living training, psychiatric nursing, and monitoring of antipsychotic medication.

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

6.7.3 Concomitant medications for anxiety and/or sleep aid

Subjects are allowed to take benzodiazepines (up to 6 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on an as needed basis. Subjects may also use non-benzodiazepine medications (e.g., zolpidem, zaleplon) as a sleep aid also on an as needed basis. Study sites must record the use of such medications in the eCRF on a per-administration basis and subject's source document.

6.8 Dose Modification

Subjects will be dosed as described in Section 6.2 and in accordance with the SoA (Table 1).

In the double-blind part, subjects will be evaluated for dose adjustments at Visits 5, 6, and 7 and at unscheduled visits. No dose adjustments are allowed after Visit 7. No other dose modifications are permissible in the double-blind part except those specified in this protocol.

In the open-label part, subjects will be evaluated for dose adjustments starting at Visit 11 through the remainder of the treatment period. Additional changes to KarXT dosing (e.g.,

temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Treatment

Based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0, study drug may be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs [redacted] may be at the discretion of the investigator.

7.2 Lost to Follow-up

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

7.3 Withdrawal from the Study

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify Sponsor medical monitor. The date and the reason for study discontinuation must be recorded on the medical records and eCRF.

For inpatients, subjects who discontinue early from the study will be discharged from the study site, if clinically warranted after completing all the early termination (ET) assessments and will be asked to return to the study site 1 week after the ET Visit to complete EOS assessments as indicated in the SoA (Table 1). For outpatients, subjects who discontinue early from the study will be asked to return to the study site within 7 (±3) days of the last administration of KarXT to complete EOS assessments as indicated in the as indicated in the SoA (Table 1).

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

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

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

- worsening of study disease or clinical symptoms

- unacceptable toxicity or AE
- subject withdrawal of consent: at any time a subject's participation in the study may be terminated at his/her request. The reason for subject withdrawal will be noted on the medical records and eCRF.
- on the basis of the investigator's clinical judgement
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria (e.g., subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (e.g., drug noncompliance [if a study subject is off study drug for >5 consecutive days in the double-blind part and for >7 consecutive days in the open-label part]).
- violation of entry criteria; i.e., subjects who are enrolled but are later discovered not to meet entry criteria
- development of suicidal or assaultive behavior
- alcohol or illegal drug use
- pregnancy, as indicated in Section 9.3.3. Any study subject who becomes pregnant while participating in the study will be unblinded to study treatment randomization. If she is found to be on active treatment assignment, she will be followed until her pregnancy reaches term.
- Sponsor's decision to discontinue study.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who leave the unit. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 General Procedures

8.1.1 Informed consent

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

The investigator (or designee) will obtain written informed consent for open-label part from the subject before the start of this part.

8.1.2 Inclusion/exclusion criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study. All screening assessment will be completed and eligibility criteria will be verified before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

During screening, subjects' eligibility will be verified by the Sponsor medical monitor.

8.1.3 Demography collection

Demographic data will be collected for all subjects at screening. The information to be captured includes date of birth, age, sex, race, and ethnicity, which will be obtained from the subject and recorded.

8.1.4 Randomization

Randomization will be conducted on Day -1 using an IRT system.

8.1.5 Admission and discharge of the study site

Subjects will be admitted to study site from screening and stay in study site to complete the double-blind part.

In the open-label part it is not mandatory to stay in study site, and the time of discharge from study site could be at the investigator's and/or subject's decision.

8.1.6 Study drug administration and dose adjustment determination

For inpatient, the study drug will be administered under the supervision of investigator site personnel at the visits indicated in the Table 1.

For outpatient, subject will self-administrate and record the dosing. On the day of discharge and subsequent visit indicated in the Table 1, the site pharmacist will dispense sufficient quantities of study drug until next clinic visit.

In the double-blind part, subjects will be evaluated for dose adjustments at Visits 5, 6, and 7 and at unscheduled visits. No dose adjustments are allowed after Visit 7.

In the open-label part, subjects will be evaluated for dose adjustments starting at Visit 11 through the remainder of the treatment period.

8.2 Clinical Efficacy Assessments

The PANSS and CGI-S scales will be obtained at the visits indicated in the SoA (Table 1). Both scales will be administered by trained raters at the site.

8.2.1 Positive and Negative Syndrome Scale

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

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

8.2.2 Clinical Global Impression–Severity

The CGI-S is a rating scale completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The modified CGI-S asks the clinician 1 question: *"Considering your total clinical experience, how mentally ill is the subject at this time?"* The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 =

borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects [17].

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

8.3 Safety Assessments

8.3.1 Medical, psychiatric and medication history collection

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

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 9.2. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

8.3.2 Vital signs

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

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

8.3.3 Physical examinations

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat, examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in Table 1. Physical examinations will be performed by a physician or qualified designee.

8.3.4 Weight, height and body mass index, waist circumference

Height (screening only), weight, and waist circumference measurements will be obtained at visits as specified in Table 1. BMI should be calculated at these visits. All findings should be recorded on the medical records and eCRF.

8.3.5 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the SoA (Table 1). During the ECG, heart rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec, QTcF = QT / (60/heart rate)$^{1/3}$) measurements will be obtained. ECG at Day 1 will be performed 2 hours (+ 15 minutes) post morning dose. ECGs at all other scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

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

8.3.6 Clinical safety laboratory assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Table 1.

Table 3 Laboratory Assessment

Haematology	Serum Chemistry	Urinalysis
Full and differential blood count	ALT	Appearance
Hct	ALP	pH
Hb	AST	Protein
MCH	Albumin	Glucose
MCHC	Uric acid	Ketone bodies
MCV	BUN or urea	Indicators of blood
Platelet count	Creatinine	Specific gravity
RBC count	Creatine kinase	Urobilinogen
WBC count with differential	Electrolytes (sodium, potassium, chloride, calcium, phosphorus)	Occult blood
	GGT	WBCs or indicators of WBCs
	Glucose	Microscopic analysis (if needed)

	LDH	
	Total bilirubin	
	Direct bilirubin	
	Total cholesterol	
	Triglycerides	
	Total protein	
Coagulation	**Serology[a]**	**Others**
PT	HBV	[redacted]
Activated PTT	HCV	Urine drug test[b,d]
Fibrinogen	HIV	Alcohol testing[c,d]
Pregnancy test: A serum pregnancy test will be performed on all women of childbearing potential at screening and a urine pregnancy test (urine HCG) is acceptable at other visits. If a urine pregnancy test is positive, serum pregnancy test is required to confirm.		

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

a. The following viral serology tests completed at screening: anti-HCV antibody, HBV surface antigen, HBV core antibody, and HIV antibody.
b. A National Institute on Drug Abuse-5 urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed at screening.
c. Alcohol testing is performed using a breathalyzer or urine alcohol test.
d. If a subject leaves the study site, he/she should have a urine drug screen and test for alcohol (breathalyzer or urine alcohol level) upon returning to the study site.

All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up with until repeat test results return to normal, stabilize, or are no longer clinically significant. [redacted]

8.3.7 Adverse event

AEs as reported by subjects or observed by clinical staff are to be obtained at all study visits. The details of AE definitions, collection and reporting see Section 9.

8.3.8 Concomitant medications

Concomitant medications are to be obtained at all study visits.

[redacted]

8.3.10 Safety related scales

The scores of following scales will be obtained at the visits indicated in the SoA (Table 1). All scales will be administered by trained raters at the site.

8.3.10.1 Simpson-Angus Scale

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

8.3.10.2 Barnes Akathisia Rating Scale

The BARS is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity [24].

8.3.10.3 Abnormal Involuntary Movement Scale

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

8.3.10.4 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study [25]. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over identification of suicidal behavior. The scale takes approximately 5 minutes to administer.

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

8.3.10.5 Mini International Neuropsychiatric Interview Version 7.0.2

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

8.4 Pharmacokinetics

8.4.1 Blood sampling

Blood samples to provide sufficient plasma for bioanalysis will be collected at each scheduled time point (see Table 2). The actual date and time of each blood sample collection will be recorded.

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

8.4.1.1 Double-blind part

During the double-blind part, PK blood samples will be collected from all subjects to maintain the study blind. However, samples from subjects randomized to placebo will not be routinely analyzed.

Blood samples for PK analysis will be collected on Visit 5/Day 8 -1/+2 days and Visit 8/Day 28 ± 2 days at the time points indicated in Table 2. On Visit 9/Day 35, a single sample will be collected within 1 hour before the morning dose.

The exact times of each dose and PK draw must be recorded on the eCRF, and PK samples must be collected within the specified times of collection. In case where visit windows are used, serial PK sampling must be done on the actual day of Visit 5. For Visit 8, serial PK sampling is meant to capture the steady-state PK profile of the subject's final KarXT dose level (125/30 or 100/20) after multiple doses. If visit windows are used for Visit 8, the PK sampling should occur at least 7 days after Visit 7 is completed, and there must be no changes in dose for at least 7 days leading up to Visit 8. PK sampling must be done on the actual day of Visit 8.

A single PK sample may be drawn if a relevant/significant AE is reported during a scheduled visit or if there is a dose adjustment or relevant/significant AE reported during an unscheduled visit. 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.

8.4.1.2 Open-label part

PK blood samples from all subjects participating in the open-label part will be analyzed regardless of their treatment assignment from the double-blind part.

On Visit 12/Day 14 and Visit 15/Day 84, a single blood sample will be collected within 1 hours before the morning dose (see Table 2).

A single PK sample may be drawn if a relevant/significant AE is reported or if there is a dose adjustment. For an ET related to an AE, collection of a PK blood sample at the ET visit is recommended.

8.4.2 Bioanalytical methodology

Concentrations of xanomeline and trospium will be measured in plasma PK samples using validated bioanalytical method(s). [redacted]

9 SAFETY INFORMATION COLLECTION AND REPORTING

9.1 Definitions

9.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a subject or clinical study subject administered a medicinal/investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition, whether it is associated with the use of the sponsor's product or not, is also an AE. Clinically significant vital signs and laboratory abnormalities should also be recorded as AEs.

Note: In a clinical study setting, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms or disease (new or exacerbated) temporally associated with the use of study intervention. The active AE collection starts from when the ICF is signed (even if no study treatment has been administered) till EOS Visit or ET (whichever later) defined in this protocol.

9.1.2 Serious adverse event

An SAE refers to an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Life-threatening
    - Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (e.g., hepatitis that resolved without hepatic failure).
- Requires hospitalisation or prolongation of existing hospitalisation
    - Note: Common usage of "hospitalization" generally would include being treated by a physician in a hospital for at least a 24-hour period. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Results in persistent or significant disability or incapacity
- Results in congenital abnormality or birth defect
- Important medical event
    - Note: Important medical events that may not be immediately result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include:
        - allergic bronchospasm requiring intensive treatment in an emergency room or at home;
        - blood dyscrasias or convulsions that do not result in inpatient hospitalization;
        - or the development of drug dependency or drug abuse.

Simply stopping the suspect drug does not mean that it is an important medical event, it needs medical and scientific judgement.

Exception: The following scenarios will not be reported as SAEs:

- Pre-planned (at time of informed consent) hospitalization for elective procedures will not be considered a criterion for an SAE. The reason for the planned hospitalization should be

captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

- A hospitalization or prolonged hospitalization due to economic issue or for purpose of reimbursement only, for protocol compliance or social reasons, or for observation will not be considered a criterion for an SAE.

SAE will be reported as described in Section 9.3.1.

9.1.3 Treatment-emergent adverse event

An event that is temporally associated with administration of study treatment is defined as a TEAE. Events meeting this definition will be those occurring during or after administration of the first dose of study drug. Events that existed before the first administration of study product and then increased in severity during or after the first administration of study product will also be considered treatment emergent. Such events will be captured on the eCRF as new events, with the onset date as the date of the increase in severity.

9.1.4 Adverse events of special interest

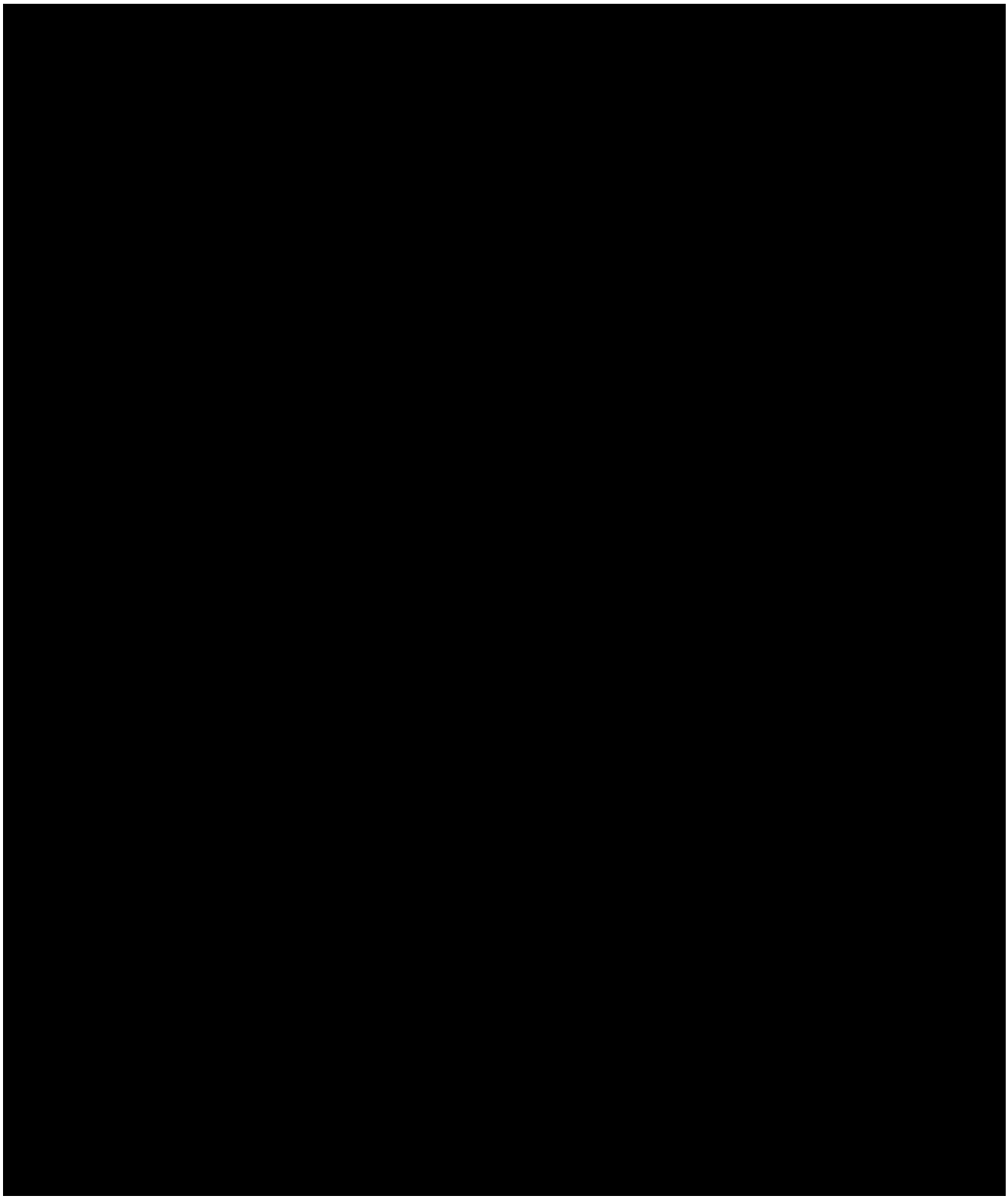
The AEs of special interest (AESIs) will be monitored and include orthostasis [redacted]. These events must be reported with the investigator's assessment of seriousness, severity, and causality.

Orthostasis is defined as the subject being **symptomatic** and having at least one of the following:

- a decrease in systolic blood pressure of ≥ 20 mmHg
- a decrease in diastolic blood pressure of ≥ 10 mmHg
- an increase in pulse rate of ≥ 30 bpm

Changes in blood pressure or pulse rate alone without the subject being symptomatic should not be considered as an AESI. This should be captured as an AE.

[redacted]



AESI will be reported as described in Section 9.3.2.

9.1.5 Special situations

9.1.5.1 Medication error and overdose

- **Medication error:** any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use. Medication errors are not regarded as AE, but AEs may occur as a consequence of the medication error.
- **Overdose:** a deliberate or accidental administration of study treatment to a study subject, at a dose greater than that which was assigned to that subject per the study protocol and under the direction of the investigator. For this study, any dose of KarXT greater than 250/60mg within 24 hours will be considered an overdose.

Medication error and overdose will be reported as described in Section 9.3.4.

9.1.5.2 Pro-cholinergic and Anti-cholinergic Adverse Events

The investigator will monitor each subject for spontaneously reported pro-cholinergic and anti-cholinergic AEs throughout the subject's participation in this study, from the time the ICF is signed through the EOS Visit or ET (whichever is later) defined in this protocol.

Spontaneously reported pro-cholinergic AEs include but are not limited to:

- Nausea
- Vomiting
- Sweating
- Excessive salivation
- Diarrhea

Spontaneously reported anti-cholinergic AEs include but are not limited to:

- Constipation
- Dry mouth
- Urinary retention
- Difficulty urinating

9.1.6 Suspected unexpected serious adverse reactions

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

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

9.2 Collection and Recording of Adverse Events

9.2.1 Method of detecting AEs and SAEs

Adverse events may be volunteered spontaneously by the subjects, or discovered by the study staff during safety assessments or by asking an open, non-leading question such as, "How have you been feeling since your last study visit?" The investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

9.2.2 Adverse event / serious adverse event / adverse events of special interest collection period

The collecting and recording of AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by subject), will be from signing ICF until EOS Visit or ET (whichever later). SAEs/AESIs considered related to study drug by the investigator should be reported to the sponsor or its designee immediately (within 24 hours), even if the event occurs after study completion.

9.2.3 Documentation of adverse events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- The adverse event term: The disease diagnosis is preferred as AE term, if a unifying diagnosis is available; if not, the associated symptoms and signs are to be captured and recorded using standard medical terminology. Once the diagnosis is confirmed with the follow up information, the symptoms and sign should be replaced with diagnosis

accordingly. One single event term to be recorded should only contain a sole event, such as a single diagnosis, sign and/or symptom. For example, if a subject experiences "vomiting and diarrhea," then it needs to be captured separately as two AEs rather than one, namely "vomiting" and "diarrhea." Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History in the eCRF and on the SAE Report Form.

- Severity: Should be differentiated from "Serious Adverse Events." Event seriousness will be determined according to the definition of an SAE in Section 9.1.2, based on clinical outcome or action criteria, while the severity of AEs will be graded according to the NCI CTCAE v5.0 (Grades 1 through 5).
- Specific guidelines for classifying AEs by intensity are generally described as below:
  - **MILD:** An event that is easily tolerated (requires minimal or no treatment) and generally not interfering with normal daily activities.
  - **MODERATE:** An event that is sufficiently discomforting to interfere with normal daily activities; intervention may be needed.
  - **SEVERE:** An event that is incapacitating, with inability to work or perform normal daily activities and may require systemic drug therapy or other treatment.
- Onset date and end date (if applicable)
- Action taken
- Causal relationship with study treatment: The investigator should evaluate and provide causal relationship between the study drug and the AE; the consideration points might be but not limited to the following points:
  - **UNRELATED:** An AE that does not follow a reasonable temporal sequence from administration of a drug; for which sufficient data exist to indicate that the etiology is unrelated to the study drug; and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.
  - **UNLIKELY:** The temporal sequence from administration of the study treatment suggests that the relationship is unlikely; the response pattern is unlike that of the study treatment (if response pattern is previously known); could be reasonably explained by the subject's clinical state.
  - **POSSIBLY:** Applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be

considered possibly relate if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) that follows a known or expected response pattern to the study treatment; and/or (3) that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

- **PROBABLY:** A reaction that follows a reasonable temporal sequence from administration of study treatment; that follows a known or expected response pattern to the study treatment; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.
- **DEFINITELY**: There is clear evidence that the event is related to the use of the study treatment. An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug); that follows a known or expected response pattern to the study treatment.

- Outcome of event (Recovered/resolved, Recovering/resolving, Not recovered/not resolved, Recovered/resolved with sequelae, Fatal, or Unknown.)
- Seriousness (Yes or No)

9.3 Safety Reporting

9.3.1 Reporting of serious adverse events

SAEs, including death due to any cause, will be actively collected from the time of signing the ICF throughout the treatment period until EOS Visit or ET (whichever later).

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, it will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event. The completed, signed, and dated SAE Report Form should be emailed to Zai Lab within 24 hours of awareness: saereporting@zailaboratory.com.

Expedited reporting will follow local and international regulations, as appropriate.

All SAEs occurring during clinical study must be reported to the sponsor or its designated representative by investigational staff immediately but **no later than 24 hours** of when he/she becomes aware of it, whether or not considered causally related to the study drug, or to the study procedure(s). This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of pregnancy cases. The sponsor representative works with the investigator to ensure that all the necessary information is provided within above timeline.

For all SAEs the investigator is obligated to pursue and provide information to the sponsor or its designated representative in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. The contact information for assistance with SAE reporting, specific to the site, is listed in the investigator folder provided to the study site. The original copy of the SAE report form must be kept with the eCRF documentation at the study site. The sponsor representative will advise the investigator/study site personnel how to proceed.

9.3.2 Reporting of adverse events of special interest

All AESIs must be reported to the sponsor or its designated representative **within 24 hours** of awareness of the event regardless of the seriousness. If the AESIs meet serious criteria, it should be reported as SAEs.

9.3.3 Reporting of pregnancy

WOCBP must have a negative pregnancy test at screening.

If any pregnancy occurs during the study or within 30 days after the last dose of study treatment, then the investigator or other site staff must inform the appropriate sponsor representatives **within 24 hours** of when he or she becomes aware of it, using "Pregnancy Reporting Form."

- Details of all pregnancies in female subjects will be collected and recorded on medical records and eCRF, after the start of study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner.
- The outcome of all pregnancies should be followed up and documented even if the subject was discontinued from the study. If pregnancy outcomes meet SAE criteria (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy), they should be reported as SAEs. All pregnancies and outcomes of pregnancy should be reported to Sponsor or its designated representative, except for the pregnancy discovered before the study subject has received any study drug. The above timelines apply when outcome information is available.

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

The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The investigator should notify Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report.

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

9.3.4 Reporting of medication error and overdose

All occurrences of medication error and overdose with any study treatment are to be captured on the medication error page of eCRF whether or not the medication error is accompanied by an AE, as determined by the investigator.

The medication error should be reported to the sponsor within 24 hours of awareness **only when associated with an SAE.**

Overdose should be reported to the sponsor within 24 hours of awareness regardless of if associated with SAE.

For medication error or overdose associated with a SAE, the standard reporting timelines apply, see Section 9.3.1.

9.3.5 Reporting of suspected unexpected serious adverse reactions

The investigator will assess whether or not an event is causally related to study treatment. The Sponsor, or their designee, will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or their designee) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or their designee) first has knowledge of them.

9.4 Follow-up of Adverse Event and Serious Adverse Event

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts.

All AEs experienced by a subject, regardless of the suspected causality, will be followed until the AE or SAE has resolved (returns to normal or baseline values), or stabilized with a satisfactory explanation for the changes observed, or the subject is lost to follow-up, or until the subject has died.

Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10 STATISTICAL CONSIDERATIONS

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

[redacted] All data will be listed, and summary tables and figures will be provided. Presentations will be separated by double-blind part and open-label part. Summary statistics will be presented by treatment group (if applicable). For continuous variables, data will be summarized with the number of subjects (N), mean and standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

Baseline for the double-blind part is defined as the last non-missing assessments prior to the first dose of study drug in the double-blind part; Baseline for the open-label part is defined as the last non-missing assessments prior to the first dose of study drug in the open-label part; unless otherwise stated.

10.1 Statistical Hypotheses

The hypothesis of this study is based on the primary efficacy endpoint, i.e., change from baseline in PANSS total score at Week 5 of the double-blind part. The null hypothesis H_0 and alternative hypothesis H_1 are as follows:

- H_0: there is no difference in the change from baseline in PANSS total score at Week 5 of the double-blind part between KarXT and placebo
- H_1: There is a difference in the change from baseline in PANSS total score at Week 5 of the double-blind part between KarXT and placebo

The null hypothesis H_0 will be rejected in favor of alternative hypothesis H_1 if p-value ≤ 0.05 using a 2-sided test.

10.2 Sample Size Determination

[redacted]

10.3 Populations for Analyses

Intent-to-Treat Population: All subjects who are randomized to the study will be included in the intent-to-treat (ITT) population. Subjects will be analyzed according to randomized treatment.

Modified Intent-to-Treat Population (mITT): 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. Subjects will be analyzed according to randomized treatment.

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. Subjects will be analyzed according to actual treatment received.

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 KarXT and have at least 1 measurable plasma concentration of xanomeline or trospium.

10.4 Statistical Analyses

10.4.1 Efficacy analyses

All efficacy analyses will be performed using the mITT population.

10.4.1.1 Analysis of primary endpoint/estimand of double-blind part

The primary estimand is only for double-blind part. The open-label part does not have an estimand defined.

The population of the primary estimand is among Chinese adult subjects (aged 18-65 years), whose disease status fulfils all of the following criteria: 1. has a primary DSM-5 diagnosis of schizophrenia and confirmed by MINI for schizophrenia; 2. are acutely psychotic and hospitalized; 3. PANSS score of 80 to 120 at time of enrollment, defined according to the inclusion/exclusion criteria.

Subjects will receive flexible-dose KarXT (or matching placebo in the double-blind part) as defined in Section 6.2, with or without permitted concomitant medication used for anxiety

and/or sleep aid as outlined in Section 6.7.3. The primary analysis will be executed on the mITT population, including all subjects with a baseline and at least 1 post-baseline PANSS measurement, grouped as randomized.

The variable is the change from baseline in PANSS total score at Week 5 in the double-blind part.

[redacted]

The population-level summary is the difference between treatment groups (KarXT vs placebo) in mean change from baseline in PANSS at Week 5 in the double-blind part, obtained from a mixed model repeated measures (MMRM) evaluation. The model will include the change from baseline PANSS total scores at Week 2, Week 3, Week 4, and Week 5 as the response.

[redacted] The least square mean and standard error of each treatment group, the least square mean difference between KarXT and placebo group at Week 5 and the corresponding 95% confidence interval and p-value will be provided. [redacted]

[redacted]

10.4.1.2 Analysis of secondary efficacy endpoints for double-blind part

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

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

10.4.1.3 Analysis of efficacy endpoints for open-label part

In the open-label part, efficacy variables will be summarized using the descriptive statistics based on the mITT population for subjects who are entering into the open-label part by scheduled visits. As these variables are summarized over time and the initial values (Day 1 in the open-label part) can be impacted by the treatment received in the double-blind part, the analyses will use a combination of double-blind/open-label treatment groups, which is intended to provide perspective on the change in these values from the double-blind part through the open-label part. Tabular or figure presentations will include Baseline of the double-blind part, Baseline of the open-label part, scheduled visits in the open-label part, and corresponding changes from double-bind and open-label baseline.

10.4.2 Safety analyses

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The proportion of subjects with TEAEs will be summarized by System Organ Class, Preferred Term, and treatment group. All AEs will be listed by subject, along with information regarding onset, duration, severity, relationship to study drug, action taken with study drug, outcome, and additional information if collected and deemed necessary.

Orthostatic vital signs, clinical laboratory values, ECG parameters, and physical examinations will be summarized descriptively by time point and treatment group, including the changes from baseline as appropriate, as well as numbers of subjects with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, SAS, BARS, AIMS, body weight, BMI, and waist circumference.

10.4.3 Pharmacokinetic analyses

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

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

PK parameter estimates for xanomeline and trospium will be derived from plasma concentration data using noncompartmental methods. Actual time elapsed from dosing will be used. The primary PK parameters of interest will include C_{max}, T_{max}, and AUC from 0 to 12 hours (or from 0 to the last measurable concentration). Additional parameters including the effective elimination half-life during a dosing interval, apparent clearance, and apparent volume of distribution will be determined if the data permit.

The details of the PK analysis will be described in the SAP. The noncompartmental analysis will be described as a part of the final clinical study report.

Apart from that, the PK data from this study may be analyzed using a population modelling approach to evaluate the PK characteristics and exposure-response relationship of KarXT for Chinese schizophrenia patients. If this is done, then a detailed analysis description will be provided in a separate population modelling analysis plan. The results of any such analyses would be reported separately from the clinical study report.

10.4.4 Methods for multiplicity control

The statistical analysis of the primary and secondary efficacy endpoints will account for multiplicity by using a fixed sequence testing procedure to control the overall Type I error rate of 0.05 (2-sided). [redacted]

10.5 Interim Analyses

No interim analysis is planned for this study.

[redacted]

11 DATA MANAGEMENT AND MONITORING

11.1 Case Report Form and Source Documents

Data recorded on source documents will be transcribed onto eCRFs. The eCRF is required to be completed for each participated subject timely after every site visit. The completed original eCRFs are the sole property of Sponsor and should not be accessible to any other third parties, except for authorized representatives of Sponsor or appropriate Regulatory Authority. Copies of completed eCRFs will be provided to Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

The investigator shall collect, report and enter all clinical, laboratory, safety data on the eCRF, medical records, or any other data collection forms (source documents) and ensure the data are in compliance with ALCOA-CCEA (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available) principles.

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

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

The required source document should include but is not limited to the following:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in study (including Protocol Number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study medication (preferably drug dispensing and return should be documented as well);

- Record of all AEs and other safety parameters (start and end date, and preferably including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of study completion and reason for early discontinuation, if applicable.

11.2 Record Retention

All clinical study documents must be retained by the investigator for a period of at least five years after approval for marketing. The investigator may be required to retain documents longer if required by applicable Regulatory Authority requirements, by local regulations, or by an agreement with the Sponsor or its designee, who will inform the investigator when these documents may be destroyed. Sponsor or its designee must be notified in writing at least 6 months prior to the intended date of disposal of any study record related to this protocol to allow Sponsor to make alternate storage arrangements.

If the investigator wishes to assign the study records to another party or move them to another location, Sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

11.3 Monitoring

The study will be monitored according to the ZL-2701-001 monitoring plan to ensure that it is conducted and documented properly according to the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

Monitoring visits, on-site and remote (telephone) or a combination and contacts will be made at appropriate times during the study. The investigator will assure himself/herself and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject. The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed will provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Regulatory Authority Approval

Sponsor will obtain approval to conduct the study from the appropriate Regulatory Authority in accordance with Chinese Regulatory Authority requirements prior to a site initiating the study in China.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with GCP. These standards respect the following guidelines:

- ICH Guideline for Good Clinical Practice E6 (R2).
- Chinese GCP.
- US Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).
- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects).
- Any additional Chinese Regulatory Authority requirements.

12.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by the IRB/IEC and Sponsor prior to initiation of the study.

The investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. Subjects must be informed that their participation is voluntary. A copy of the signed ICF will be provided to the subject or the subject's legally authorised representative. The original will be retained by the investigator.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

If a subjects' partner becomes pregnant during or within 30 days after the last dose of study drug, the partner is asked to sign the relevant consent form and provide information about the pregnancy accordingly.

12.4 Confidentiality

12.4.1 Confidentiality of data

By signing this protocol, the investigator affirms to Sponsor that information furnished to the investigator by Sponsor will be maintained in confidence and such information will be divulged to the IRB/IEC, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication.

12.4.2 Confidentiality of subject/patient records

By signing this protocol, the investigator agrees that Sponsor (or other authorised representative), IEC/IRB members, or Regulatory Authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. The subject must be informed that his/her personal study-related data will be used by Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

Each subject will be assigned a unique identifier by Sponsor. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique identifier only; full names/initials, or any information which would make the subject identifiable will be masked prior to transmission to Sponsor. In addition, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws, rules and regulations.

12.5 Quality Control and Assurance

Sponsor is responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that studies are conducted, and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by Sponsor, or other authorized third-party(ies) that working with or on behalf of Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that the investigator(s) and other study relevant site staff are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

12.6 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Sponsor before submission. This allows Sponsor to protect proprietary information and to provide comments.

Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX A Leading Site and Sponsor Information

Study Title:	A Phase 3, Multicenter, Two-part Study with a 5-week Double-blind Part (Randomized, Parallel-group, Placebo-controlled) followed by a 12-week Open-label Extension Part, to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Chinese Adult Subjects with DSM-5 Schizophrenia
Leading Site:	Name: Beijing Anding Hospital, Capital Medical University Address: No. 5 Ankang Hutong, Xicheng District, Beijing, China

[redacted]