Statistical Analysis Plan

A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia

Study Number TV46000-CNS-30078

NCT03893825

SAP Approval Date: 07 July 2020

Statistical Analysis Plan

Study TV46000-CNS-30078 with Protocol Amendment 01

A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia

A Study to Evaluate Safety, Tolerability, and Effect of TV-46000 in Adults and Adolescents with Schizophrenia

A Study to Test if TV-46000 is Safe for Maintenance Treatment of Schizophrenia

Safety and Tolerability Study (Phase 3)

IND number: 124384;   **NDA number: 213586;**

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Sponsor

**Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway West Chester, Pennsylvania 19380
United States**

Prepared by: ▮▮▮▮▮▮

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.:   TV46000-CNS-30078

Study Title: A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia

Statistical Analysis Plan for:

☐ **Interim Analysis**   ☐ **Integrated Summary of Efficacy**

☒ **Final Analysis**   ☐ **Integrated Summary of Safety**

Amendment: Not applicable

Author: ███████████████████

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Approver: ████████   **Date**

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Approver: ████████   **Date**

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	analysis of covariance
BARS	Barnes Akathisia Rating Scale
bpm	beats per minute
BMI	body mass index
CDSS	Calgary Depression Scale for Schizophrenia
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression of Severity
CGI-SS	Clinical Global Impression-Severity of Suicidality
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRF	case report form
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DAI-10	Drug Attitudes Inventory 10-item version
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram/Electrocardiography
EoT	End-of-Treatment Visit
EQ-5D-5L	5-Level EuroQol Five Dimensions Questionnaire
ER	Emergency room
ET	Early Termination
GFR	Glomerular filtration rate
ICF	Informed consent form
IMP	investigational medicinal product
INN	international nonproprietary name
IRT	Interactive Response Technology

ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
msec	milliseconds
NDA	New Drug Application
PANSS	Positive and Negative Syndrome Scale
███	████████████████
PP	Per-Protocol
PSP	Personal and Social Performance Scale
PT	Preferred term
q1m	every month
q2m	every 2 months
q4w	every 4 weeks
q8w	every 8 weeks
QTcF	QT interval corrected using Fridericia's formula
R&D	Research and Development
RTSM	Randomization and Trial Supply Management
SAS	Simpson-Angus Scale
SCID-5	Structured Clinical Interview for DSM-5
SD	Standard Deviation
SE	Standard Error
SI	standard international
SOC	system organ class
SOP	standard operating procedure
SQLS	Schizophrenia Quality of Life Scale
ULN	upper limit of normal range
VAS	visual analogue scale
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study TV46000-CNS-30078 (A Study to Evaluate the Safety, Tolerability, and Effect of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia), and was written in accordance with GSD-SOP-704 (Final Statistical Analyses for Clinical Studies).

The reader of this Statistical Analysis Plan is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The Statistical Analysis Plan is intended to be in agreement with the protocol, especially with regards to the primary endpoint and its respective analysis. However, the Statistical Analysis Plan may contain more details regarding the primary endpoint of interest, or other types of analyses (eg, other endpoints).When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

The primary objective and endpoint are presented below. There are no secondary study objectives and endpoints.

Objectives	Endpoints
The **primary objective** of the study is to evaluate the long-term safety and tolerability of TV-46000 administered in adult and adolescent patients with schizophrenia.	The primary endpoint is the frequency of all adverse events, including serious adverse events.

1.2. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are as follows:

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2. STUDY DESIGN

2.1. General Design

This is a multicenter, double-blind, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of TV-46000 administered q1m or q2m at doses of 50 to 250 mg sc (equivalent to 2 to 5 mg/day of oral risperidone) for up to 56 weeks in adult and adolescent patients with schizophrenia. As a precautionary measure, adolescent patients will receive doses equivalent to 2 to 4 mg/day oral risperidone.

Eligible female and male patients with schizophrenia who did not experience a relapse and completed the Phase 3 pivotal efficacy Study TV46000-CNS-30072 (roll-over patients) and new patients (who did not participate in Study TV46000-CNS-30072) may enter this long-term study if they meet the inclusion/exclusion criteria and provide informed consent or assent, as applicable.

For new patients, the study duration will consist of a screening period (up to 4 weeks), a conversion/stabilization stage (12 weeks on oral risperidone, Stage 1), a double-blind, active-treatment maintenance stage (up to 56 weeks; Stage 2), and a follow-up period (8 weeks). Per definition, an exacerbation in symptoms during Stage 1 (new patients) cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. During the baseline visit, new patients who meet the stability criteria will be randomized in a 1:1 manner to receive TV-46000 q1m or q2m sc injections at the TV-46000 dose equivalent to the oral dose on which they were stabilized in Stage 1 of this study and will enter Stage 2 of the study (double-blind maintenance stage).

Patients who require a stabilization dose below 2 mg/day will not be randomized in the study. As a precautionary measure, adolescent patients who will require a stabilization dose of more than 4 mg/day during the stabilization stage will not be randomized.

For roll-over patients, the study duration will consist of a double-blind, active-treatment maintenance stage (up to 56 weeks; Stage 2) and a follow-up period (8 weeks). Roll-over patients will begin this study at the baseline visit and start at Stage 2 of the study (double-blind maintenance stage). For these patients, the end-of-treatment (EoT) visit in Study TV46000-CNS-30072 will serve as the baseline visit. Some baseline procedures will be performed as part of the EoT visit in the TV46000-CNS-30072 study, and the results will be transferred to this study's clinical database. During Stage 2 of this study, patients who were treated with TV-46000 q1m or q2m during Study TV46000-CNS-30072 will continue their assigned arm and dose from Study TV46000-CNS-30072. Patients who were treated with placebo during Study TV46000-CNS-30072 will be randomized in a 1:1 manner to receive TV-46000 q1m or q2m sc injections at the TV-46000 dose equivalent to the oral dose on which they were stabilized in Stage 1 of Study TV46000-CNS-30072 (see Section 2.2).

After new and roll-over patients are assigned to receive TV-46000 q1m or q2m sc injections during the baseline visit, the study will continue on an outpatient basis. The maximal dose of TV-46000 administered to adult patients will be equivalent to an oral risperidone dose of

5 mg/day, and the maximal TV-46000 dose administered to adolescents will be equivalent to 4 mg/day oral risperidone.

Patients who started Stage 2 who relapse or meet 1 or more of the withdrawal criteria should be invited to perform the early termination (ET) visit as soon as possible within 4 weeks of the last injection.

End of study (EoS) is defined as the date when the last patient in Stage 2 has completed all efficacy and safety assessments at the final visit per protocol (Follow-up Visit 2).

Study procedures and assessments with their timing for the pre-treatment period (screening and Stage 1) are summarized in Table 1 of the study protocol. Study procedures and assessments starting from baseline, through the double-blind maintenance stage (Stage 2), EoT/ ET and follow-up are summarized in Table 2 of the study protocol.

2.2.   **Randomization and Blinding**

To avoid unblinding, all patients enrolled in Study TV46000-CNS-30078 will be assigned to a treatment group via the Interactive Response Technology (IRT) at their baseline visit according to the following specifications:

- **New patients** will be randomized via the IRT to receive sc injections of either TV-46000 q1m or TV-46000 q2m in a 1:1 ratio. Randomization will be stratified by the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg/day). The dose of TV-46000 will be equivalent to the 2 to 5 mg/day dose of oral risperidone on which the patient was stabilized in Stage 1. As a precautionary measure, adolescent patients who will require a stabilization dose of more than 4 mg/day during the stabilization stage will not be randomized. Patients who are randomized to TV-46000 q1m will receive an sc injection of TV-46000 at baseline and every 4 weeks (q4w) thereafter. To ensure blinding, patients who are randomized to TV-46000 q2m will receive an sc injection of TV-46000 at baseline and every 8 weeks (q8w) thereafter and an sc injection of placebo 4 weeks after baseline and q8w thereafter.

- **Roll-over patients who were assigned to TV-46000 q1m during Study TV46000-CNS-30072** will be assigned via the IRT to continue the same dosing frequency and same dose as in Study TV46000-CNS-30072. Note that the EoT visit in Study TV46000-CNS-30072 will serve as the baseline visit for roll-over patients in this study (ie, roll-over patients receive their last injection of investigational medicinal product (IMP) at the EoT visit in Study TV46000-CNS-30072 and receive their next injection at week 4 in this study). They will receive an sc injection of TV-46000 at the EoT visit in Study TV46000-CNS-30072 and q4w thereafter (ie, weeks 4, 8 and so on in this study).

- **Roll-over patients who were assigned to TV-46000 q2m during Study TV46000-CNS-30072** will be assigned via the IRT to continue the same dosing frequency and same dose as in Study TV46000-CNS-30072. Note that the EoT visit in Study TV46000-CNS-30072 will serve as the baseline visit for roll-over patients in this study (ie, roll-over patients receive their last injection of IMP at the EoT visit in Study TV46000-CNS-30072 and receive their next injection at week 4 in this study). To maintain the blind, they will be injected q4w, but will alternate between TV-46000 sc and placebo injections. Their injection at week 4 will depend on their injection at the EoT visit of Study

TV46000-CNS-30072 (ie, if their last injection in Study TV46000-CNS-30072 was placebo, then their Study TV46000-CNS-30078 week 4 injection will be TV-46000 and vice versa).

- **Roll-over patients who were assigned to placebo during Study TV46000-CNS-30072** will be randomized via the IRT to receive sc injections of either TV-46000 q1m or TV-46000 q2m in a 1:1 ratio. Randomization will be stratified by the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg/day). The dose of TV-46000 will be equivalent to the 2 to 5 mg/day dose of oral risperidone (adolescent TV-46000 doses will be equivalent to 2 to 4 mg/day oral risperidone) on which the patient was stabilized in Stage 1 of Study TV46000-CNS-30072. Note that the EoT visit in Study TV46000-CNS-30072 will serve as the baseline visit for roll-over patients in this study (ie, roll-over patients receive their last injection of IMP at the EoT visit in Study TV46000-CNS-30072 and receive their next injection at week 4 in this study). Patients who are randomized to TV-46000 q1m will receive an sc injection of TV-46000 at week 4 in this study and q4w thereafter. To ensure blinding, patients who are randomized to TV-46000 q2m will receive an sc injection of TV-46000 at week 4 in this study and q8w thereafter, and an sc injection of placebo at week 8 and q8w thereafter.

Patients and investigators will remain blinded to the identity of the treatment administered to each patient. Due to the differences between TV-46000 and placebo and the alternation between placebo and TV-46000 for the TV-46000 q2m arm, an unblinded nurse, who is not associated with rating the patient (including assessment of the injection site if needed) and is independent from the study team, will be required at each site to administer the drug.

Additional measures to mitigate the risk of unblinding are described in Section 5.9 of the study protocol.

The sponsor's clinical personnel (and delegates) involved in the study will not be blinded to the identity and dosing regimens of the IMPs received by the new patients during the course of this study.

Since the roll-over of patients from Study TV46000-CNS-30072 into this study is expected to occur prior to Study TV46000-CNS-30072 database lock, the sponsor's clinical personnel (and delegates) involved in the TV46000-CNS-30072 study will be blinded to the identity of their IMP treatment assignments in the TV-46000-CNS-30072 and TV46000-CNS-30078 studies, until the TV46000-CNS-30072 database is locked for final analysis and the IMP assignment is known. However, certain personnel (ie, site unblinded pharmacist/nurse, IRT study staff, and Clinical Supply Chain) who have been unblinded since the beginning of the TV46000-CNS-30072 study, will remain unblinded during the roll-over transition period until the database of Study TV46000-CNS-30072 is locked.

New patients and roll-over patients in the placebo group of Study TV46000-CNS-30072 will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

In the event of an emergency, it will be possible to determine to which treatment group and dose the patient has been allocated by accessing the Randomization and Trial Supply Management (RTSM) system. All investigational centers will be provided with details of how to access the

system for code breaking at the start of the study. The medical monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents.

The randomization list will be assigned to the relevant treatment groups through a qualified service provider, eg, via the RTSM system. The generation of the randomization list and management of the RTSM system will be done by a qualified service provider under the oversight of the responsible function at Teva.

The unblinded nurse at the investigational center who will dispense the IMPs will know the IMP assignments for each patient. In addition, up to 2 other individuals from the investigational center may know the IMP assignments to provide quality assurance and oversight in their preparation and administration, as necessary. These individuals will not be involved in the conduct of any study procedures or assessments of any adverse events.

Additional details regarding maintenance of randomization and blinding can be found in Section 5.10 of the study protocol.

2.3.   Data Monitoring Committee

There will be no Data Monitoring Committee/Data and Safety Monitoring Board in this study.

2.4.   Sample Size and Power Considerations

This study is safety-oriented in nature; therefore, no formal hypothesis testing is planned. Based on regulatory requirements, up to approximately 300 patients are planned to be enrolled in Stage 2 of this study in order to collect data on at least 100 patients exposed to TV-46000 for at least 1 year. Adolescent patients will only be enrolled in the US; any enrolled adolescents will be in addition to the aforementioned total.

2.5.   Sequence of Planned Analyses

2.5.1.   Planned Interim Analysis

There will be a planned data cut with statistical output produced before the New Drug Application (NDA) submission. This intermediary analysis is not a formal, pre-planned interim analysis but rather a "snapshot" of the data that will be performed when sufficient exposure and safety data are collected.

An interim CSR describing the data obtained until this time-point will be prepared for the submission.

2.5.2.   Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of study as defined in the study protocol.

This Statistical Analysis Plan and any corresponding amendments will be approved before interim database lock, in accordance with GSD-SOP-702: Statistical Analysis Plan (SAP).

A full CSR detailing the final analyses will be prepared after study completion and the final database lock.

3.   ANALYSIS SETS

3.1.   Enrolled Patients Set

The enrolled patients set will include all new patients who have met study eligibility requirements for Stage 1 and received at least one dose of oral risperidone in Stage 1 and all roll-over patients from Study TV46000-CNS-30072.

3.2.   Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients who were randomized either in Study TV46000-CNS-30072 for roll-over patients or in Study TV46000-CNS-30078.

In the ITT analysis set, treatment will be assigned based on the TV-46000 treatment to which the patients were randomized in this study, regardless of which treatment they actually received.

The ITT analysis set will include all randomized patients, including new patients who did not take any IMP.

3.3.   Per-Protocol Analysis Set

The per-protocol analysis set will include all patients in the safety analysis set who have no important protocol deviations. In this analysis set, treatment will be assigned based on the treatment the patients actually received. If patients erroneously received a wrong drug assignment in some visits, a decision to which treatment group they will be assigned will be determined in a case-by-case manner before database lock. The PP analysis set will be discussed before database lock and findings will be documented in the study data review document.

3.4.   Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of TV46000 in TV-46000-CNS-30072 study or in TV46000-CNS-30078 study. In the safety analysis set, treatment will be assigned based on the treatment the patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

3.5.   Pharmacokinetics Analysis Set

The pharmacokinetics analysis set will include all patients from the safety analysis set who also have ≥ 1 plasma concentration measurement.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages, missing category will be displayed as appropriate. Least squares means and 95% confidence intervals (CIs) may be used for selected parameters.

For presentations by oral risperidone dose, the patient's last dose up to and including visit 5, will be considered the oral risperidone dose.

All tables will be presented for all patient (adult and adolescent) populations, unless otherwise specified. Separate summary tables for adolescents will be presented only if a sufficient number of adolescent patients is enrolled (>=10) according to the clinical judgement.

4.2. Specification of Baseline Values

Roll-over patients will begin this study at the baseline visit and start at Stage 2 of the study (double-blind maintenance stage). For these patients, the EoT visit in Study TV46000-CNS-30072 will serve as the baseline visit. Some baseline procedures will be performed as part of the EoT visit in the TV46000-CNS-30072 study, and the results will be transferred to this study's clinical database.

For new patients, the baseline value of Stage 1 (Oral Conversion and Stabilization Stage) is the last observed value before the first oral risperidone administration as part of the conversion and stabilization stage, unless otherwise noted.

For the double-blind maintenance stage (Stage 2: Relapse Prevention), baseline is defined as the last observed data before the first study drug injection. However, for efficacy endpoints if the patient was already injected and some of the efficacy data was collected on the same day but after the injection, then this data will still be used as baseline.

4.3. Handling Withdrawals and Missing Data

Despite the best efforts to obtain complete data, missing data is unavoidable. For all variables, only observed patient data will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified.

Ad-hoc imputation for safety summary tables will be performed only for the specific cases described below. There will be no imputation in the data listings (including ad-hoc imputation); all values will be displayed as recorded in the clinical database.

4.3.1. Ad-hoc Imputation for Safety Data

Any adverse event with unknown severity will be considered as 'severe' for the tabulations. During Stage 2 of the study, for any adverse event with unknown relationship, the treatment will be considered as 'related'.

Any laboratory values given as '<x' or '>x' in the database will be assigned with the absolute value of x without the sign for the descriptive statistics and the calculation of changes from baseline (eg, a value of <0 .1 will be imputed as 0.1 for the calculations).

4.3.2. Missing Items in the Quality of Life Questionnaires

Missing items will not be imputed. For SQLS, CDSS, AIMS, SAS and BARS questionnaires, however, if the number of missing items in a scale (or sub-scale) is less than half, then the missing items will be assigned with the value of the arithmetic mean of the non missing items in the scale within the patient and visit.

4.3.3. Handling of Adverse Events with Missing Dates

The date of First Study Treatment, referred to below, corresponds to the first injection of TV-46000 (IMP) that the patient received in Study TV46000-CNS-30078. For the purpose of this study, oral risperidone is not considered an IMP. Any adverse event with incomplete start dates will be handled as described below, end dates will not be imputed.

- If only the day is missing, then the day will be imputed to the first day of the month, unless the adverse event month-year corresponds to the month-year of the Date of First Study Treatment. In that case, the day will be imputed with the Date of First Study Treatment, unless the adverse event end date occurred prior to Date of First Study Treatment.

- If both the day and month are missing and the year is the year of the Date of First Study Treatment then the date will be imputed to Date of First Study Treatment, unless the adverse event end date occurred prior to Date of First Study Treatment, in which case the start day-month will not be imputed. In addition, if the Date of First Study Treatment year < year of ADVERSE EVENTS start year then start day-month will be imputed to 01JAN.

4.3.4. Handling of Concomitant Medication with Missing Dates

For determination of prior vs concomitant medication, missing start or end month are imputed to JAN or DEC respectively and missing start or end day are imputed to day 01 and 30 respectively, unless the month is not missing then missing day is imputed to 28.

4.4. Study Days and Visits

Study days are numbered relative to the first day of study drug administration, namely the beginning of the Stage 2. The start of treatment (Day 1) is defined as the date on which a patient receives the first dose of study drug, as recorded on the Case Report Form (CRF). Days will be numbered relative to treatment start (ie, ..., −2, −1, 1, 2, ...; with Day 1 being the first day of study drug administration and day −1 being the day before the first day of study drug administration).

For summary tables of safety, unscheduled visits will be mapped to the closest scheduled visit according to the allowed time window specified in Tables 1 and 2 of the study protocol. Unscheduled visits that occurred after ET/EoT visit will be mapped to follow-up visits. If both

ET/EoT and follow-up 1 visits occurred on the same day and the ET/EoT results are missing, the results from the follow-up 1 visit will be mapped to the ET/EoT visit, and vice versa.

For summary tables of efficacy, unscheduled visits will be mapped to windows between the scheduled visits according to the date of the visit. The visit windows will be labeled 'Unsc visit after visit X' and will be presented sequentially in summaries with the scheduled visits.

For by-visit summaries, if there are multiple assessments at a post-baseline visit day, then the last non-missing assessment at that visit day will be used for the summary. If the multiple assessments include a scheduled assessment, the scheduled will be used.

For last safety assessment, the last available non-missing value will be used. For last efficacy assessment, the last available non-missing value not later than ET/EoT visit will be used. Unscheduled visits that could not be mapped will not be displayed in the by-visit summaries, but they will be considered for the endpoint/last assessment visit.

5. STUDY POPULATION

5.1. General

The ITT analysis set (Section 3.2) will be used for study population summaries of the double blind treatment stage unless otherwise specified. Summary tables will be presented by treatment group and for all patients and by source of patients (new patients and roll-over patients). For the endpoints that are evaluated only in the adult population, the analysis will be conducted on the ITT subset of adults. The enrolled patients set (Section 3.1) will be used for data summaries for new patients before the double blind treatment stage.

It is intended to also present summary tables by age subgroups (adults/adolescents) as applicable.

However since the number of adolescent patients may be too sparse (below 10 randomized adolescents), these summary tables might not be presented.

In addition, and if data permit, coronavirus disease 2019 (COVID-19) subgroups (eg,COVID-19-impacted patients/ COVID-19- non-impacted patients and/or home visits, before/after COVID-19 pandemic, etc.) of the ITT analysis set and safety analysis set will be presented.

5.2. Patient Disposition

The following will be summarized using descriptive statistics of data for all patients:

- new patients screened in Stage 1;
- new patients who were screened and not enrolled in the Oral Conversion and Stabilization Stage (Stage 1) and reason for screen failure/not enrolled;
- new patients screened and enrolled in Stage 1;
- new patients who were enrolled in Stage 1 but not randomized for the double blind stage (Stage 2) and reason for not randomized;
- all patients who were randomized;
- new patients who were randomized but not treated;
- all patients in the ITT, adult patients in the ITT, or adolescents in the ITT, PP, safety, and pharmacokinetics analysis sets;
- all patients who completed the treatment and/or study;
- patients who withdrew from the treatment or the study and reason for withdrawal from the treatment or the study including due to COVID-19.

Adolescent patient disposition may be summarized separately, if applicable.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics, including age, age group (adolescents [ages 13-17] and adults [18 years of age and above]), gender, race, ethnicity, baseline weight (kg),

baseline height (cm), baseline body mass index (BMI) (kg/m^2) and categorization, and injection site will be summarized using the descriptive statistics.

The randomization stratification factor levels (see Section 2.2), will be summarized using the descriptive statistics for each variable category.

Psychiatric history will be assessed using years since the initial diagnosis of schizophrenia for all patients and months since the most recent relapse for adults.

The ITT analysis set, the ITT subset of adults, the ITT subset of adolescents, and safety analysis set will be used for the summaries.

In addition, some of the demographic and screening characteristics may be summarized using the descriptive statistics for the enrolled patients set.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients are counted only once in each PT and SOC category. Summaries will be presented by treatment group and for all patients and by source of patients.

5.5. Prior Therapy and Medication

Any prior therapy, medication, or procedure a patient has had within 30 days before study drug administration will be recorded on the CRF. Trade name or international nonproprietary name (INN), indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Prior therapies and medications will include all medications taken and therapies administered before the first day of study drug administration. This will be collected twice during the study: at screening (before Stage 1) and Stage 2 (at baseline) of the study. Note that the prior therapy and medication for Stage 2 will include the concomitant medications in Stage 1.

5.5.1. Pre Study Risperidone Exposure

Pre-study risperidone treatment use for new patients will be defined based on patients' or investigator's report on the first and last days of pre-study risperidone treatment. Summary of the number and percentage of patients exposed to risperidone will be summarized by treatment and all patients and by source of patients.

5.6. Childbearing Potential and Methods of Contraception

For new female patients, information related to childbearing potential will be collected at each in-clinic visit at both study periods and information related to menopause will be collected at the screening visit (see Section 8.6.2.2). Data will be listed.

For new female and male patients, methods of contraception will be collected at screening. Data will be listed.

5.7. Study Protocol Deviations

Data from patients with any important protocol deviations as defined in Appendix C of the study protocol, and as recorded in protocol deviation spreadsheet during the study, will be summarized overall and for each category using descriptive statistics.

Data pertaining to deviations will be reviewed and important protocol deviations will be determined by the study team on ongoing basis and documented in the Statistical Data Review meeting minutes prior to the database lock.

6. EFFICACY ANALYSIS

6.1. General

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The enrolled patients analysis set (Section 3.1) will be used for data summaries during Stage 1 (for new patients) of the study; summaries will be presented for new patients in this set and for all patients by the ITT or the ITT subset of adults as appropriate. Unless otherwise specified, for the enrolled analysis set, data will be presented by randomized, not-randomized patients and overall, as appropriate.

The pharmacokinetic analysis set will be used for all pharmacokinetic/pharmacodynamics analyses which will be presented in a separate statistical analysis plan and report.

In the event of an emergency situation (eg, the COVID-19 pandemic), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), remote assessment of efficacy scales via TC and/or VC, with VC being the preferred method, may be allowed. The results of the scale rating will be directly entered into the eCRF per the usual process.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the original protocol instructions will be followed whenever the new instructions are not required.

6.2. Primary Efficacy Endpoint and Analysis

As this is a safety-oriented study, there is no primary efficacy endpoint or analysis for this study (efficacy endpoints are exploratory only).

6.3. Secondary Efficacy Endpoints and Analysis

There are no secondary efficacy endpoints for this study.

6.4. Other Efficacy Endpoints Analysis

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6.4.1. Proportion of Patients Who Experienced a Relapse in the Study

6.4.1.1. Definition

Patients meeting any 1 or more of the below relapse criteria are considered relapsed. Relapse is defined as 1 or more of the following items:

1. CGI-I of ≥5 (greater than or equal to minimally worse, ie, minimally worse, much worse or very much worse) **AND**

   a) an increase of any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥2 on that specific item since randomization, **OR**

   b) an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase[1] of ≥4 on the combined

---

[1] The absolute increase of the combined score is the sum of the increase of those scores (ignoring the decreases).

score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization.

2. hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons

3. CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2

4. violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

For simplicity, the assigned numbers 1-4 of the aforementioned relapse criteria will be used henceforth.

It should be noted that criteria 2 and 4 could happen anytime during the study without regard to study visits, whereas criteria 1 and 3 are evaluated at the study in-clinic visits (including unscheduled visits) and thus could be recorded simultaneously at the same visit.

Per definition, an exacerbation in symptoms during Stage 1 cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. Therefore, for efficacy evaluation, relapse can occur from the first injection until the end of treatment (ie, EoT/ ET Visit). In the follow-up time window patients will be treated according to the investigator's judgment and may not comply with the study protocol and therefore will not be counted for relapse.

6.4.1.2.   Analysis

The proportion of patients who experienced a relapse in the study will be analyzed.

The number and proportion of patients and Kaplan-Meier estimates of time to relapse that met each one of the relapse criteria 1-4 will be presented separately and overall.

6.4.2.   Drug Attitudes Inventory 10-item Version

6.4.2.1.   Definition

The Drug Attitudes Inventory (DAI) initially consisted of 30 items which focused on the subjective effects of the neuroleptic medications in patients with schizophrenia. The scale was developed to obtain a more complete understanding of factors influencing medication compliance in these patients.

A brief 10-item scale (DAI-10) that focuses on medication effects was constructed. It demonstrated a high correlation with medication compliance and treatment outcome. The DAI-10 is used in this study.

The response for each item is either "True" (T) or "False" (F) as applies to the patient. An interpretation is required because "true" may indicate either a positive or negative view about medications. Table 1 contains the standard of a compliant response for each DAI-10 item/statement.

Table 1: **Drug Attitudes Inventory 10-item Version – Standard of a Compliant Response**

Item	Statement	Compliant response
1	For me, the good things about medication outweigh the bad.	T
2	I feel weird, like a "zombie", on medication	F
3	I take medications of my own free choice	T
4	Medications make me feel more relaxed	T
5	Medication makes me feel tired and sluggish	F
6	I take medication only when I am sick	F
7	I feel more normal on medication.	T
8	It is unnatural for my mind and body to be controlled by medications.	F
9	My thoughts are clearer on medication	T
10	By staying on medications, I can prevent getting sick.	T

F = false; T = true

The scoring of the DAI-10 will be done as follows:

1. For each item, a compliant response as appears in Table 1 will be scored as plus 1; an incompliant response will be scored as minus 1.

2. The total score is the sum of the item scores from #1.

The total score ranges from -10 to +10. A positive total score indicates a positive attitude toward psychiatric medications and thus corresponds to a compliant response, and vice versa.

The DAI-10 will be assessed in adult patients only at screening (for new patients), baseline (for new patients and roll-over patients), the ET/EoT visit and at the follow-up visit 2 (8-weeks after the last dosing visit).

6.4.2.2. Analysis

By visit change from baseline to each visit and endpoint in the DAI-10 total score will be calculated. Least squares means and 95% CI of change from baseline to endpoint will be performed using a repeated measures analysis of covariance (ANCOVA) model with treatment arm (trt: q1m and q2m), subject id (subjid) and study visit (avisit), stratification variable (rand_strata) as factors and baseline DAI-10 score (Baseline) as a covariate. If for some visits there are less than 15 observations, these visits will not be incorporated into the model, as convergence problems might occur. For these cases only mean with 95% CI approximation using t-distribution will be presented. If the number of observation is below 5 then 95% CI will not be calculated.

A sample of SAS® code for the repeated measures ANCOVA is as follows:

```
Proc Mixed method=reml;
Class trt rand_strata subjid avisit;
Model Change=trt avisit rand_strata Baseline /DDFM=KR CL;
Repeated avisit / subject= subjid type = un;
LSMeans trt*avisit /CL;
Run;
```

The unstructured covariance matrix for repeated observations within patients will be used. In case that the model does not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS). The Kenward-Rodger (KR) method will be used to calculate the denominator degrees of freedom. In addition, if data in a visit is too sparse (below 5 patients) confidence intervals will not be presented.

The DAI-10 total score change from baseline will also be summarized using descriptive statistics and least-squares means at each time point by treatment group and by source of patients. Shift table for items 1, 3, 7 and 10 will be displayed; all items may be presented in the shift table as applicable.

6.4.3.   Schizophrenia Quality of Life Scale

6.4.3.1.   Definition

Schizophrenia Quality of Life Scale (SQLS) comprises 33 items categorized in 2 domains: psychosocial feelings (20 items - Items 3, 4, 5, 6, 8, 10, 11, 13, 15, 16, 17, 18, 19, 21, 22, 24, 25, 27, 29, 30) and cognition and vitality (13 items – Items 1, 2, 7, 9, 12, 14, 20, 23, 26, 28, 31, 32, 33). The items are scored on a five-point scale (1 - never, 2 - rarely, 3 - sometimes, 4 - often, 5 - always). For all items, except the specific 4 items discussed below, higher scores indicate comparatively lower quality of life.

The following four items have reversed scaling and refer to positive aspects of life:

7. I was able to carry out my day to day activities;

12. I felt that I could cope;

14. I slept well;

26. I felt happy.

The above are to be recoded such as 6 minus recorded score (eg. 6-ITEM_7) before the scale total is calculated. Individual domain and total scores are standardized by scoring algorithm to a 0 (best health status) to 100 (worst health status) scale, with higher scores indicating comparatively lower quality of life.

Therefore, the total score, namely TS, is calculated as the total of all 33 items minus the number of items answered (RS_{tot}), divided by the maximum possible total score, namely $RS_{max} = 33 \times 4 = 132$, and multiplied by 100.

$$TS = \frac{RS_{tot}}{RS_{max}} \times 100$$

Similarly, each scale score, 'Psychosocial feelings' and 'Cognition and vitality' will be calculated in the same way using the total score and number of items in the scale.

SQLS will be assessed in adult patients only at screening (for new patients), baseline (for new patients and roll-over patients), week 12, and every 12 weeks thereafter, including the ET/EoT visit, and at follow-up visit 2 (8 weeks after the last dosing visit).

For handling the missing items per each scale score see Section 4.3.2.

6.4.3.2.   Analysis

The by visit change from baseline of the total score will be calculated. Least squares means and 95% CI of change from baseline in the SQLS will be presented using a repeated measures ANCOVA method, with treatment arm (trt: q1m and q2m), stratification variables (rand_strata), subject id (subjid) and study visit (avisit), and baseline (Baseline, SQLS score) as a covariate. A sample of SAS® code for the analysis for each post baseline visit could be found in Section 6.4.2.2.

SQLS total and domain score and change from baseline will be summarized using descriptive statistics (least-squares mean will be presented as appropriate) at each time point for all treatment groups and by source of patients.

6.4.4.   5-Level EuroQol Five Dimensions Questionnaire

6.4.4.1.   Definition

The 5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L) consists of the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The values for each of the dimensions are: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems and 5=unable to/extreme problems.

The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled '100=Best imaginable health state' and '0=Worst imaginable health state'.

EQ-5D-5L will be assessed in adult patients only at screening (for new patients), baseline (for new patients and roll-over patients), week 12, and every 12 weeks thereafter, including the ET/EoT visit, and at follow-up visit 2 (8 weeks after the last dosing visit).

6.4.4.2.   Analysis

By visit change from baseline and to endpoint in each of the EQ-5D-5L domains will be calculated. The analysis of change from baseline to each visit and endpoint in each of the EQ-5D-5L domains will be performed similarly to Section 6.4.2.2, using the appropriate baseline EQ-5D-5L domain as a covariate, respectively.

The change from baseline for each of the EQ-5D-5L domains will also be summarized using descriptive statistics, and least squares means at each time point by treatment group and by source of patients as appropriate.

6.4.5.   Healthcare Resource Utilization

6.4.5.1.   Definition

The percentage of patients who were hospitalized, number of hospitalizations, and length of hospital stay (number of days); percentage of patients who had emergency room (ER) visits and number of ER visits (ie, not including protocol-mandated outpatient visits); and percentage of patients who had outpatient visits (ie, not including protocol-mandated outpatient visits) and number of outpatient visits will be calculated.

6.4.5.2.   Analysis

The parameters defined above in Section 6.4.5.1will be assessed in all patients (ie, both adults and adolescents) and will be summarized using descriptive statistics for both study periods, as applicable.

6.4.6.   Change in PANSS Total Score from Baseline to Endpoint

6.4.6.1.   Definition

The PANSS comprises a total of 30 items. Each item is scored using 7 rating points, with an increasing level of psychopathology, as follows 1 – absent; 2 – minimal; 3 – mild; 4 – moderate; 5 - moderate severe; 6 – severe; 7 – extreme.

7 of the PANSS items constitute a Positive scale (P1-P7) with a maximum score of 49, 7 a Negative scale (N1-N7) with a maximum score of 49, and 16 a General Psychopathology scale with a maximum score of 112. The score for these scales are generated by a summation of ratings. The total or overall PANSS score is the sum of all of the 30 items, and it will only be calculated if all the items are present. The maximum total score is 210.

PANSS will be assessed at all in-clinic visits during the study.

Percent reduction of the total score from screening or baseline (=reference) will be conducted by calculating

$$\text{Reduction(\%) at visit k} = 100 - \frac{100 \cdot (Total\ score\ at\ visit\ k - 30)}{Total\ score\ at\ reference\ visit\ -\ 30}$$

If total score at baseline or screening is 30 then the denominator will be set to 1(see Leucht et al 2010).

6.4.6.2.   Analysis

The change in the PANSS total score from screening to each visit will be calculated for Stage 1 for new patients. The change from baseline in total score will be calculated to each visit and to endpoint for Stage 2 for all patients. The PANSS total score from baseline to endpoint analysis will be performed similarly to Section 6.4.2.2.

PANSS total score and change from screening will be summarized using descriptive statistics for each dose at each time-point during Stage 1 for new patients. PANSS total score and change from baseline will be summarized using descriptive statistics for each treatment arm at each time

point and to endpoint during Stage 2 for all patients, as well as for the follow up visits, using least squares means and 95% CI calculated by a repeated measures ANCOVA model.

Individual PANSS items and/or scales might be summarized using descriptive statistics during Stage 1, 2 or both.

Percent reduction will be summarized in a frequency table, with percent reduction using the categories ≤0%, 1%-24%, 25%-49%, 50%-74%, 75%-100%.

6.4.7. CGI-I Score at Endpoint

6.4.7.1. Definition

The Clinical Global Impression–Improvement (CGI-I) scale permits a global evaluation of the patient's improvement in symptoms overall. The CGI-I scale rates the patient's improvement relative to his or her symptoms on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-I will be administered by the investigator/trained rater at all in-clinic visits during the study according to the schedule of assessment (except for the screening and baseline visits).

CGI-I during Stage 1 will be relative to screening for new patients; CGI-I during Stage 2 will be relative to the baseline visit for new and roll-over patients.

6.4.7.2. Analysis

CGI-I will be analyzed in the same way as described in Section 6.4.2.2 except that the baseline Clinical Global Impression of Severity (CGI-S) will be included as a covariate in the model as the efficacy measure at baseline and the target variable of the actual value by visit will be analyzed rather than change from baseline for the parameter itself; subsequently this model is measuring change from a reference (baseline).

CGI-I will be summarized using descriptive statistics during Stage 1 – by oral dose, and during Stage 2 and the follow up visits – by treatment group and by source of patients.

6.4.8. Personal and Social Performance Scale

6.4.8.1. Definition

The Personal and Social Performance Scale (PSP) is a clinician-rated instrument that measures personal and social functioning in patients with schizophrenia. The PSP is a 100-point single-item rating scale, divided into 10 equal intervals. The score is based on the assessment of patient's functioning in 4 categories in the past: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. These 4 patient functioning categories are assessed via the degree of difficulty ranging from 1 (absent) to very severe (6).

Higher PSP (also called total) scores represent better personal and social functioning, with ratings from 91 to 100 indicating more than adequate functioning, while scores under 30 indicating functioning so poor that intensive supervision is required.

PSP will be assessed for adult patients only at screening (for new patients), baseline (for new patients and roll-over patients), week 12, and after every 12 weeks thereafter, including ET/EoT visit, and at follow-up visit 2 (8 weeks after the last dosing visit).

6.4.8.2.   Analysis

By visit change from baseline in the PSP (also called total) score will be calculated. The PSP total score will be analyzed in the same way as described in Section 6.4.3.2 except that the baseline PSP score will be included in the model as the efficacy measure at baseline.

PSP total score and change from baseline will be summarized using descriptive statistics by treatment group and source of patients at each timepoint and to endpoint.

The areas of functioning assessments will be summarized using descriptive statistics by treatment group and source of patients at each timepoint and to endpoint.

7.   MULTIPLE COMPARISONS AND MULTIPLICITY

There are no primary efficacy endpoints in this study. Therefore no adjustments will be made for the preplanned multiple comparisons/endpoints.

8. SAFETY ANALYSIS

8.1. General

Safety analyses for Stage 1 will be performed for new patients on enrolled patients set (Section 3.1), unless otherwise noted. Safety analyses will be performed for new patients and roll-over patients on the safety analysis set for Stage 2 (Section 3.4). Summaries of treatment emergent adverse events for Stage 1 will be presented on the Enrolled patients set (Section 3.1) by randomized and not-randomized groups and overall, unless otherwise stated. Summaries of treatment emergent adverse events for Stage 2 will be presented by treatment group and by source of patients, unless otherwise stated.

Selected safety data will also be presented by site of injection (abdomen vs arm), as applicable.

Safety assessments and time points are provided in Table 1 and Table 2 of the study protocol.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point, as appropriate. For categorical variables, patient counts and percentages will be provided as appropriate.

8.2. Duration of Exposure to Risperidone during Study

Duration of exposure to risperidone will be analyzed at the different study stages as the number of days a patient received drug (last day of study drug and first day of study drug). Duration of treatment calculation for the oral and the injectable risperidone will be different in order to account for the difference in frequency of administration and, for roll-over patients, will not take into account exposure in the TV46000-CNS-30072 study. The exposure at each stage will be summarized using descriptive statistics.

8.2.1. Oral Stabilization Period – Stage 1

For the individual new patient, duration of exposure to oral risperidone (days) during Stage 1 is the number of days the patient received the oral risperidone during the study (last day of oral risperidone drug – first day of oral risperidone + 1). In patients not randomized to Stage 2 of the study, in case of missing end of study date or a lost-to-follow-up patient, (planned) randomization date will be considered as last date of subject assessments.

Duration of treatment (days) will be summarized only for new patients using descriptive statistics.

8.2.2. Relapse Prevention - Stage 2

Duration of treatment (days treated) during Stage 2 will be defined based on the first and last days of IMP injection in this study. Duration of treatment calculation for the different treatment regimens will be as follows:

- q1m - last day – first injection day in this study + 29;
- q2m - last day – first injection day in this study + 57.

For roll-over placebo patients the first TV46000 dose is the week 4visit.

Weeks of IMP treatment using the categories ≤13 week, >13 to ≤26 weeks, >26 to ≤39 weeks, >39 to ≤52 weeks or >52 to ≤56 weeks will be summarized using descriptive statistics. Duration of treatment (weeks) will also be summarized using descriptive statistics.

8.2.3. Total of Exposure to Risperidone in the Study

For an individual new patient, total exposure to risperidone during the study is the sum of Stage 1 and Stage 2. Total weeks on risperidone in the study using the categories ≤13 weeks, >13 to ≤26 weeks, >26 to ≤39 weeks, >39 to ≤52 weeks or >52 to ≤56 weeks or more than 56 weeks will be summarized using descriptive statistics. Duration of study (weeks) will also be summarized using descriptive statistics.

For roll-over patients, total exposure to risperidone in Stage 2 of this study is described in Section 8.2.2.

8.3. Study Drug Compliance

8.3.1. Oral Stabilization Period – Stage 1

Per the study protocol, a new patient with the total compliance of less than 80% will be considered noncompliant during Stage 1 (i.e., compliance will be calculated only for new patients). This is an important criterion in regard to compliance with the study protocol, which is required for the patient to be eligible for randomization.

The compliance is defined as the ratio between the dose taken and the dose required:

$$\% \, Compliance = \frac{Actual \, drug \, taken \, (mg)}{Expected \, drug \, to \, be \, taken \, (mg)} \times 100\%$$

'Actual drug taken' will be calculated as the total amount of drug dispensed less total amount of drug returned, both during the entire oral stage, based on "study drug accountability – oral" field in the CRF. Drug dispensed (in mg) will be the number of dispensed tablets (Total Number Dispensed) multiplied by the corresponding dose (Dispensed Units). The total amount of drug dispensed will be the sum over all the visits where the drug dispensation occurred, both scheduled and unscheduled. The same calculation will be done to obtain the total amount of drug returned, replacing "dispensed" by "returned".

'Expected drug to be taken' will be calculated as sum(dose × days to be taken), where 'dose' is the dose prescribed (with one exception, below) by the investigator from the 'Study drug administration - oral medication' field in the CRF and 'days to be taken' is the number of days between the corresponding 'Start Date of Treatment' dates from the same CRF or the randomization date (for patients with missing randomization data, or lost to follow up the last assessment data will be used). For patients that the oral dose prescribed is below 2mg/day, 2mg/day will be used as the expected dose and not the actual dose (eg 1mg or 0.5mg a day).

If no drug was returned, it will be accounted for as '0' returned amount for this visit in the compliance calculation. It should be noted that if the investigator or the sponsor determines that the patient was not in compliance with the study protocol, the case will be evaluated on a case-

by-case basis, and the investigator and the sponsor will determine whether the patient will be randomized to the double-blind period (Stage 2).

Oral drug compliance during Stage 1 will be categorized as <60%, 60% to < 80%, 80% to < 100%, and ≥100% and summarized using descriptive statistics. A numerical example of compliance calculation during Stage 1 is given below.

8.3.1.1.   Numerical Example of Oral Drug Compliance during Stage 1

Assuming that after looking at the Start Dates of Treatment, the patient had a total 84 days of the oral period, of which of 2 days were on 1mg/day, 40 days on 3 mg/day and 42 days on 4 mg/day – the expected drug to be taken (mg) would be $2 \times 2 + 3 \times 40 + 4 \times 42 = 292$ mg.

For the entire oral stage period, the patient was dispensed a certain amount (2 tablets of 1 mg/day, 68 tablets of 3 mg/day and 50 tablets of 4 mg/day) and returned a certain amount (30 tablets of 3 mg/day and 10 tablets of 4 mg/day) –

- the total drug dispensed would be $2 \times 1 + 68 \times 3 + 50 \times 4 = 406$ mg;

- the total drug returned would be $30 \times 3 + 10 \times 4 = 130$ mg;

- Actual drug taken would be $406 - 130 = 276$ mg

Drug compliance would be Drug consumed/ Drug prescribed=276/292=95% (>80%)

$$\% \ Compliance = \frac{Actual \ drug \ taken \ (mg)}{Expected \ drug \ to \ be \ taken \ (mg)} \times 100\% = \frac{276}{292} \times 100\% = 95\%$$

8.3.2.   Relapse Prevention - Stage 2

Not applicable. Drug compliance during Stage 2 will not be assessed.

8.4.   Adverse Events

For recording of adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period. All adverse events will be coded using the MedDRA. Each patient will be counted only once in each PT or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), including adverse events determined by the investigator to be related to oral risperidone (Stage 1) or TV-46000 (Stage 2) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by randomized, not-randomized and overall using the enrolled patients set (Stage 1) or treatment group and by source of patients using the safety analysis set (Stage 2).

Summaries will include treatment-emergent adverse events which are defined as adverse events occurring at or after the first day of oral risperidone until the last day of oral risperidone for new patients for Stage 1 and for Stage 2 as adverse events occurring at or after the first IMP injection.

No protocol-defined adverse events of special interest were identified for this study.

In case of the missing dates and severity, the imputation will be performed as described in Section 4.3.

Multiple records with the same PT and adverse event onset date for the same patient, or with overlapping or consecutive dates, are counted only once selecting the adverse event with the highest severity and seriousness. For injection site reactions, multiple records with overlapping or consecutive dates are counted only once only if the injection site is the same, selecting the adverse event with the highest severity and seriousness. If the onset date of adverse events with the same PT is partially unknown or duration is < 24 hours, then these adverse events will be counted as separate adverse events, except for the cases where an adverse event with duration of < 24 hours has the same onset date as another adverse event with a longer duration, then the adverse events with the longer duration adverse events will be counted. The event rate per 100 years (PY) of patient treatment exposure is calculated as 100*(Number of cases/PY).

Safety data collected in Stage 1 for new patients will also be summarized using descriptive statistics in the enrolled patients set. Adverse events that started in Stage 1 and ended in Stage 2 will be reported only in oral phase.

Selected safety data will also be presented by site of injection (abdomen vs arm).

Separate summaries for adolescent patients may be presented separately for some analyses, as applicable.

Patient listings of all adverse events, serious adverse events and adverse events leading to withdrawal and adverse events leading to death will be presented.

Summary of the number of adverse events per week following each sc injection will be presented.

8.5.   Deaths

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

8.6.   Clinical Laboratory Tests

The clinical laboratory tests (serum chemistry, hematology and urinalysis) are detailed in Table 7 of the study protocol.

Laboratory test results will be presented in standard international (SI) units.

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented at time points detailed in the schedule of assessment Tables 1 and 2 of the study protocol including last assessment (as a separate visit). Laboratory values and changes from screening or baseline (as appropriate) to each visit will be summarized using descriptive statistics.

Boxplots for selected laboratory tests, including neutrophils, alanine aminotransferase, aspartate aminotransferase and bilirubin, will be presented by visit and treatment group and by source of patients.

Shifts (below, within, and above the normal range) from screening or baseline (as appropriate) to each visit and endpoint assessment will be summarized using patient counts.

Summaries of potentially clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially

clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics with the criteria specified in Table 2.

Table 2:   Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value
Serum chemistry	
Alanine aminotransferase (ALT)	≥3x ULN
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase	≥3x ULN
Lactate dehydrogenase (LDH)	≥3x ULN
Blood urea nitrogen (BUN)	≥10.71 mmol/L
Creatinine	≥177 μmol/L
Uric acid Men	≥625 μmol/L
Women	≥506 μmol/L
Bilirubin (total)	≥2x ULN
Potassium	≤3 mmol/L ≥6 mmol/L
Calcium	≤1.5 mmol/L ≥3.5 mmol/L
Hematology	
Hemoglobin Men	≤115 g/L
Women	≤95 g/L
White blood cell (WBC) counts	≤3 x 10^9/L ≥20 x 10^9/L
Absolute neutrophil counts (ANC)	≤1 x 10^9/L
Platelet counts	≤75 x 10^9/L ≥700 x 10^9/L

ULN=upper limit of normal range.

8.6.1.   Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- ALT or AST increase of $>3\times$ the upper limit of the normal range (ULN)

- total bilirubin increase of $>2\times$ ULN

- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

All incidences will be listed.

8.6.2. Other Clinical Laboratory Tests

8.6.2.1. Virology and Thyroid Screening Tests

At screening (new patients only) and baseline (new patients and roll-over patients), patients will be tested for HIV, hepatitis B surface antigen, hepatitis C antibody. Due to potential effects on clinical psychiatric symptoms, levels of thyroid hormones (thyroid stimulating hormone, triiodothyronine, and thyroxine) will also be assessed at these time points.

The data will be presented as listings.

8.6.2.2. Human Chorionic Gonadotropin Tests

A FSH test will be performed at the screening visit (new patients only) for any female who has been without menses for at least 12 months to confirm post-menopausal status. Women may be allowed not to use contraceptives during the study if they had no menses for at least 12 months (without an alternative medical cause) and the FSH concentration is above 35 U/L.

A serum beta human chorionic gonadotropin (β-HCG) test will be performed for all women of child bearing potential at screening (new patients only), baseline, and the follow-up/exit visits (see Table 1 and Table 2 of the study protocol). At baseline, both a serum and a urine β-HCG test will be performed. Urine β-HCG (dipstick) test will be performed for women of child bearing potential at all visits where study drug is administered (prior to study drug administration). A negative result must be obtained prior to study drug administration.

The FSH, serum and urine β-HCG data will be listed.

8.6.2.3. Urine Drug Screen

A urine drug screen will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The urine drug screen detects the presence of drugs of abuse, including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol.

Any findings will be listed.

8.6.2.4. Prolactin

Blood samples will be obtained for prolactin test at the time points specified in Table 1 and Table 2 of the study protocol. The test results of the roll-over patients will remain blinded to the sponsor until the database of the TV46000-CNS-30072 study is locked and the IMP assignment is revealed.

The test results will be presented as described for all the clinical laboratory test results outlined in Section 8.6 above. In addition, shift tables from screening (for new patients) and baseline (new patients and roll-over patients) - from normal to 2x ULN and 5x ULN - will be presented.

8.6.2.5. Glomerular Filtration Rate

Glomerular Filtration Rate (GFR) will be calculated based on plasma creatinine levels, weight, gender and age using the Cockcroft-Gault equation.

The estimated GFR values and changes from baseline will be presented by visit using descriptive statistics. The individual GFR measurements will also be presented in the listing.

8.7. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit for new patients and at the baseline visit for adolescent roll-over patients) and weight, will be performed at the time points detailed in Table 1 and Table 2 of the study protocol. The full physical examination will consist of examining the following body systems: cardiovascular, respiratory, abdominal, skin, neurological, and musculoskeletal systems. The physical examination will also include examination of general appearance, including head, eyes, ears, nose, and throat; chest; abdomen; skin; lymph nodes; and extremities. Body weight and tympanic temperature will be measured at each visit. Systolic and diastolic blood pressure and pulse rate will be measured with the patient in a seated position. Any physical examination finding that is judged by the investigator as a clinically significant (except at the screening visit [new patients]) will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2 of the study protocol.

Descriptive statistics for weight and height will be provided. All the data will be listed. Boxplots for weight will be presented by visit and treatment group.

In addition, BMI results and percent changes from screening to each visit in Stage 1 (new patients only) for the enrolled patients set and percent changes from baseline to each visit in Stage 2 (new patients and roll-over patients) for the safety analysis set will be presented. BMI shifts from reference to each visit by treatment group and by source of patients will be presented, where the reference is the screening measurement for Stage 1 (new patients only) and the baseline measurement for Stage 2 (new patients and roll-over patients), using the following limits: '<0', '≥0-5%', '≥5-10%' and '≥10%'.

8.8. Vital Signs

Summary statistics for vital signs (blood pressure [systolic/diastolic], respiratory rate, tympanic temperature, and pulse) will be presented at the time points including last assessment (as a separate visit) detailed in Table 1 and Table 2 of the study protocol.

Vital signs values and changes from screening (for new patients) or baseline (for new patients and roll-over patients) to each visit will be summarized by stage of study using descriptive statistics. All the data will be listed.

Boxplots for selected vital signs, including pulse, systolic blood pressure and diastolic blood pressure, will be presented by visit and treatment group and by source of patients.

Summaries of potentially clinically significant abnormal values will include all post baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal vital sign values, specified by the criteria in Table 3, will be summarized using descriptive statistics. Systolic and diastolic blood pressure will be included in all summaries.

Table 3:   Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value
Pulse	≥120 bpm
	≤50 bpm
Systolic blood pressure	≥180 mm Hg
	≤90 mm Hg
Diastolic blood pressure	≥105 mm Hg
	≤50 mm Hg
Body temperature	≥38.3°C

bpm = beats per minute; mm Hg = millimeters of mercury.

8.9.   Electrocardiography

A standard 12-lead ECG will be recorded at the time points detailed in Tables 1 and 2 of the study protocol. Triplicate measurements will be performed at screening (for new patients) and baseline (for new patients and roll-over patients) and single measurements at all other in-clinic visits.

Electrocardiogram (ECG) findings (normal and abnormal) at screening (for new patients) and baseline (for new patients and roll-over patients) will be summarized using descriptive statistics; the data presentation will include both eResearch Technology (the central ECG vendor) and investigator interpretation. The average of the 3 ECG screening and baseline assessments will be calculated; if more measurements are taken, the 3 last measurements taken prior to first dose administration will be used both for the average calculation and for choosing the worst result for the interpretation.

If the investigator interpretation is missing, the following derivation rule will be used:

1. If ERT interpretation is 'normal' then investigator interpretation on the same date will be derived as 'normal';

2. Otherwise investigator interpretation will not be derived.

Shifts (normal and abnormal) from screening to baseline (for new randomized patients) and from baseline to overall result interpretation at each visit and last assessment will be summarized using patient counts. For overall result interpretation the worst post baseline finding for the patient (the abnormal finding if there are both normal and abnormal findings) will be used in the summaries. Summary statistics for ECG variables values will be presented. Actual values and changes from screening to baseline and from baseline to each visit and last assessment will be summarized using descriptive statistics.

The incidence of potentially clinically significant abnormal values for ECG variables will be summarized using descriptive statistics with the criteria specified below:

- QT interval corrected using Fridericia's formula (QTcF) values >450 msec or >480 msec or >500 msec.
- QTcF change from baseline values >30 or >60.

- PR change from baseline ≥25% and a value >200.
- QRS change from baseline ≥25% and a value >110.
- Heart rate value <60 bpm or >100 bpm.

8.10. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Concomitant medications and treatments will be recorded from screening (for new patients) or from baseline (for roll-over patients) through the final visit. Details of prohibited medications may be found in Section 5.7 of the study protocol. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category and PT. Patients are counted only once in each therapeutic class, and only once in each PT category.

A distinction will be made between the study stages. For Stage 1, concomitant therapies and medications will be presented for new patients using the enrolled patients set (Section 3.1) and will include all medications up to randomization day (Day 1), excluding the randomization day. For Stage 2, the concomitant therapies and medications will be presented using the safety analysis set and will include all medications from the day of randomization (baseline, Day 1) and up to the end of study as defined in the study protocol.

Descriptive statistics for allowed rescue medications (see Section 5.7 in the study protocol and Appendix A) will be presented by treatment group and by source of patients and by study stage.

8.11. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors. Any positive answer to the behavior subcomponents at screening or baseline identifies a patient with "Suicidal Behavior at Screening" or "Suicidal Behavior at Baseline" respectively.

For new patients, the C-SSRS will be administered at screening (baseline/screening version), and the "since last visit" version will be administered at all post-screening visits and telephone contacts during the study.

For roll-over patients, the "since last visit" version will be administered at baseline and all subsequent visits and telephone contacts during the study.

For the derivation of Screening Behavior, all assessments until the beginning of Stage 1 should be used for new patients, while for the derivation of Baseline Behavior, all assessments after the beginning of Stage 1 and till the beginning of Stage 2 should be used for new and roll-over patients. Same derivation will be done also for "Suicidal Ideation at Screening" and "Suicidal Ideation at Baseline". A patient identified with either "Suicidal Behavior at Screening/Baseline" or with "Suicidal Ideation at Screening/Baseline" is also classified as with "Suicidal Behavior or Ideation at Screening/Baseline".

For post-screening/ post-baseline periods, any positive answer to the behavior subcomponents in any of the post screening or baseline assessments, according to the study period (Oral or sc), identifies a patient as with "Suicidal Behavior Post Dosing" for that period. Same derivation will be done also for Suicidal Ideation post Dosing" for both the oral and sc periods. A patient identified with either "Suicidal Behavior Post Dosing" or with "Suicidal Ideation Post Dosing" is also classified as with "Suicidal Behavior or Ideation Post Dosing", the derivation should be done for both periods.

Frequency counts and percentages of the C-SSRS outcomes: Suicidal Behavior at Screening/Baseline, Suicidal Ideation at Screening/Baseline, Suicidal Behavior or Ideation at Screening/Baseline, Suicidal Behavior Post Dosing, Suicidal Ideation Post Dosing, Suicidal Behavior or Ideation Post Dosing, and shifts from screening/baseline for Stage 1/Stage 2 will be summarized.

8.12.   Abnormal Involuntary Movement Scale (AIMS)

The AIMS will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The AIMS scores the occurrence of tardive dyskinesia in patients receiving neuroleptic medications. The AIMS is a 14-item scale that includes assessments of orofacial movements, extremity and truncal dyskinesia, examiner's judgment of global severity, subjective measures of awareness of movements and distress, and a yes/no assessment of problems concerning teeth and/or dentures. Higher scores indicate greater severity of the condition.

AIMS total score will be calculated as a sum of items 1 through 7.

The AIMS total score and the individual score for each of the AIMS items 8-10 and changes from screening during Stage 1 for new patients will be presented using descriptive statistics. Shift from screening analysis of AIMS items 11-14 during Stage 1 will be presented.

The AIMS total score and the individual score for each of the AIMS items 8-10 and changes from baseline during Stage 2 for new patients and roll-over patients will be presented using descriptive statistics. Shift from baseline analysis of AIMS items 11-14 during Stage 2 will be presented.

Enrolled patients set and ITT analysis set will be used as appropriate.

8.13.   Simpson-Angus Scale (SAS)

The SAS will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The SAS is a 10-item instrument for the assessment of neuroleptic-induced parkinsonism. The items on the scale include measurements of hypokinesia, rigidity, glabellar reflex, tremor, and salivation. Each item is rated on a 5-point scale (0 to 4), with a higher score indicating greater severity of symptoms. The mean score is calculated by adding the individual item scores and dividing by 10.

The SAS mean score and changes from screening during Stage 1 will be presented for new patients using descriptive statistics by enrolled patients set.

The SAS mean score and changes from baseline during Stage 2 will be presented for new patients and roll-over patients using descriptive statistics by treatment group and by source of patients.

8.14. Barnes Akathisia Rating Scale (BARS)

The BARS will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The BARS is an instrument that assesses the severity of drug-induced akathisia. The BARS includes 3 items for rating objective restless movements, subjective restlessness, and any subjective distress associated with akathisia that are scored on a 4-point scale of 0 to 3, and summed yielding a total score ranging from 0 to 9. The BARS also includes a global clinical assessment of severity scored on a scale of 0 to 5. Higher scores are indicative of greater severity of akathisia.

BARS total score, global clinical assessment of severity values, and changes from screening (for new patients) and baseline (for new patients and roll-over patients) to each visit will be summarized using descriptive statistics - during Stage 1 by enrolled patients set and during Stage 2 by treatment group and by source of patients.

8.15. Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and EPS in schizophrenia. This clinician-administered instrument consists of

9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe) that are added together to form the CDSS depression score of the patient.

Descriptive statistics of CDSS depression score values and changes from screening (for new patients) and baseline (for new patients and roll-over patients) to each visit will be presented - during Stage 1 by enrolled patients set and during Stage 2 by treatment group and by source of patients.

8.16. Clinical Global Impression-Severity of Suicidality (CGI-SS)

The CGI-SS scale provides an overall clinician-rated assessment of the risk of suicidality. The CGI-SS consists of a 5-point scale in Part 1 ranging from 1 (not at all suicidal) to 5 (attempted suicide) and a 7-point scale in Part 2 ranging from 1 (very much improved) to 7 (very much worse).

The CGI-SS will be assessed at screening (for new patients) and all in-clinic visits during the study according to the schedule of assessment.

Descriptive statistics of CGI-SS Part 1 and 2 will be presented - during Stage 1 (for new patients) by enrolled patients set and during Stage 2 (for new patients and roll-over patients) by treatment group and by source of patients.

8.17. Clinical Global Impression of Severity (CGI-S)

The CGI-S will be administered by the investigator/trained rater at all in-clinic visits. The CGI-S scale was developed to rate the severity of a patient's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

Descriptive statistics of CGI-S Part 1 and 2 will be presented - during Stage 1 (for new patients) by enrolled patients set and during Stage 2 (for new patients and roll-over patients) by treatment

group and by source of patients. Shift tables from screening (for new patients) and baseline (new patients and roll-over patients) to each visit and last assessment will be presented.

8.18. Structured Clinical Interview for DSM-5 (SCID-5)

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making DSM-5 diagnoses. It will be administered to new patients only at screening by a clinician or trained mental health professional that is familiar with the DSM-5 classification and diagnostic criteria.

The SCID-5 will be presented in listings.

9. TOLERABILITY VARIABLES AND ANALYSIS

9.1. Assessment of Local Tolerability and Pain

In case an adverse event related to an injection site reaction is reported, an assessment of the sc injection site (ie, local tolerability [skin at injection site]) will be made. The presence and severity of erythema, swelling, induration, and pain at the injection site may be assessed using the scales described in the Protocol Section 7.8.

Data will be summarized as follows:

- Descriptive analysis of frequency counts and percentages of the initial subject's *maximal* (per injection type) scoring of erythema, edema, induration and nodule assessment, and of injection pain intensity assessment using the Numeric Pain Rating Scale (NPRS);

- Descriptive analysis of subject's *mean* time to stabilization, namely until the score of 0, of erythema, edema, and of induration and nodule assessment.

This analysis will be presented by both

- treatment group (q1m and q2m) and the injection type (placebo or TV-46000), thus dividing the patients into non-intersecting groups, and distinguishing between the 2 types of injections for patients randomized to the TV-46000 q2m group, and by low (≤0.3ml) and high (>0.3ml) volume (the cut off is equivalent to the 100 mg dosage, which is the only overlapping dose between the 2 regimens, see Table 4);

- injection type – injection type will be identical to the treatment arm for the TV-46000 q1m patients, while the TV-46000 q2m patients will appear under 2 categories (placebo or TV-46000).

Table 4:   Oral Risperidone Doses and Corresponding TV-46000 Doses

	Oral Risperidone Doses and Corresponding TV-46000 Doses[ab]			
	2 mg/day (mL)	**3 mg/day (mL)**	**4 mg/day (mL)**	**5 mg/day (Adults Only) (mL)**
TV-46000 q1m	50 mg (0.14 mL)	75 mg (0.21 mL)	100 mg (0.28 mL)	125 mg (0.35 mL)
TV-46000 q2m	100 mg (0.28 mL)	150 mg (0.42 mL)	200 mg (0.56 mL)	250 mg (0.70mL)

[a] Placebo dosing volume is 0.31 ml

[b] The administered volume corresponding to each dose is shown in parentheses next to it

9.2. All-cause Discontinuation Rate Assessment

All-cause discontinuation rates and discontinuation rates due to adverse events (dropout rates) will be calculated as the number of patients who withdrew early for all reasons, and the number

of patients who withdrew early due to adverse events, respectively, divided by number of patients in each treatment group, and will be analyzed using descriptive statistics.

Time to all-cause discontinuation will be calculated as the discontinuation date minus the randomization date plus 1. The date of last contact will be used for the lost to follow-up patients. Kaplan Meier curves for the time to discontinuation as a result of all causes will be plotted by treatment group and by source of patients.

The ITT analysis set will be used for the analysis. Separate summaries for adolescent patients might be presented separately for some analyses, according to the total number of the adolescents.

10.   PHARMACOKINETIC ANALYSIS

All concentration data will be summarized by age subset (adult, adolescent), treatment group (q1m, q2m or oral), dose and visit using descriptive statistics (n, mean, standard deviation, median, minimum, geometric mean, and coefficient of variation). Drug concentrations over time [C(t)] reported by age subset, time (visit) and treatment will be presented for risperidone, 9-hydroxyrisperidone (9-OH-risperidone), and total active moiety. Total active moiety is defined as the sum of risperidone and 9-OH-risperidone corrected by molecular weight, according to the following formula:

$$[Active\ Moiety] = [risperidone] + [9 - OH - risperidone] \times (410/426)$$

Individual plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety will be listed by age subset, treatment group, dose and visit. Unscheduled visits will be listed separately.

For summary tables, the values of 0.000 ng/mL will be replaced by half the LLOQ value i.e. 0.05 ng/mL for Risperidone, 0.15 ng/mL for 9-OH-Risperidone, 0.05 ng/mL for total active moiety (a footnote will be added to tables to present LLOQ values for each analyte). Data from unscheduled visits and early termination visits will not be used in descriptive summaries.For listings if individual plasma concentration value is 0.000 ng/mL then this value is reported as BLQ.

Additional pharmacokinetic parameters may be determined if data permits (see Section 1.2).

The analysis will include both structural model development and evaluation of the influence of patient covariates on pharmacokinetic variability. Example for potential covariates may be: Patient characteristics (demographics, CYP2D6 metabolizer status, and renal function), disease characteristics (disease state, prior treatment) and treatment characteristics (site of injection, and interacting concomitant medication).

In addition, if data permits the pharmacokinetics of TV-46000 in adolescent population will be characterized in comparison to the adult population.

Population pharmacokinetics analysis results will be reported separately from the main study report.

Importantly, independent pharmacokinetic modeling and population-based modeling analysis will take place during the study conduct by an external vendor, while maintaining the blind, as described in the pharmacokinetics analysis plan.

11. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

12.   BIOMARKER AND PHARMACOGENETICS ANALYSIS

Genetic variability in the metabolizer gene, CYP2D6, may be evaluated using descriptive statistics for an association with drug concentrations, pharmacokinetic parameters and safety variables.
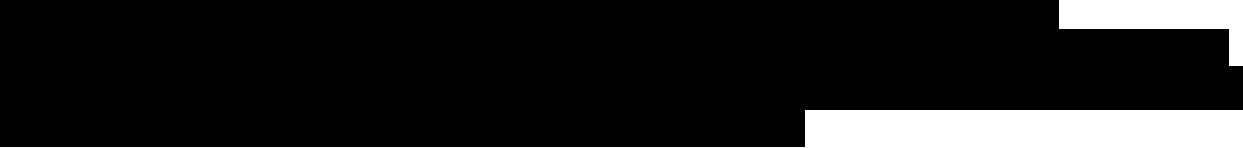
The biomarker sample analyses will be performed if and when required. Since new techniques continue to be developed, the method and laboratory to be recommended for analyses cannot be anticipated.

Biomarker and pharmacogenetics analysis plans and results will be reported separately from the main study results.

13. PLANNED INTERIM ANALYSIS

There will be a planned data cut with statistical output produced before the New Drug Application submission. This intermediary analysis is not a formal, pre-planned interim analysis but rather a "snapshot" of the data that will be performed when sufficient exposure and safety data are collected.

An interim CSR describing the data obtained until this time-point will be prepared for the submission.

14. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

15.   CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

For roll-over patients on-going adverse events that started in TV46000-CNS-30072 Study will not be counted as adverse events. Since the primary interest of the safety summary tables is to evaluate the incidence (risk) to experience AEs, taking on-going AEs that started during TV46000-CNS-30072 Study are prevalence cases and therefore bias the risk.

16. REFERENCES

Leucht S, Kissling W, Davis JM. The PANSS should be rescaled. Schizophr Bull. 2010;36(3):461–2.

APPENDIX A.   LIST OF CONCOMITANT MEDICATIONS THAT MAY BE RELATED TO INCREASED RISK OF RELAPSE

Antipsychotics, sleep aids and antidepressants that may potentially may indicate a need for symptoms reduction are listed below. This list is not exhaustive and may be updated at the Statistical Data Review meeting prior to data closure.

Medication Class	Standardized Medication Name
ANTIEPILEPTICS	LORAZEPAM
PSYCHOANALEPTICS	AMITRIPTYLINE
PSYCHOANALEPTICS	AMITRIPTYLINE HYDROCHLORIDE
PSYCHOANALEPTICS	BUPROPION
PSYCHOANALEPTICS	BUPROPION HYDROCHLORIDE
PSYCHOANALEPTICS	CITALOPRAM
PSYCHOANALEPTICS	CITALOPRAM HYDROBROMIDE
PSYCHOANALEPTICS	DOXEPIN
PSYCHOANALEPTICS	DULOXETINE
PSYCHOANALEPTICS	DULOXETINE HYDROCHLORIDE
PSYCHOANALEPTICS	ESCITALOPRAM
PSYCHOANALEPTICS	ESCITALOPRAM OXALATE
PSYCHOANALEPTICS	FLUOXETINE
PSYCHOANALEPTICS	FLUOXETINE HYDROCHLORIDE
PSYCHOANALEPTICS	MIRTAZAPINE
PSYCHOANALEPTICS	PAROXETINE
PSYCHOANALEPTICS	PAROXETINE HYDROCHLORIDE
PSYCHOANALEPTICS	SERTRALINE
PSYCHOANALEPTICS	SERTRALINE HYDROCHLORIDE
PSYCHOANALEPTICS	TRAZODONE
PSYCHOANALEPTICS	VENLAFAXINE
PSYCHOANALEPTICS	VENLAFAXINE HYDROCHLORIDE
PSYCHOANALEPTICS	VILAZODONE
PSYCHOANALEPTICS	VILAZODONE HYDROCHLORIDE
PSYCHOANALEPTICS	VORTIOXETINE
PSYCHOLEPTICS	ALPRAZOLAM
PSYCHOLEPTICS	AMISULPRIDE
PSYCHOLEPTICS	ARIPIPRAZOLE

Medication Class	Standardized Medication Name
PSYCHOLEPTICS	ASENAPINE MALEATE
PSYCHOLEPTICS	BREXPIPRAZOLE
PSYCHOLEPTICS	BUSPIRONE
PSYCHOLEPTICS	BUSPIRONE HYDROCHLORIDE
PSYCHOLEPTICS	CARBAMAZEPINE
PSYCHOLEPTICS	CARIPRAZINE
PSYCHOLEPTICS	CARIPRAZINE HYDROCHLORIDE
PSYCHOLEPTICS	CHLORPROTHIXENE
PSYCHOLEPTICS	CHLORPROTHIXENE HYDROCHLORIDE
PSYCHOLEPTICS	CLONAZEPAM
PSYCHOLEPTICS	CLOZAPINE
PSYCHOLEPTICS	DIAZEPAM
PSYCHOLEPTICS	DULOXETINE HYDROCHLORIDE
PSYCHOLEPTICS	ESZOPICLONE
PSYCHOLEPTICS	FLUOXETINE
PSYCHOLEPTICS	FLUPENTIXOL DECANOATE
PSYCHOLEPTICS	FLUPHENAZINE
PSYCHOLEPTICS	FLUPHENAZINE DECANOATE
PSYCHOLEPTICS	HALOPERIDOL
PSYCHOLEPTICS	HALOPERIDOL DECANOATE
PSYCHOLEPTICS	HYDROXYZINE
PSYCHOLEPTICS	HYDROXYZINE EMBONATE
PSYCHOLEPTICS	HYDROXYZINE HYDROCHLORIDE
PSYCHOLEPTICS	ILOPERIDONE
PSYCHOLEPTICS	LEVOSULPIRIDE
PSYCHOLEPTICS	LITHIUM
PSYCHOLEPTICS	LITHIUM CARBONATE
PSYCHOLEPTICS	LORAZEPAM
PSYCHOLEPTICS	LURASIDONE
PSYCHOLEPTICS	LURASIDONE HYDROCHLORIDE
PSYCHOLEPTICS	MELATONIN
PSYCHOLEPTICS	OLANZAPINE
PSYCHOLEPTICS	PALIPERIDONE

Medication Class	Standardized Medication Name
PSYCHOLEPTICS	PALIPERIDONE PALMITATE
PSYCHOLEPTICS	PAROXETINE
PSYCHOLEPTICS	PERPHENAZINE
PSYCHOLEPTICS	QUETIAPINE
PSYCHOLEPTICS	QUETIAPINE FUMARATE
PSYCHOLEPTICS	RISPERIDONE
PSYCHOLEPTICS	SERTRALINE HYDROCHLORIDE
PSYCHOLEPTICS	TASIMELTEON
PSYCHOLEPTICS	TEMAZEPAM
PSYCHOLEPTICS	THIORIDAZINE
PSYCHOLEPTICS	TIOTIXENE
PSYCHOLEPTICS	VALPROATE SEMISODIUM
PSYCHOLEPTICS	VENLAFAXINE
PSYCHOLEPTICS	ZIPRASIDONE
PSYCHOLEPTICS	ZIPRASIDONE HYDROCHLORIDE
PSYCHOLEPTICS	ZOLPIDEM
PSYCHOLEPTICS	ZOLPIDEM TARTRATE
PSYCHOLEPTICS	ZUCLOPENTHIXOL
PSYCHOLEPTICS	ZUCLOPENTHIXOL HYDROCHLORIDE