1 Title Page

Clinical Study Report	
Study Title:	A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly- dosed, Multicenter Study to Evaluate the Efficacy and Safety of SYM-23 in Acutely Psychotic Adult Subjects With Schizophrenia
Investigational Drug Name:	SYM-23
Indication:	Schizophrenia
Protocol Number:	Doc Compare POC
Drug Development Phase:	2
Study Initiation Date:	
Study Completion Date:	
GCP Statement:	This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice or Trials on Medicinal Products, including archiving of essential study documents.
Date of Report:	08-02-2023

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed:	Date: ____/____/_____
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2 Study Synopsis

<table>
<tr><td>Name of Sponsor:

XXX Pharmaceuticals, Inc.</td><td>INDIVIDUAL STUDY TABLE</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
N/A</td><td rowspan="2">Referring to Module 5 of the Dossier

<u>Volume:</u> <u>Page:</u></td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient(s):</td></tr>
<tr><td>Title of Study</td><td colspan="2">A 4-Week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexibly- dosed, Multicenter Study to Evaluate the Efficacy and Safety of SYM-23 in Acutely Psychotic Adult Subjects With Schizophrenia</td></tr>
<tr><td>Investigator(s)</td><td colspan="2"></td></tr>
<tr><td>Study Center(s)</td><td colspan="2">Approximately 35 centers globally</td></tr>
<tr><td>Publication</td><td colspan="2">N/A</td></tr>
<tr><td>Study Period</td><td>From:

To:</td><td>Phase:

2</td></tr>
<tr><td>Objectives</td><td colspan="2">Study Objectives:
Primary:</td></tr>
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	To evaluate the efficacy of flexibly dosed SYM-23 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS). **Secondary:** • To evaluate the efficacy of flexibly-dosed SYM-23 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by: • Clinical Global Impression-Severity (CGI-S) • PANSS subscale scores (positive, negative, and general psychopathology) • Brief Negative Symptom Scale (BNSS) • Montgomery-Asberg Depression Rating Scale (MADRS) • To evaluate the safety and tolerability of SYM-23 (50 or 75 mg/day) using • physical examinations (PE) • 12-lead electrocardiograms (ECG) • vital signs • adverse event (AE) reports • clinical laboratory results • body weight and body mass index (BMI) • Columbia – Suicide Severity Rating Scale (C-SSRS)
Methodology	In a 1:1 ratio, the treatment group will be divided within each clinical center, randomized, double-blind, parallel-group study evaluating SYM-23's effectiveness and safety in acutely psychotic adult subjects with schizophrenia using SyM-24 (50 or 75 mg/day [ie, once daily] for randomized control. The study will consist of three phases: Screening/Washout (up to 14 days), Intervention (4 weeks in-patient), and a Follow-up visit (7 days after the last research drug dose for patients who stop smoking before or not enroll in the open-label extension study [SYM-202]) as shown in Figure 1.

Number of Patients	
Diagnosis and Main Criteria for Inclusion	**Diagnosis and Main Criteria for Subject Inclusion:** See Section 8 of full protocol for the complete list of inclusion and exclusion criteria information. **Inclusion criteria (not all inclusive):** To qualify for participation, subjects must meet all of the following inclusion criteria: • Male or female subject between 18 to 40 years of age (inclusive) at the time of consent. • Subject meets DSM-5 criteria for schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the SCID-CT). The duration of the subject's illness whether treated or untreated must be ≥ 6 months. • Subject must have a CGI-S score ≥ 4 (moderate or greater) at screening and Baseline (Day 1). • Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 (moderate) on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at screening and Baseline (Day 1). • Subject has an acute exacerbation of psychotic symptoms (no longer than 2 months). • Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene. • Subject requires hospitalization for an acute psychotic exacerbation at the time of screening or has been hospitalized for the purpose of treating an acute psychotic exacerbation for no more than 2 consecutive weeks immediately before screening. Subjects who have been hospitalized for more than 2 weeks for reasons unrelated to acute psychotic exacerbation may be included if such a hospitalization was for a condition other than an acute psychotic relapse. For example, subjects in a long-term hospital setting who have an acute exacerbation and are transferred to an acute unit are eligible for the study. • Subject has had no more than 2 prior hospitalizations for the treatment of an acute exacerbation of schizophrenia (not including the current hospitalization). This history must be confirmed based on report by a reliable informant (eg. caregiver or family member) or

	medical records available at the time of screening. • At Baseline, subject must have a total score < 5 on the SAS.
Test Product, Dose and Mode of Administration	**Name of Investigational Product:** SYM-23 **Investigational Product, Dosage and Mode of Administration:** SYM-23 treatment will be size 0, Swedish-orange capsules (50 mg or 75 mg) administered orally once daily. Study drug will be taken at the same time each evening before bed time and may be taken with or without food. Subjects will receive SYM-23 50 mg/day on Day 1 through 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase is necessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposes is permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, with no dose adjustments allowed thereafter.
Reference Therapy, Dose, Mode of Administration, and Batch Numbers	Matching placebo treatment will be size 0, Swedish-orange capsules administered orally once daily. Study drug will be taken at the same time each evening before bed time and may be taken with or without food. Subjects randomized to placebo will receive placebo throughout the study.
Duration of Treatment	4 weeks
Criteria for Evaluation	The CBB will assess the effect of SYM-23 on cognition by collecting physical examination (PE) results, ECGs, vital signs, AEs', clinical laboratory data, C-SSRS, and MADRS scores throughout the study. Subjects with significant findings for suicidal ideation after completion of the C-SSRS at any time during the study must be referred to the researcher for follow-up analysis by using the AIMS, BARS, and SAS scales. POPPK measurements for plasma SYM-23 and SyM-22 concentrations will be collected on Day 1 (predose) and Page 29; the results of which will not be announced separately. The effect of cytochrome (CYP) P450 metabolizer status on plasma SYM-23 exposure using population PK/pharmacodynamics (PD) methods exposure will be investigated and reported separately.
Bio-analytical Methods	
Statistical Methods	**Statistical Methods:**

	The change from Baseline to Test Effects (mITT) population, which includes all subjects that are random, have received at least one dose of study drug, and have performed at minimum one post-Baseline evaluation in PANSS or CGI-S, is the measurement of safety. The Safety population will be based on the change between Baselines' testing superiority of SYM-23 relative to placebo, according to the current research findings. The MMRM's primary outcome variable will be determined as a covariate, and the Kenward-Rogers approximation will determine the denominator degree of freedom for the treatment, visit (Day 4, Weeks 1, 2, 3, and 4; as an identifiable attribute), pooled center, study-by-visit interaction, etc. The secondary effect variables of change from Baseline's CGI-S score, PANSS subscale scores, BNSS total score and MADRS total rank will be determined similarly to the primary endpoint. Baseline PANSS total score, including laboratory results, clinical findings, and C-SSRS will be summarized as the dependent variable in this case. AEs will be further described by severity and in relation to the study drug, as well as any adverse events that occurred before or after the first dose of study medication. A nonparametric rank analysis of covariance (ANCOVA) will be applied to prolactin, HbA1c, lipids, and glucose levels, as well as body weight and BMI in order to compare changes from Baseline to treatment groups with adjustments for Baselines. **Sample Size:** Based on a review of published research into other antipsychotics for the short-term treatment of schizophrenia, 80% power will be found in change from Baseline in PANSS total score at Week 4 for SYM-23 and placebo) with t-test method with two independent sample randomized design methods with 2-sided significant difference size of 0.05 was expected. The total sample size will be 240 random subjects (or 120 subjects per treatment group), with an upward adjustment of the sample number being used to compensate for missing data from subjects that are randomly chosen and discontinue from the study.

RESULTS
Disposition: **Efficacy:**

Safety:
CONCLUSIONS
Date of Report: 08-02-2023

3 Table of Contents

4 List of Abbreviations & Definition of Terms

Abbreviations	Terms
5-HT	5-hydroxytryptamine (serotonin)
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BNSS	Brief Negative Symptom Scale
BOLD	Blood oxygen level dependent
BUN	Blood urea nitrogen
C-SSRS	Columbia – Suicide Severity Rating Scale
CDR	Clinical data repository
CFR	Code of Federal Regulations

CGI-I	Clinical global impression - improvement
CGI-S	Clinical global impression - severity
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
CYP	cytochrome
DEQ	Drug Effects Questionnaire
ECG	Electrocardiogram
EDC	Electronic data capture
EEG	Electroencephalogram
ET	Early termination
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging (fMRI)
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
IXRS	Interactive voice/web response system
LIMS	Laboratory information management system
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MID	Monetary incentive delay
mITT	Modified Intention-to-Treat
MMRM	Mixed-effects Models Repeated Measures
MoA	Mechanism of action
MTD	Maximum tolerated dose
N2	NREM sleep stage 2
N3	NREM sleep stage 3
NCS	Not clinically significant
NREM	Non-rapid eye movement sleep
PANSS	Positive and negative syndrome scale
PD	Pharmacodynamic(s)

PE	Physical examination
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
POPPK	Population pharmacokinetics
PR	Time between P wave and QRS in electrocardiography
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred term
QD	Once daily
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
REM	Rapid eye movement
RR	Respiration rate
SAD	single ascending dose
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SCID-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SOC	System organ class

TAAR1	trace amine associated 1 receptors
US, USA	United States, United States of America
USP	United States Pharmacopeia
VAS	Visual analogue scale
WBC	White blood cells
WHO	World Health Organization

5 Ethics and Regulatory Approval

5.1 Independent Ethics Committee Approval

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committees as detailed in table one below.

Table 1: Ethics committees

Centre name and number		
Investigator		
Ethics committee		
Chairman		
Date of approval of the final protocol		
Date of approval of amendment 1		
Date of approval of amendment 2		
Date of approval of amendment 3		

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5.2 Ethical Conduct of the Study

The study was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP)

5.3 Patient Information and Consent

All patients provided written informed consent to participate in the study prior to being screened. The patient information sheet detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was given the opportunity to consider the information presented before signing and dating the informed consent form to indicate that he/she fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for his/her information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records. A sample of the patient information sheet and consent form can be found in Appendix *[insert]*

6 Investigators and Study Administrative Structure

Table 2 shows the principal study personnel involved in the study.

Table 2: Principal study personnel

Title	Name and affiliation
Principal Investigator	
Sponsor	
Project Managers	
Project Leaders	
Clinical Research Associate(s)	
Medical Adviser	
Laboratory investigator	
Data Management	

Table 3: Organizations Critical to the conduct of the study

Responsibility	Name	Address
eg, data cleaning		
eg, medical writing		

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7 Introduction

7.1 Rationale for the Study

SYM-23 is a CNS-active compound, which shows broad efficacy in animal models of schizophrenia (positive and negative symptoms), cognition and depression. The molecular target responsible for the profile effects has not been completely elucidated, but may include actions at 5-HT1A and trace amine associated 1 (TAAR1) receptors. Rat electroencephalogram (EEG) studies showed that SYM-23 suppressed rapid eye movement (REM) sleep in a dose dependent manner. In nonhuman primate functional magnetic resonance imaging (fMRI) experiments, similar to risperidone, pretreatment with SYM-23 also reduced the ketamine brain fMRI response in rhesus monkey supporting an antipsychotic-like profile. Taken together,these data demonstrate that SYM-23 exhibits clear, functional CNS PD signals in rats and nonhuman primates.

To date, 210 subjects have received oral doses of SYM-23 in six Phase 1 clinical studies. Five Phase 1 studies have been completed (SYM-101, SYM-103, SYM-105,

SYM-106, and SYM-108). One Phase 1 study has been clinically completed (SYM-104).The first in human clinical study, a single ascending dose study (SAD; Study SYM-101), was designed to determine the safety, tolerability, maximum tolerated dose (MTD), and PK of a single oral dose of SYM-23 in normal, healthy, adult male subjects.

Study SYM-103 was a randomized, double-blind, placebo-controlled, crossover polysomnography (PSG) study that investigated the effect of a single oral dose (50 mg and 10 mg) of SYM-23 on REM sleep suppression and PK in healthy adult male subjects. A single 50 mg oral dose of SYM-23 suppressed REM sleep in all subjects (increased latencyto REM sleep and reduced time spent in REM sleep) and increased NREM sleep stage 2 (N2), and NREM sleep stage 3 (N3) (deep or slow wave sleep). A single oral 10 mg dose of
SYM-23 also increased latency to REM sleep to a lesser extent, but did not reduce time spentin REM sleep. Taken together, results from these 2 studies in healthy adult male subjects demonstrated acceptable safety profile as well as robust CNS effect.

Study SYM-105 was a randomized, single-blind, placebo-controlled, SAD study assessing the safety, tolerability, and PK of SYM-23 in male and female subjects with schizophrenia.

Study SYM-106 was a 2-part, randomized, single-blind, placebo-controlled, multiple ascending oral dose (MAD) and open-label study in male and female schizophrenic patients assessing the safety, tolerability, and PK of SYM-23 in the target patient population. Resultsfrom this study demonstrates an acceptable safety and tolerability profile of SYM-23 up to 28 days in schizophrenia patients. Additionally, in Part 2, treatment with SYM-23 at 75 mg/day for 28 days demonstrated improvement in efficacy measures (PANSS total score, CGI-S) compared with Baseline. Furthermore, ad hoc subgroup analyses showed a significantly greater decrease from Baseline in PANSS total scores at the end of the 28 day treatment period in subjects who had less frequent hospitalizations per year of illness compared with subjects who had more frequent hospitalizations per year of illness.

Study SYM-104 was a randomized, double-blind, placebo-controlled, single dose study of the effects of SYM-23 (50 mg) and amisulpride (400 mg) on BOLD-fMRI signal in healthy adult male and female subjects with high or low schizotype characteristics. Subjects with high schizotype characteristics and patients with schizophrenia share many similar features including positive, cognitive, negative and anhedonia symptoms, although in high schizotypes the features present in an attenuated form. In this study, fMRI was used in combination with a validated monetary incentive delay (MID) task to examine

the single dose effects SYM-23 on changes in reward processing. During the anticipation/motivational phase of the task, SYM-23 modulated striatum, insula and orbitofrontal cortex brain activity, and fMRI effects of
SYM-23 were similar to those observed with the D2 antagonist amisulpride. During the outcome/hedonic phase of the task, SYM-23 generally increased brain activity in core reward areas (striatum, insula), whereas amisulpride decreased brain activity in these same regions. Taken together the overall pattern of activity during MID task performance support specific hypotheses for the potential of SYM-23, a novel MoA molecule, to improve positive and negative symptoms of schizophrenia. Overall, the known molecular pharmacology profile, animal model evidence, and clinical experience in healthy adult male and female subjects, adult male and female subjects with high and low schizotype characteristics, and patients with schizophrenia provide further support to evaluate SYM-23 as a potential treatment for schizophrenia.

The present study is designed to evaluate efficacy and safety of SYM-23 50 and 75 mg/dayfor 4 weeks in adult male and female subjects with an acute exacerbation of schizophrenia.

8 Study Objectives

8.1 Primary Objective

To evaluate the efficacy of flexibly dosed SYM-23 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS).

8.2 Secondary Objective

• To evaluate the efficacy of flexibly dosed SYM-23 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:

- Clinical Global Impression-Severity (CGI-S)
- PANSS subscale scores (positive, negative, and general psychopathology)
- Brief Negative Symptom Scale (BNSS)
- Montgomery-Asberg Depression Rating Scale (MADRS)

• To evaluate the safety and tolerability of flexibly dosed SYM-23 (50 or 75 mg/day) using:

- physical examinations (PE)
- 12-lead electrocardiograms (ECG)
- vital signs
- adverse event (AE) reports
- clinical laboratory results
- body weight and body mass index (BMI)
- Columbia – Suicide Severity Rating Scale (C-SSRS)

9 Investigational Plan

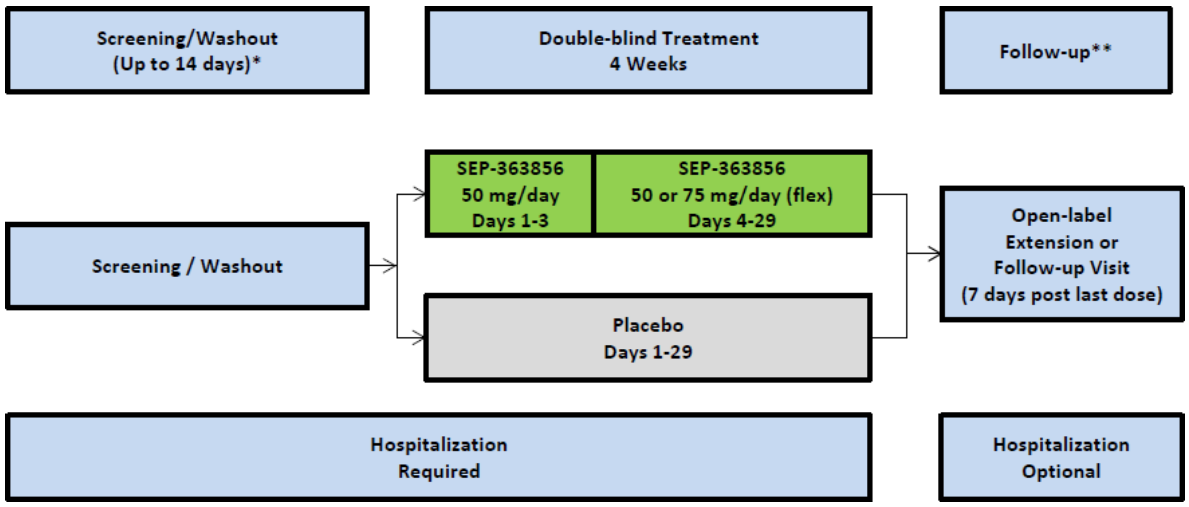
9.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, parallel-group, flexibly-dosed, study evaluating the efficacy and safety of SYM-23 in acutely psychotic adult subjects with schizophrenia using SYM-23 (50 or 75 mg/day [ie, once daily]) versus placebo over a 4-week treatment period. This study is projected to randomize at least 240 subjects to 2 treatment groups (SYM-23 or placebo) in a 1:1 ratio. Treatment assignment will be balanced within each clinical site. Subjects randomized to placebo will receive placebo treatment throughout the study.Study drug will be dosed at bed time with or without food.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (4 weeks in-patient), and a Follow-up visit (7 days after last study drug dose for subjects who discontinue prior to Visit 7 or who complete the study but do not elect to enroll in the open-label extension study [SYM-202]).

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 1: Study Schematic



* Screening/washout period will be up to 14 days.

** Follow-up visit 7 ± 2 days after last dose only for subjects not continuing in to open-label extension study SYM-202. Hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary

Screening/Washout Period (up to 14 days)

Informed consent will be obtained from each subject before any study procedures are performed. Subjects will be evaluated for eligibility during a screening phase of up to 14 days, during which they will be tapered off all psychotropic medications (except as noted in the protocol) in a manner that is

consistent with labeling recommendations and conventional medical practices.

Subjects will remain hospitalized for the duration of the screening/washout period.

Double-Blind Treatment Period (4 weeks)

During the double-blind phase, subjects will be in-patient through Week 4. Subjects will be eligible for hospital discharge after the Week 4 visit (Day 29).

Randomization/Treatment: At double-blind Baseline (Day 1), subjects who have successfully completed the washout of prior medication (see Section 10.3.1) and have met the randomization criteria (see below) will be randomly assigned via interactive web/voice response system (in a 1:1 ratio) to one of two treatment arms: SYM-23 or placebo. Study drug dosing will initiate the evening of the Baseline visit. Treatment will continue once-daily at night for the remainder of study during which procedures outlined in Table 2 will be conducted.

Subjects will receive SYM-23 50 mg/day on Day 1 through 3. On Day 4, subjects are permitted (but not required) to titrate up to a dose of 75 mg/day. Thereafter, if a dose increase isnecessary to optimize efficacy it should occur at regular scheduled study visits/weekly intervals starting from Visit 4 based on Investigator judgement. A dose reduction for tolerability purposesis permitted to occur more frequently than at weekly intervals. Subject can be flexibly dosed up until Visit 6, but no dose adjustments are allowed thereafter.

End of Double-Blind Period:

Subjects who complete the 4-week double-blind treatment phase will be eligible to participate in a separate open-label 26-week extension study (Study SYM-202). Subjects who discontinue early from the study or complete the study and do not enter the 6-month extension study will be required to complete the follow-up visit 7 days (± 2 days) post last dose of study drug.

Upon completion or early discontinuation from the study, hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary. Prior authorization for the hospitalization must be approved by the Medical Monitor. After completion of the follow-up visit or upon study discontinuation, all subjects will be referred for appropriate continued treatment and follow-up care as determined by the Investigator.

Efficacy, Safety, and Pharmacokinetic Evaluations

Efficacy will be evaluated using the PANSS total and subscale scores, as well as CGI-S, BNSS, and MADRS scores. Effect of SYM-23 on cognition will be assessed by the CBB.

Safety and tolerability will be monitored throughout the study by collection of PE results, ECGs, vital signs, AEs, clinical laboratory parameters, C-SSRS, body weight, and BMI. Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

Subjects will provide information on subjective drug effects via administration of the DEQ. In addition, effects on movement disorders will be measured using the AIMS, BARS and SAS scales. Subjective effects on sleep will be measured by the PSQI scale.

Blood samples for plasma SYM-23 and SYM-22 concentrations will be collected on Day 1 (predose) and Day 29. POPPK analysis will be performed using plasma SYM-23 concentrations; the results of which will be reported separately. The relationship between PANSS total score and plasma SYM-23 exposure using population PK/pharmacodynamics (PD) methods exposure will be explored and reported separately. The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SYM-23 exposure will be explored and reported separately.

9.1.1 Study Timing

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9.1.2 Study Location

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9.2 Discussion of Study Design

This is a multiregional, randomized, double-blind, parallel-group, flexibly-dosed study evaluating the efficacy and safety of SYM-23 in acutely psychotic adult subjects with schizophrenia using SYM-23 (50 or 75 mg/day) versus placebo over a 4-week treatment period. The 4-week study duration will provide an adequate timeframe within which to evaluatethe effects of SYM-23 compared to placebo in this subject population.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

To qualify for participation, subjects must meet all of the following inclusion criteria:

1. Subject must give written informed consent and privacy authorization prior to participation in the study. Separate consent will be obtained from a caregiver or legal guardian if required by local law.

2. Subject must be willing and able to comply with the study procedures and visit schedules, including required hospitalization for the washout period and the double-blind treatment period, and must be able to understand and follow verbal and written instructions.

3. Male or female subject between 18 to 40 years of age (inclusive) at the time of consent.

4. Subject meets DSM-5 criteria for schizophrenia as established by clinical interview (using the DSM-5 as a reference and confirmed using the SCID-CT). The duration of the subject's illness whether treated or untreated must be ≥ 6 months.

5. Subject must have a CGI-S score ≥ 4 (moderate or greater) at screening and Baseline (Day 1).

6. Subject must have a PANSS total score ≥ 80 and a PANSS item score ≥ 4 (moderate) on 2 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content at screening and Baseline (Day 1).

7. Subject has an acute exacerbation of psychotic symptoms (no longer than 2 months).

- Subject has marked deterioration of functioning in one or more areas, such as occupational, social, or personal care or hygiene.

- Subject requires hospitalization for an acute psychotic exacerbation at the time of screening or has been hospitalized for the purpose of treating an acute psychotic exacerbation for no more than 2 consecutive weeks immediately before screening.

Subjects who have been hospitalized for more than 2 weeks for reasons unrelated to an acute psychotic exacerbation may be included if such a hospitalization was for a condition other than an acute psychotic relapse. For example, subjects in a long-term hospital setting who have an acute exacerbation and are transferred to an acute unit are eligible for the study.

8. Subject has had no more than 2 prior hospitalizations for the treatment of an acute exacerbation of schizophrenia (not including the current hospitalization) This history must be confirmed based on report by a reliable informant (eg., caregiver or family member) or medical records available at the time of screening.

9. Subject's BMI must be at least 18 kg/m^2 but no more than 35 kg/m^2.

10. Female subject must have a negative serum pregnancy test at screening.

11. Female subject of reproductive potential agrees to remain abstinent or use highly effective and reliable contraception throughout the study and for at least 30 days after the last dose of study drug has been taken (See Section 21 Appendix II Highly Effective

Contraceptive procedures). In the Investigator's judgment, the subject will adhere to this requirement.

12. Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use highly effective methods of birth control (outlined in

Section 21) from screening until at least 30 days after the last study drug administration.

13. Subject must be able and agree to remain off prior antipsychotic medication for the duration of the study.

14. Subject must have a total score < 5 on the SAS at Baseline (Day 1).

15. Subject is, in the opinion of the Investigator, generally healthy based on screening medical history, PE, neurological examination, vital signs, clinical laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin).

16. Subject has had a stable living arrangement at the time of screening and agrees to return to a similar living arrangement after discharge. This criterion is not meant to exclude subjects who have temporarily left a stable living arrangement (eg, due to psychosis). Such subjects remain eligible to participate in this protocol. Chronically homeless subjects should not be enrolled.

17. Subject must agree to comply with all restrictions for the required length of time (see Concomitant Medications and Restrictions in Section 10.3).

9.3.2 Exclusion Criteria

To qualify for participation, subjects must not meet any of the following exclusion criteria:

1. Subject answers "yes" to "Suicidal Ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at or during the Screening period (ie, in the past one month) and/or at Baseline (ie, since last visit).

2. Subject does not tolerate venipuncture or has poor venous access that would cause difficulty for collecting blood samples.

3. Subject is currently participating, or has participated in, a study with an investigational or marketed compound or device within 6 months prior to signing the informed consent, or has participated in 2 or more studies within 24 months prior to signing informed consent.

4. Subject has previously received SYM-23.

5. Subject has any clinically significant unstable medical condition or any clinically significant chronic disease that in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in the study:

   a. Hematological (including deep vein thrombosis) or bleeding disorder, renal, metabolic, endocrine, pulmonary, gastrointestinal, urological, cardiovascular, hepatic, neurologic, or allergic disease that is clinically significant or unstable (except for untreated, asymptomatic, seasonal allergies at time of dosing).

   b. Subject has a history of neuroleptic malignant syndrome.

   c. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pituitary tumors of any duration are excluded.

   d. Disorder or history of a condition, or previous gastrointestinal surgery (eg, cholecystectomy, vagotomy, bowel resection, or any surgical procedure) that may interfere with drug absorption, distribution, metabolism, excretion, gastrointestinal motility, or pH, or a clinically significant abnormality of the hepatic or renal system, or a history of malabsorption.

   e. Subject has Alcohol or Substance Abuse Disorder (DSM-5 criteria). The only exceptions include caffeine or nicotine.

   f. Subject has a clinically significant abnormal 12-lead ECG that may jeopardize the subject's ability to complete the study or a screening 12-lead ECG demonstrating any one of the following: heart rate > 100 beats per minute, QRS > 120 ms, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 ms (males),

   QTcF > 470 ms (females), or PR > 220 ms.

g. Subjects with known history of human immunodeficiency virus (HIV) seropositivity.

6. Female subject who is pregnant or lactating.

7. Subject who has a lifelong history or presence of symptoms consistent with a major psychiatric disorder other than schizophrenia as defined by DSM-5. Exclusionary disorders include but are not limited to alcohol use disorder (within past 12 months), substance (other than nicotine or caffeine) use disorder within past 12 months, major depressive disorder, bipolar depression, mania, schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder. Previous or current symptoms of mild to moderate mood dysphoria or anxiety are allowed so long as these symptoms have not been a focus of primary treatment.

8. Subject tests positive for drugs of abuse at screening, however, a positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of subjects if the investigator determines that the positive test is as a result of prescription medicine(s). In the event a subject tests positive for cannabinoids (tetrahydrocannabinol), the Investigator will evaluate the subject's ability to abstain from using this substance during the study. This information will be discussed with the Medical Monitor prior to study enrollment.

9. Subject is at significant risk of harming self, others or objects based on the Investigator's judgment.

10. Subject has attempted suicide within 3 months prior to screening.

11. Subject is involuntarily hospitalized.

12. Subject has received depot antipsychotics unless the last injection was at least one treatment cycle or at least 30 days (whichever is longer), prior to the screening phase.

13. Subject is judged to be resistant to antipsychotic treatment by the Investigator, based on failure to respond to 2 or more marketed antipsychotic agents, given at adequate dose for at least 4 weeks within a 1 year period prior to Screening.

14. Subject has a history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine (for any reason) within 4 months of Screening.

15. Subject is receiving a total dose of antipsychotic medication equivalent to $\geq$ 12.0 mg/day of haloperidol at Screening (see Section 22, Appendix III for table of haloperidol dose equivalents). Subject may be eligible if such treatment is less than 2 weeks in duration after consultation with the Medical Monitor.

16. Subject has received electroconvulsive therapy treatment within the 3 months prior to screening or is expected to require ECT during the study.

17. Subject takes or has taken other disallowed recent or concomitant medications (see Section 10.3). Subjects must taper off antipsychotic medications by Day -1.

18. Subject has a history of allergic reaction or suspected sensitivity to any substance that is contained in the formulation (gelatin).

19. Subject has any clinically significant abnormal laboratory values (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, thyroid panel, and serum prolactin (Note: abnormal findings that may be clinically significant or of questionable significance will be discussed with the Medical Monitor prior to including subject).

20. Subject demonstrates evidence of acute hepatitis, clinically significant chronic hepatitis, or evidence of clinically significant impaired hepatic function through clinical and laboratory evaluation.

Note: Subjects with serum alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 3 times the upper limit of the reference ranges provided by the central laboratory require retesting. If on retesting, the laboratory value remains ≥ 3 times the upper limit, the subject will be excluded.

21. Subject has a serum blood urea nitrogen (BUN) or serum creatinine (Cr) value ≥ 1.5 times the upper limit of normal for the reference range.

22. Subject has experienced significant blood loss (≥ 473 mL) or donated blood within 60 days prior to first dose of study drug; has donated plasma within 72 hours prior to the first dose of study drug or intends to donate plasma or blood or undergo elective surgery during study participation or within 60 days after the last study visit.

23. Subject has used disallowed prescription or disallowed nonprescription drugs, vitamins, or dietary or herbal supplements within 14 days prior to dosing or anticipates the need for any disallowed medication during their participation in this study [exception: female subjects who are taking oral, patch, or intrauterine device (IUD) hormonal contraceptives, or progestin implant or injection].

24. Subject is a staff member or the relative of a staff member.

25. Subjects with a fasting blood glucose at screening ≥ 126 mg/dL (7.0 mmol/L) or HbA_{1c} ≥ 6.5% will be excluded.

26. Subject has a prolactin concentration > 100 ng/mL at screening or has a history of pituitary adenoma. **NOTE:** Subjects with prolactin levels > 100 ng/mL and ≤ 200 ng/mL at the Screening visit are permitted to enroll after discussion with the Medical Monitor to ensure exclusion of non-psychotropic drug-related causes of elevated prolactin levels.

27. .Subject is in the opinion of the Investigator, unsuitable in any other way to participate in this study.

9.3.3 Removal of Patients from Therapy or Assessment

Criteria for Study Drug Discontinuation

Subjects may be discontinued from the study drug at any time for any of the following reasons:

- Adverse event (specify)
- Lack of efficacy (specify)
- Withdrawal by subject (specify)

- Non-compliance with study drug (specify)
- Protocol deviation (specify)
- Death
- Progressive disease
- Pregnancy
- Other (specify)

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug.

The reason and information on the epoch for study drug discontinuation will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Clinical Assessments After Study Drug Discontinuation

Subjects who have not received study drug will not be followed up on leaving the study.

For subjects who have received study drug and who prematurely discontinue from the study treatment (ie, do not complete through Visit 7), every effort should be made to complete the final evaluation procedures, in accordance with the early termination (ET) visit described in Section 11.8.5.

Subjects who complete the study but do not elect to enroll in the open-label extension study (Study SYM-202) and those subjects who discontinue the study early will complete a follow up visit 7 (±2) days after the last visit to assess any post study discontinuation adverse effects as described in Section 11.8.6.

9.4 Treatments

9.4.1 Treatments Administered

Please fill or remove the Subsection in the Template

9.4.2 Description of Investigational Product{s}

Table 5: Investigational Product

Attribute	Investigational Product		
Product name	SYM-23	SYM-23	Placebo
Dosage form	Capsule	Capsule	Capsule
Unit dose	50 mg	75 mg	NA
Route of administration	Oral	Oral	Oral

Physical description	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule	Size #0, Swedish Orange Capsule
Excipients	None	None	Microcrystalline cellulose

9.4.3 Method of Assigning Patients to Treatment Groups

Treatment Assignment

The randomization schedule will be generated by a non-study biostatistician. Once a subject is deemed eligible to be randomized at Day 1 (Visit 2), an IXRS will perform treatment assignment. Subjects will be randomized to one of the following treatment groups in a 1:1 ratio and balanced within each clinical site:

- SYM-23 (50 or 75 mg/day flexible dosing for 4 weeks)
- Placebo (once daily for 4 weeks)

Once a randomization number has been assigned, it cannot be reused.

Blinding

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories (including imaging) will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods; (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of bioanalytical personnel involved in the analysis of PK samples; (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Actual subject identity for plasma concentrations of SYM-23 and SYM-22 will not be disclosed before the database lock and the unblinding of the double-blind treatment phase.

Emergency Unblinding Procedures

In the case of a medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IXRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation. The subject should return for a final study assessment as described in Section 11.8.6.

9.4.4 Selection of Doses in the Study

Please fill or remove the Subsection in the Template

9.4.5 Selection and Timing of Dose for Individual Patients

Please fill or remove the Subsection in the Template

9.4.6 Prior and Concomitant Therapy

See Section 10.3 for a complete description of medications permitted during the study. Site study staff will record all medications used to treat schizophrenia taken within 1 month prior to screening visit in the eCRF. Also, the following parameters will be recorded for all concomitant medications: drug name, route of administration, total daily dose, unit, frequency, start/stop dates, indication, and whether the medication was started after last dose of study medication. The prior and concomitant medications will subsequently be coded using the World Health Organization Drug Dictionary (WHO-DD).

9.4.7 Treatment Compliance

The Investigator will record the dose of the study drug and the dates of the initial and final administration for each dose.

Compliance must be monitored closely and determined at each visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. All subjects will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment and for the successful outcome of the study. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Evidence of noncompliance must be immediately reported to the Clinical Research Associate (CRA) and/or Medical Monitor.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

See Table 2 Schedule of Assessments, for a summary of procedures at each study visit. See Section 11.1 to Section 11.5 for detailed information on conducting assessments.

Screening: Visit 1 (Day -14 to -1);Inpatient

A unique screening number will be assigned to each subject.

The subject's eligibility assessment will be reviewed by the contract research organization's (CRO) oversight quality team along with the sponsor based on protocol specified inclusion and exclusion criteria. The sponsor will participate in the eligibility review process with the CRO to ascertain the subject's eligibility and will be copied on all communications between the CRO and the site. In the event the CRO/sponsor and site do not agree on a subject's eligibility then the subject will not be enrolled.

Subjects will be evaluated at the screening visit (1 to 14 days before the first dose of study drug) to determine their eligibility for the study. The following procedures will be conducted during this visit:

- Obtain signed informed consent and privacy authorization from the subject before conducting any other visit procedures.
- Inclusion and exclusion criteria

- Obtain demographic information
- Prior/concomitant medications
- Pretreatment events
- Medical history
- Psychiatric history/mental status
- SCID-CT
- Physical and neurological examination including height and weight; clinical site staff to calculate and record BMI
- Vital sign measurements (prior to ECG)
- Perform ECG
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel, and lipid panel).
- Blood samples for serum pregnancy test (serum human chorionic gonadotropin [β-hcG]) for female subjects and serum follicle stimulating hormone (FSH) for female subjects if menopause is suspected.
- Urine sample for urinalysis and urine drug screen (UDS)
- Duplicate subject check
- PANSS
- BNSS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS

Procedures should be completed in the following sequence.

Screening Visit	**Visits 2 through Visit 8**
1. SCID-CT (study center rater)	1. PANSS (study center rater)
2. PANSS (study center rater)	2. BNSS (study center rater)
3. BNSS (study center rater)	3. MADRS (study center rater)
4. C-SSRS (study center rater)	4. C-SSRS (study center rater)

5. CGI-S (study center rater)	5. CGI-S
	6. AIMS/BARS/SAS
	7. PSQI
	8. DEQ
	9. CBB

Note: With the exception of SCID-CT and DEQ, all rating assessments will be performed by the rater using a tablet. In the event that a tablet is not available, the rating assessments will be performed by the rater using a paper version of the assessment.

Subjects found to be ineligible during Visit 1 will not be required to complete all the Visit 1 assessments and will not be followed up on leaving the study.

Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator.

Re-screened subjects will be re-consented and all Visit 1 procedures will be repeated.

Baseline: Visit 2 (Day 1); Inpatient

The following procedures will be conducted during this visit:

- Review inclusion and exclusion criteria and randomization criteria.
- Prior/concomitant medications.
- Randomize to treatment
- Blood sample for determination of plasma SYM-23 and SYM-22 (pre-dose)
- Vital sign measurements (prior to ECG)
- Weight and waist circumference
- Perform standard 12-lead ECG.
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glucose panel and lipid panel).
- If subject signed separate genetic informed consent, collect blood samples for pharmacogenomics (CYPP450 2D6)
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S

- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CBB
- Administer study drug
- Adverse events

Visit 3 (Day 4); Inpatient

The following procedures will be conducted during this visit:

- Concomitant medications.
- Perform study drug accountability
- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- Administer study drug
- Adverse events

Visit 4 (Week 1; Day 8), Visit 5 (Week 2; Day 15), and Visit 6 (Week 3; Day 22); Inpatient

The following procedures will be conducted during each visit (unless otherwise specified):

- Concomitant medications.
- Perform study drug accountability

- Vital sign measurements
- PANSS
- BNSS
- MADRS
- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- Administer study drug
- Adverse events

Visit 7 (Week 4; Day 29/Early Termination); Inpatient

The following procedures will be conducted during this visit:

- Concomitant medications
- Study drug accountability
- Physical and neurological examination including
- Weight and waist circumference
- Vital sign measurements (prior to ECG).
- Perform standard 12-lead ECG.
- Fasted blood samples for clinical laboratory evaluation (hematology, serum chemistry, serum prolactin, glycosylated hemoglobin [HbA_{1c}], glucose panel, and lipid panel).
- Blood sample for determination of plasma SYM-23 and SYM-22 concentration (post dose)
- Urine sample for urinalysis, UDS, and β-hcG (for female subjects).
- PANSS
- BNSS
- MADRS

- C-SSRS
- CGI-S
- AIMS
- BARS
- SAS
- PSQI
- DEQ
- CBB
- Adverse events
- Duplicate subject check

At this visit, subjects who have completed treatment will have the option to enroll and continue treatment for an additional 26 weeks in an open-label extension study (Study SYM-202). For subjects entering the extension study, Week 4 in this study will be Baseline for the extension study and subjects will not need to return for further visits in this study.

Subjects who do not enter the extension study will complete the inpatient follow-up period.

Visit 8 (+ 7 days); Inpatient Follow-up

All subjects who discontinue early or do not elect to enroll in the open-label extension study (Study SYM-202) will have an inpatient/outpatient safety follow-up prior to discharge (7 ± 2 days) after their last dose of study drug. The following procedures will be conducted during this visit:

- Concomitant medications
- C-SSRS
- Adverse events
- Duplicate subject check

Please fill the section

9.5.2 Appropriateness of Measurements

Please fill or remove the Subsection in the Template

9.6 Data Quality Assurance

Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the subject's electronic CRF. Data will be entered into source documents prior to being transcribed into the CRF. This transcribing will be done once a subject has passed screening (Visit 1). Data for screen failures will not be collected. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations (CFR) Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator or delegate.

Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 8: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent	A
Review inclusion/exclusion criteria	A
Demographics	A
Prior/concomitant medication review	A
Randomize (IXRS) to treatment	E
Dispense study drug	A, E
Study drug accountability	A
Medical history	A
Psychiatric history/mental status	A
SCID-CT	A
Physical examination	A
Height	A
Vital sign measurements	A
Weight	A
Waist circumference	A
Electrocardiogram (ECG)	C
Hematology, chemistry, and urinalysis	B

Table 8: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Serum prolactin	B

Glycosylated hemoglobin (HbA1c)	B
Glucose and Lipid panel	B
Serum follicle stimulating hormone (FSH)	B
Serum human chorionic gonadotropin (β-hCG)	B
Blood sample for pharmacogenomics (CYPP450 2D6)	D
Blood sample for SYM-23 PK	D
Urine drug screen	B
Urine β-hCG (local)	A
Urine drug screen (central)	B
Positive and Negative Syndrome Scale (PANSS) – Total Score	F
Clinical Global Impression – Severity (CGI-S)	F
Montgomery-Asberg Depression Rating Scale (MADRS)	F
Columbia Suicide Severity Rating Scale (C-SSRS)	F
Drug Effects Questionnaire (DEQ)	A
Abnormal Involuntary Movement Scale (AIMS)	F
Barnes Akathisia Rating Scale (BARS)	F
Simpson-Angus Scale (SAS)	F
Brief Negative Symptoms Scale (BNSS)	F
Pittsburg Sleep Quality Index (PSQI)	F
CogState Brief Battery (CBB)	G
Pretreatment event monitoring	A
Adverse events (AE) monitoring	A
Provide meals	A
Statistical analysis	SAS®, version 9.2 or higher

A = EDC (MediData RAVE); B = LIMS; C = Core Lab Over-read; D = LIMS/ASCII; E = IXRS; F = Bracket; G = CogState.

Abbreviations: EDC = electronic data capture; CDR = clinical data repository; CIMS = Clinical Inventory Management System; IXRS = interactive response technology; IVRS = interactive voice recognition system; LIMS = laboratory information management system.

Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of centre facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/centre SOPs, protocol, ICH GCP and local regulations. The Investigator or appropriate

designee must also agree to inspection of all study documents by the regulatory authorities and the IEC. Should the Investigator or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director's curricula vitae and a current, dated copy of normal range values.

A local laboratory may optionally be used for analysis of serum pregnancy at Visit 2 in this study. The local laboratory/site personnel will provide Sponsor/P1vital with laboratory certification(s) and a current dated copy of normal range values for the local clinical laboratory selected to analyse clinical specimens.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Please fill or remove the Subsection in the Template

9.7.2 Determination of Sample Size

A sample size of 100 subjects per treatment group (SYM-23 and placebo) will provide 80% power to detect a treatment effect size of 0.4 in change from Baseline in PANSS total score at Week 4 for SYM-23 versus placebo, using a two independent sample t-test method with 2-sided significant level of 0.05. A clinically meaningful effect size of 0.4 was estimated based on review of published studies of other antipsychotics for the short-term treatment of schizophrenia. It is anticipated that 17% of all randomized subjects will discontinue early from the study. An upward adjustment of the sample size is thus used to compensate for missing data from subjects who are randomized and discontinue from the study. The total sample size will be 240 randomized subjects (or 120 subjects per treatment group).

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Amendments

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately/within five business days of the occurrence, or in accordance with applicable regulatory requirements.

9.8.2 Changes to the Planned Analyses

Please fill or remove the Subsection in the Template

10 Study Population

10.1 Disposition of Patients

Please fill or remove the Subsection in the Template

10.2 Protocol Deviations

Please fill or remove the Subsection in the Template

11 Efficacy Evaluation

11.1 Data Sets Analyzed

Please fill or remove the Subsection in the Template

11.2 Demographic and Other Baseline Characteristics

Please fill or remove the Subsection in the Template

11.3 Measurements of Treatment Compliance

Please fill or remove the Subsection in the Template

11.4 Efficacy Results and Tabulations of Individual Subject Data

Please fill or remove the Subsection in the Template

11.5 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/ Pharmacogenetic Results

Please fill or remove the Subsection in the Template

11.6 Efficacy {and Clinical Pharmacology} Conclusions

Please fill or remove the Subsection in the Template

12 Safety Evaluation

12.1 Extent of Exposure

Please fill or remove the Subsection in the Template

12.2 Adverse Events

12.2.1 Overview of Adverse Events

Please fill or remove the Subsection in the Template

12.2.2 Frequency of Treatment-Emergent Adverse Events

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12.2.3 Analysis of Adverse Events

12.2.3.1Severity

Please fill or remove the Subsection in the Template

12.2.3.2Relationship to Study Drug

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12.2.4 Immunization Tolerance

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12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Deaths

Please fill or remove the Subsection in the Template

12.3.2 Serious Adverse Events

Please fill or remove the Subsection in the Template

12.3.3 Adverse Events Leading to Dose Modification

Please fill or remove the Subsection in the Template

12.3.4 Adverse Events Resulting in Treatment Discontinuation

Please fill or remove the Subsection in the Template

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Please fill or remove the Subsection in the Template

12.4.2 Evaluation of Each Laboratory Parameter

Please fill or remove the Subsection in the Template

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Please fill or remove the Subsection in the Template

12.6 Concomitant Medication Use

Please fill or remove the Subsection in the Template

12.7 Safety Conclusions

Please fill or remove the Subsection in the Template

13 Discussion and Overall Conclusions

Please fill the section

14 Tables, Listings and Figures/Graphs

15 References

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16 Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

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16.1.2 Case Report Form

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16.1.3 Ethics Committees and Subject Information

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16.1.4 Regulatory Approval

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16.1.5 Investigators and Study Personnel

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16.1.6 Sponsor and Investigator Signatures

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16.1.7 Randomization Code

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16.1.8 Study Drugs

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16.1.9 Audit Certificate

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16.1.10 Statistical Analysis Plan

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16.1.11 Laboratory Quality Assurance

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16.1.12 Publications Based on the Study

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16.1.13 Publications Referenced in the Report

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16.2 Patient Data Listings

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16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for AE

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16.3.2 Other CRFs Submitted

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