

## **Clinical Study Protocol**

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

Protocol with Amendment 01 Approval Date: 03 June 2020

**Clinical Study Protocol with Amendment 01**

**Study Number 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**

**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  
(The SHINE Study – Safety in Humans of TV-46000 sc Injection Evaluation)**

**Safety and Tolerability Study (Phase 3)**

**IND number: 124384; NDA number: 213586; BLA number: Not applicable; EudraCT number: 2019-000063-24**

**EMA Decision number of Pediatric Investigation Plan: Not applicable**

**Article 45 or 46 of 1901/2006 does not apply**

**Protocol Approval Date: 29 January 2019**

**Protocol with Amendment 01 Approval Date: 03 June 2020**

**Sponsor**

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

**Information regarding clinical laboratories and other departments and institutions is found in [Appendix A](#)**

**COVID-19 pandemic-related operational updates are provided in [Appendix N](#)**

This clinical study will be conducted in accordance with current Good Clinical Practice as directed by the provisions of the International Council for Harmonisation; United States Code of Federal Regulations, and European Union Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures.

**Confidentiality Statement**

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc. and/or its affiliates. The recipient agrees that no information contained herein may be published or disclosed without written approval from the sponsor.

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**AMENDMENT HISTORY**

The protocol for study TV46000-CNS-30078 (original protocol dated 29 January 2019) has been amended and reissued as follows:

Amendment 01	<p>03 June 2020 (136 patients enrolled to date)</p> <p>The management of study activities during the COVID-19 pandemic are detailed in <a href="#">Appendix N</a>.</p> <p>The following sections are affected:</p> <p>Section 3.1. General Study Design and Study Schematic Diagram;</p> <p>Section 3.5. Schedule of Study Procedures and Assessments;</p> <p>Section 5.1.1. Test Investigational Medicinal Product;</p> <p>Section 5.1.2. Placebo Investigational Medicinal Product;</p> <p>Table 4. Investigational Medicinal Products Used in the Study;</p> <p>Section 5.2.1. Storage and Security;</p> <p>Section 5.2.3. Accountability;</p> <p>Section 5.9. Randomization and Blinding;</p> <p>Section 6. Assessment of Efficacy;</p> <p>Section 7. Assessment of Safety;</p> <p>Section 7.4. Clinical Laboratory Tests;</p> <p>Section 7.6. Vital Signs;</p> <p>Section 7.7. Electrocardiography;</p> <p>Section 8.1. Pharmacokinetic Assessment</p> <p>Section 9.5.3.3. Exploratory Efficacy Analysis;</p> <p>Section 10. Quality Control and Quality Assurance;</p> <p>Appendix C. Quality Control and Quality Assurance;</p> <p>Appendix F. Lost to Follow-Up;</p>
Administrative Letter 02	09 February 2020
Letter of Clarification 01	22 July 2019

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

## **INVESTIGATOR AGREEMENT**

**Original Protocol Dated 29 January 2019**

**Protocol with Amendment 01 Dated 03 June 2020**

**IND number: 124384; NDA number: 213586; BLA number: Not applicable; EudraCT number: 2019-000063-24**

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**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**

**(The SHINE Study – Safety in Humans of TV-46000 sc Injection Evaluation)**

**Principal Investigator:** \_\_\_\_\_

**Title:** \_\_\_\_\_

**Address of Investigational Center:** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

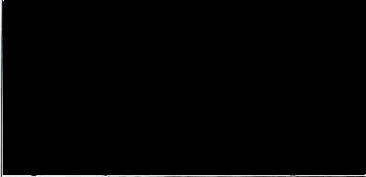

**Tel:** \_\_\_\_\_

I have read the protocol with Amendment 01 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the investigational medicinal products (IMPs) and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

<b>Principal Investigator</b>	<b>Signature</b>	<b>Date</b>

### SPONSOR PROTOCOL APPROVAL

<b>Sponsor's Authorized Representative</b> 	<b>Signature</b> 	<b>Date</b> 3/June/2020
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## COORDINATING INVESTIGATOR AGREEMENT

**Original Protocol Dated 29 January 2019**

**Clinical Study Protocol with Amendment 01 Dated 03 June 2020**

**IND number: 124384; NDA number: 213586; BLA number: Not applicable;**

**EudraCT number: 2019-000063-24**

**EMA Decision number of Pediatric Investigation Plan: Not applicable**

**Article 45 or 46 of 1901/2006 does not apply**

**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**

**(The SHINE Study – Safety in Humans of TV-46000 sc Injection Evaluation)**

I have read the protocol with Amendment 01 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I agree to keep records on patient information and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition, I will assume the responsibility of the coordinating investigator according to a separate contract.

**Coordinating Investigator:** [REDACTED]

**Title:** [REDACTED]

**Address of Investigational Center:** [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Tel:** [REDACTED]

**E-mail:** [REDACTED]

Coordinating Investigator	Signature	Date

**Executed signature pages are maintained within the Trial Master File.**

## CLINICAL STUDY PROTOCOL SYNOPSIS

### Study TV46000-CNS-30078

**Title of Study:** 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

(The SHINE Study – Safety in Humans of TV-46000 sc Injection Evaluation)

**Sponsor:** Teva Branded Pharmaceutical Products R&D, Inc.

**Investigational New Drug Number:** 124384

**New Drug Application Number:** 213586

**Biological License Application (BLA) Number:** Not applicable

**EudraCT Number:** 2019-000063-24

**European Medicines Agency Decision number of Pediatric Investigation Plan:** Not applicable

**Article 45 or 46 of 1901/2006 does not apply**

**Name of Test Investigational Medicinal Product (IMP):** Risperidone extended-release injectable suspension (TV-46000) for subcutaneous (sc) use

**EudraVigilance code for the IMP, if applicable:** SUB10335MIG

**Type of the Study:** Safety and Tolerability Study (Phase 3)

**Indication:** Maintenance treatment of schizophrenia

**Is this study conducted to investigate the New Use of an approved, marketed product?** No

**Number of Investigational Centers Planned:** The study is planned to be conducted in approximately 100 investigational centers (new centers and those that participated in Study TV46000-CNS-30072 [the RISE Study]).

**Countries Planned:** The study is planned to be conducted in the United States and Bulgaria.

**Planned Study Period:** The study is expected to start in Quarter 1 (Q1) 2019 and last until approximately Quarter 1 (Q1) 2021.

**Number of Patients Planned (total):** The total number of patients that are planned to be enrolled is up to approximately 300 patients. Adolescent patients will only be enrolled in the US; any enrolled adolescents will be in addition to the aforementioned total.

**Study Population:** Male and female patients, 13 to 65 years of age, who have a confirmed diagnosis of schizophrenia, are clinically stable, and are eligible for risperidone treatment. The study population will consist of 2 subgroups:

- Patients rolling over from the Phase 3 pivotal efficacy Study TV46000-CNS-30072 (roll-over patients)
- New patients (patients not rolling over from Study TV46000-CNS-30072)




**Primary and Secondary Objectives and Endpoints**

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

Objectives	Endpoints
The <b>primary objective</b> 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.

**Exploratory Objectives and Endpoints**

Exploratory objectives and endpoints are as follows:

Objectives	Endpoints
	

Objectives	Endpoints
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
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<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED]	[REDACTED]
	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]

**General Study Design:** This is a multicenter, double-blind, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of TV-46000 administered every month (q1m) or every 2 months (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 adolescent patients, it is mandatory that a parent/caregiver accompanies the patient to each visit and serves as a reliable informant. It is recommended that a caregiver is identified for each adult patient. Local requirements should be followed. The caregiver may be contacted in case of loss of contact with the patient or to provide additional information about the patient, if needed. Adult patients could be accompanied by caregivers to visits.

#### **A. New Patients: Screening through beginning of Stage 2**

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).

**Screening:** These patients will undergo screening procedures/assessments within 4 weeks before the start of Stage 1. Adult patients (aged 18-65) should have had a diagnosis of schizophrenia for >1 year, and adolescent patients (aged 13-17) should have had a diagnosis of schizophrenia for >6 months (diagnosis must be reconfirmed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition [DSM-5] [SCID-5]) and have been generally responsive to antipsychotics in the past year based on discussions with family members or healthcare professionals. Adult patients should also have had  $\geq 1$  episode of relapse in the last 24 months. Patients will provide informed consent or assent, as applicable, at the screening visit, before any study-related procedures or assessments are performed.

**Stage 1 (12-week oral conversion and stabilization stage):** New patients on any antipsychotic (other than clozapine) who can benefit from conversion to oral risperidone based on the investigator's judgment will be converted to oral risperidone to stabilize the patients on the treatment. Oral risperidone (at a dose of 2 to 5 mg/day, based on clinical judgment) will be given for 12 weeks to ensure that the patients can tolerate risperidone and that the doses are adequate to treat their positive symptoms. Adolescent patients will receive a maximal dose of 4 mg/day. Patients will come to the clinic for 4 visits (weeks -12, -10, -8, and -4) for various assessments and dose adjustments. Additional visits may be required for dose adjustments. Patients will be evaluated using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression of Severity (CGI-S), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), Columbia Suicide Severity Rating Scale (C-SSRS), Calgary Depression Scale for Schizophrenia (CDSS), Clinical Global Impression-Severity of Suicidality (CGI-SS), and Clinical Global Impression-Improvement. Additionally, telephone contact will take place at weeks -6 and -2, or more frequently if required in the judgment of the investigator.

Stability (as assessed at the baseline visit) is defined as meeting all of the following criteria for at least 4 consecutive weeks prior to the baseline visit:

- outpatient status

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

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.

If a patient withdraws from the study prior to the randomization (baseline) visit (Visit 6), the case report form for the patient's last visit will be marked as "Not Continuing", and the reason for discontinuation will be recorded. No extra testing or procedures will be required in addition to the regular visits.

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) described below.

#### **B. Roll-Over Patients: Screening through beginning of Stage 2**

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.

### **C. New and Roll-Over Patients: Stage 2**

After 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. All patients will attend in-clinic visits q1m (ie, the dosing visits) and will undergo various procedures and assessments as detailed in the Schedule of Study Procedures and Assessments. Throughout the duration of the study, telephone contact will take place weekly between clinic visits.

Patients who complete all scheduled visits will have EoT/early termination (ET) procedures and assessments performed at week 56 and follow-up procedures and assessments performed at weeks 60 and 64.

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

Patients who withdraw from the study before completing the 56-week maintenance stage will have follow-up procedures and assessments performed at their follow-up visits. During the follow-up period, patients will be treated according to the investigator's judgment.

**Brief Summary of Study Design for the Trial Registry(s):** The purpose of the study is to evaluate the long-term safety, tolerability, and efficacy of TV-46000 administered q1m or q2m for up to 56 weeks in adult and adolescent patients with schizophrenia. The study will include male and female patients, 13 to 65 years of age, who have a confirmed diagnosis of schizophrenia, are clinically stable, and are eligible for risperidone treatment. The study population will consist of 2 subgroups: i) patients rolling over from the Phase 3 pivotal efficacy Study TV46000-CNS-30072 (roll-over patients) and ii) new patients (patients not rolling over from Study TV46000-CNS-30072). Roll-over patients who were assigned to either TV-46000 q1m or 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. Roll-over patients who were assigned to placebo during Study TV46000-CNS-30072 and new patients will be randomized to receive sc doses of either TV-46000 q1m or TV-46000 q2m in a 1:1 ratio. The doses of TV-46000 will be equivalent to 2 to 5 mg/day of oral risperidone, and the maximal TV-46000 dose administered to adolescents will be equivalent to 4 mg/day oral risperidone. The primary safety and tolerability endpoint is the frequency of all adverse events, including serious

adverse events. For new patients, the total duration of patient participation in the study is planned to be up to 80 weeks (including a screening period of up to 4 weeks, a 12-week oral conversion/stabilization stage [Stage 1], a 56-week double-blind maintenance stage [Stage 2], and a follow-up period [8 weeks]). For roll-over patients, the total duration of patient participation in the study is planned to be up to 64 weeks (including up to 56 weeks in the maintenance stage [Stage 2] and a follow-up period [8 weeks]). Patients who started Stage 2 who relapse or meet 1 or more of the withdrawal criteria should be invited to perform the ET visit as soon as possible within 4 weeks of the last injection. Patients who withdraw from the study before completing the 56-week maintenance stage will have follow-up procedures and assessments performed at their follow-up visits. During the follow-up period, patients will be treated according to the investigator's judgment.

### **Method of 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 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 will include the following:

- The unblinded nurse will prepare the syringe for injection in a room separate from the patient.
- The unblinded nurse will wrap a blinding film (so that the original appearance is masked) around the barrel of the syringe.
- To maintain the patient blind, a cover will be used over the injection site during treatment administration.
- The unblinded nurse will administer the injection to the patient (additional details about administering the injection can be found in the Pharmacy Manual).

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 TV46000-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.

**Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate**

**Test IMP:** TV-46000 will be supplied as a ready-to-use, extended-release injectable product in a single-use 2-mL vial or as a 1 mL Luer lock prefilled syringe containing 50, 75, 100, 125, 150, 200, or 250 mg of risperidone. TV-46000 contains 30% (weight by weight) risperidone.

The product will be stored under refrigerated conditions (2°C to 8°C [36°F to 46°F]), protected from light, and kept in the outer carton until use. Under these conditions, the product is frozen. Preparation of the syringes and dose administration will be performed according to a detailed set of instructions that will be contained in a separate document from the protocol and shall be provided to the investigative teams before the beginning of the study.

Each syringe will be prepared immediately prior to dosing. Time between preparation of the syringe and administration to the patient will be recorded. The administration will be performed by a trained medical professional according to local regulations. Measures to mitigate the risk of unblinding will be implemented. During administration, care must be taken to avoid inadvertent injection into a blood vessel. Additional details about sc injection administration can be found in the Pharmacy Manual and the Investigator's Brochure for TV-46000.

In the event that prefilled syringes of TV-46000 become unavailable during the study, the unblinded nurse responsible for study drug administration will use vials (instructions on how to use vials can be found in the Pharmacy Manual).

**Reference IMP:** None.

**Placebo IMP:** TV-46000 Placebo is available as an extended-release injectable product supplied in a single-use 2-mL vial or prefilled syringe. TV-46000 Placebo should be stored under refrigerated conditions (2°C to 8°C [36°F to 46°F]), protected from light, and kept in the outer carton until use. Under these conditions, the product is frozen.

TV-46000 Placebo is composed of the same vehicle as TV-46000 (biodegradable polymers and biocompatible organic solvent).

For patients in the TV-46000 q2m group, placebo will be administered by sc injection on the months between each injection of TV-46000.

The volume of the TV-46000 Placebo (0.31 mL) chosen for the study has been selected as an approximate match to the intermediate volume of the TV-46000 q1m and q2m doses used in this study.

Additional details about sc injection administration can be found in the Pharmacy Manual.

<b>IMP name</b>	<b>Test IMP</b>	<b>Placebo IMP</b>																		
<b>Trade name and INN, if applicable, or company-assigned number</b>	TV-46000; risperidone extended-release injectable suspension for sc administration	TV-46000 Placebo																		
<b>Formulation</b>	Sterile extended-release injectable product	Sterile extended-release injectable product																		
<b>Unit dose strengths/dosage levels</b>	<table border="1"> <thead> <tr> <th>Treatment</th><th>Dosing volume (mL)</th></tr> </thead> <tbody> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> <tr><td>[REDACTED]</td><td>[REDACTED]</td></tr> </tbody> </table> <p>[REDACTED]</p> <p>Further dosing instructions are detailed in the Pharmacy Manual.</p>		Treatment	Dosing volume (mL)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Treatment	Dosing volume (mL)																			
[REDACTED]	[REDACTED]																			
[REDACTED]	[REDACTED]																			
[REDACTED]	[REDACTED]																			
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[REDACTED]	[REDACTED]																			
[REDACTED]	[REDACTED]																			
[REDACTED]	[REDACTED]																			
<b>Storage conditions</b>	Store under refrigeration at 2-8°C (36-46°F); protect from light; keep product in outer carton.	Store under refrigeration at 2-8°C (36-46°F); protect from light; keep product in outer carton.																		
<b>Route of administration</b>	sc injection in abdomen or upper arm (per investigational center in which the patient is enrolled); the injection site that is chosen for an individual patient should remain consistent throughout the study.	sc injection in abdomen or upper arm (per investigational center in which the patient is enrolled); the injection site that is chosen for an individual patient should remain consistent throughout the study.																		
<b>Dosing instructions</b>	<p>Injections will be administered q1m or q2m per the patient's assigned treatment group.</p> <p>The injection will be administered by an unblinded independent nurse.</p>	<p>Placebo injections will be administered every other month only to patients in the q2m treatment group.</p> <p>The injection will be administered by an unblinded independent nurse.</p>																		
<b>Packaging</b>	[REDACTED]	[REDACTED]																		
<b>Manufacturer</b>	[REDACTED]	[REDACTED]																		

**Duration of Patient Participation and Maximal Exposure to IMP:**

For new patients (ie, patients not rolling over from the pivotal efficacy study), the total duration of patient participation in the study is planned to be up to 80 weeks (including a screening period of up to 4 weeks, a 12-week oral conversion/stabilization stage [Stage 1], a 56-week maintenance stage [Stage 2], and a follow-up period [8 weeks]).

For patients rolling over from the pivotal efficacy Study TV46000-CNS-30072, the total duration of patient participation in the study is planned to be up to 64 weeks (including up to 56 weeks in the maintenance stage [Stage 2] and a follow-up period [8 weeks]).

TV-46000 will be administered either q1m or q2m during the maintenance stage at an equivalent of 2 to 5 mg/day of oral risperidone. As a precautionary measure, adolescents will not receive a TV-46000 dose that is equivalent to more than 4 mg/day oral risperidone.

**Study Duration:** The study duration will be approximately 25 months, from Quarter 1 (Q1) 2019 to Quarter 1 (Q1) 2021.

**End of Study:** End of study 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).

**Plans for Treatment or Care after the Patient Has Ended Participation in the Study:** In cases where the patient is withdrawn from this study, no further treatment is planned by the sponsor after the patient completes their participation in this study. In addition, continued access to IMP will not be provided to study participants once the study ends. Investigators should advise the study participants to return to the care of their primary physicians. Patients may be treated in the meantime per investigator judgment and instruction as applicable.

**Inclusion Criteria:** Patients may participate in this study only if they meet all of the following criteria:

***Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072***

- a. The patient must sign and date the informed consent document. For adolescent patients, written informed consent will be obtained from each patient's parent or legal guardian, and written assent will be obtained from each patient.
- b. The patient must have participated in the pivotal efficacy study (Study TV46000-CNS-30072) without experiencing relapse events and without important protocol deviations.
- c. If the patient was taking antidepressants or mood stabilizers (including the cytochrome P450 [CYP] 2D6 inhibitors fluoxetine, paroxetine, and duloxetine) in Study TV46000-CNS-30072, no dose changes or initiation of treatment with these medications will be permitted.
- d. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the required visits throughout the duration of the study period, including for the follow-up procedures and assessments as specified in this protocol.

- e. The patient, in the investigator's judgment, requires chronic treatment with an antipsychotic medication.
- f. The patient, in the investigator's judgment, can benefit from participation in this study.
- g. The patient is able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens (oral and sc administration) and non-use of prohibited concomitant medications; can read and understand the written word in order to complete patient-reported outcomes measures; and can be reliably rated on assessment scales.
- h. The patient has had a stable place of residence for the previous 3 months before the baseline visit in this study, and changes in residence are not anticipated over the course of study participation.
- i. The patient has no significant life events (such as pending loss of housing, family status change, long travel abroad, surgery, etc) that could affect study outcomes expected throughout the period of study participation.
- j. The patient is a male or female of any ethnic origin, 13 through 65 years of age (note the exception for roll-over patients who may have exceeded 65 years of age during the course of Study TV46000-CNS-30072; these patients will still be permitted to participate in this study).
- k. The patient is in adequate health as determined by medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, urinalysis, and serology.
- l. Women of childbearing potential and sexually active female adolescents must agree not to try to become pregnant, and, unless they have exclusively same-sex partners, must agree to use a highly effective method of contraception and agree to continue use of this method beginning 1 month before the first administration of study drug and for the duration of the study and for 120 days after the last injection of study drug. Highly effective methods of contraception include the following:
  - combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - intrauterine device (IUD) and intrauterine hormone-releasing system in place at least 2 months before screening
  - bilateral tubal occlusion
  - vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process
  - Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

- m. The patient, if adult or adolescent male, is surgically sterile, or, if capable of producing offspring, has exclusively same-sex partners or is currently using an approved method of birth control and agrees to the continued use of this method for the duration of the study (and for 120 days after the last dose of study drug). Male patients with sex partners who are women of childbearing potential must use condoms even if surgically sterile. In addition, male patients may not donate sperm for the duration of the study and for 120 days after taking the study drug.

***New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072)***

- a. [Revision 01] The patient is an adult (age 18-65) and has a diagnosis of schizophrenia according to the DSM-5 for >1 year (diagnosis must be reconfirmed by SCID-5) and ≥1 episode of relapse in the last 24 months, **OR** the patient is an adolescent (age 13-17) with a diagnosis of schizophrenia according to the DSM-5 for > 6 months (diagnosis must be reconfirmed by SCID-5).
- b. The patient has been responsive to an antipsychotic treatment (other than clozapine) in the past year based on investigator judgment (and discussions with family members, caregivers, or healthcare professionals as applicable).
- c. The patient has provided written informed consent and is competent to do so. For adolescent patients, written informed consent will be obtained from each patient's parent or legal guardian, and written assent will be obtained from each patient.
- d. The patient, in the investigator's judgment, requires chronic treatment with an antipsychotic medication.
- e. The patient, in the investigator's judgment, can benefit from participation in this study.
- f. The patient is able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens (oral and sc administration) and non-use of prohibited concomitant medications; can read and understand the written word in order to complete patient-reported outcomes measures; and can be reliably rated on assessment scales.
- g. The patient has a PANSS total score lower than 100 at screening.
- h. The patient has had a stable place of residence for the previous 3 months before screening, and changes in residence are not anticipated over the course of study participation.
- i. The patient has no significant life events (such as pending loss of housing, family status change, long travel abroad, surgery, etc) that could affect study outcomes expected throughout the period of study participation.
- j. The patient is a male or female of any ethnic origin, 13 through 65 years of age.
- k. The patient has a body mass index between 18.0 and 38.0 kg/m<sup>2</sup>, inclusive.
- l. The patient is in adequate health as determined by medical and psychiatric history, medical examination, ECG, serum chemistry, hematology, urinalysis, and serology.
- m. Women of childbearing potential and sexually active female adolescents must agree not to try to become pregnant, and, unless they have exclusively same-sex partners, must agree to use a highly effective method of contraception and agree to continue use of this method beginning 1 month before the first administration of study drug and for the duration of the study and for 120 days after the last injection of study drug. Highly effective methods of contraception include the following:

- combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - IUD and intrauterine hormone-releasing system in place at least 2 months before screening
  - bilateral tubal occlusion
  - vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process
  - Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- n. The patient, if adult or adolescent male, is surgically sterile, or, if capable of producing offspring, has exclusively same-sex partners or is currently using an approved method of birth control and agrees to the continued use of this method for the duration of the study (and for 120 days after the last dose of study drug). Male patients with sex partners who are women of childbearing potential must use condoms even if surgically sterile. In addition, male patients may not donate sperm for the duration of the study and for 120 days after taking the study drug.
- o. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the required visits throughout the duration of the study period, including for the follow-up procedures and assessments as specified in this protocol.

**Randomization Criteria for New Patients:**

The following criteria are randomization criteria and must be fulfilled at the baseline visit before randomization in addition to other relevant inclusion criteria:

- a. The patient has not experienced mental or physical deterioration, which prevents participation in the study per investigator judgement.
- b. The patient has demonstrated good compliance in following protocol requirements during Stage 1 of the study.
  - 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 in the double-blind period (Stage 2).
- c. The patient has been stabilized per the following criteria for at least 4 consecutive weeks prior to the baseline visit:
  - outpatient status

- PANSS total score  $\leq 80$

[REDACTED]

[REDACTED]

[REDACTED]

**Exclusion Criteria:** Patients may not participate in this study if they meet any of the following criteria:

***Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072***

- a. The patient has a finding in the baseline 12-lead ECG that is considered clinically significant in the judgment of the investigator.
- b. Poor compliance with study procedures (in the opinion of the investigator or sponsor) during the pivotal efficacy Study TV46000-CNS-30072. This should be discussed on a case-by-case basis.

***New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072) and Roll-Over Patients***

- a. The patient has a current clinically significant DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, or amnesic or other cognitive disorders, or borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.
- b. The patient is currently on clozapine or has received electroconvulsive therapy in the last 12 months.
- c. The patient has a history of epilepsy or seizures, neuroleptic malignant syndrome, tardive dyskinesia, or other medical condition that would expose the patient to undue risk.
- d. The patient has a positive serology for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen, and/or hepatitis C. If serology is positive for hepatitis C but the ribonucleic acid test is negative and the patient has no history of liver disease, enrollment will be considered following discussion between the investigator and the medical monitor as needed.
- e. The patient has current or a history of known hypersensitivity to risperidone or any of the excipients of TV-46000 or the oral formulation of risperidone used in the stabilization phase.
- f. The patient has a substance use disorder, including alcohol and benzodiazepines but excluding nicotine and caffeine.
- g. The patient has a significant risk of violent behavior based on the patient's medical history or the investigator's judgement.
- h. The patient has a significant risk of committing suicide based on the patient's medical history or the investigator's judgement and/or the C-SSRS (lifetime). Patients with a C-SSRS (current) positive response to suicidal ideation items 3, 4, or 5 are not eligible.

- i. The patient has a clinically significant deviation from normal in the physical examination.
- j. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results.
- k. If the patient has a prolonged QTcF interval (defined as a QTcF interval of >450 msec for males and >470 msec for females) at screening or baseline, calculated as the mean of the triplicate ECG measurements, eligibility will be decided on a case-by-case basis following discussion between the investigator and the sponsor.
- l. The patient has any clinically significant uncontrolled medical condition (treated or untreated). The investigator may discuss with the medical monitor as needed.
- m. The patient is a pregnant or lactating female.
- n. The patient has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery).
- o. The patient has any other disease or condition that, in the opinion of the investigator, would make participation not in the best interest of the patient or that could prevent, limit, or confound the protocol-specified assessments.
- p. The patient has used an investigational drug other than TV-46000 within 3 months prior to screening or has participated in a non-drug clinical trial within 30 days prior to screening.
- q. The patient is using or consuming medications prohibited in this study.
- r. Vulnerable patients (eg, people kept in detention).

### Statistical Considerations

**Sample Size Rationale:** 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.

### Analysis Sets

**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 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.

**Safety Analysis Set:** The safety analysis set will include all patients who receive at least 1 dose of TV-46000 during this 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.

**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.



**Pharmacokinetics Analysis Set:** The pharmacokinetics analysis set will include all patients from the safety analysis set who also have  $\geq 1$  plasma concentration measurement.

**Additional Analysis Sets:** Additional analysis sets will be defined in the statistical analysis plan.

**Efficacy Analysis:** Efficacy analysis will be descriptive and will be described in the statistical analysis plan.

**Multiple Comparisons and Multiplicity:** No adjustments will be made for the preplanned multiple comparisons/endpoints.

**Safety Analysis:** Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in the Schedules of Study Procedures and Assessments.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class 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 the test IMP (ie, reasonable possibility, defined as related or with missing relationship), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by source of patients (new patients and roll-over patients) and by treatment group as well as total. Summaries will include both incidence and person-time incidence (number of events divided by the total exposure to drug). A summary table of adverse events that includes adverse events from Study TV46000-CNS-30072 for roll-over patients will be presented as well. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory, ECG, and vital sign measurement data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

Descriptive statistics for allowed rescue medications will be presented by treatment group.

Safety outcomes, including changes from baseline in extrapyramidal symptoms (EPS) scale scores (BARS, AIMS, and SAS) and CDSS during Stage 2, will be presented using descriptive statistics by treatment group.

The incidence of treatment-emergent adverse events related to EPS will be summarized by the following event categories: akathisia, dyskinesia, dystonia, parkinsonism, and tremor. The C-SSRS and CGI-SS will be used to assess the risk of suicide events during the study. Descriptive statistics will be presented by treatment group.

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 clinical study report.

Selected safety data will also be presented by site of injection (abdomen versus arm) and by age group (adolescents [ages 13 through 17] and adults [18 years of age or older]), as applicable.

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. For categorical variables, patient counts and percentages will be provided.

Safety data collected in Stage 1 will also be summarized using descriptive statistics for new patients.

**Tolerability Analysis:** In cases where 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 and summarized using descriptive statistics.

**Pharmacokinetic Analysis:** Pharmacokinetic analysis will be descriptive and will be described in the statistical analysis plan.

**Pharmacokinetic/Pharmacodynamic Analysis:** The results of the pharmacokinetic/pharmacodynamic analysis (if relevant data permit) will be presented in a separate report.

**Biomarker and Pharmacogenetics Analysis:** Genetic variation in CYP2D6, and corresponding metabolizer status, will be assessed using descriptive statistics for an association with pharmacokinetic endpoints. Biomarker and pharmacogenetics analysis plans and results will be reported separately from the main study results.

**Planned Interim Analysis:** There will be a planned data cut with statistical output produced before the New Drug Application submission.

**TABLE OF CONTENTS**

TITLE PAGE .....	1
AMENDMENT HISTORY .....	2
INVESTIGATOR AGREEMENT.....	4
COORDINATING INVESTIGATOR AGREEMENT .....	6
CLINICAL STUDY PROTOCOL SYNOPSIS.....	7
TABLE OF CONTENTS.....	26
LIST OF TABLES .....	32
LIST OF FIGURES .....	33
LIST OF ABBREVIATIONS.....	34
1. INTRODUCTION AND BACKGROUND INFORMATION.....	37
1.1. Introduction .....	37
1.2. Findings from Nonclinical and Clinical Studies .....	39
1.2.1. Nonclinical Studies .....	39
1.2.2. Clinical Studies .....	40
1.2.2.1. Clinical Pharmacology Studies .....	40
1.2.2.2. Clinical Safety and Efficacy Studies.....	41
1.3. Known and Potential Benefits and Risks to Patients .....	41
1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) .....	41
1.3.2. Overall Benefit and Risk Assessment for This Study .....	42
2. STUDY OBJECTIVES AND ENDPOINTS .....	43
2.1. Primary and Secondary Study Objectives and Endpoints.....	43
2.1.1. Justification of Primary Endpoint .....	43
2.2. Exploratory Objectives and Endpoints .....	43
3. STUDY DESIGN.....	47
3.1. General Study Design and Study Schematic Diagram.....	47
3.2. Planned Number of Patients and Countries .....	52
3.3. Justification for Study Design and Selection of Population .....	52
3.4. Stopping Rules for the Study .....	53
3.5. Schedule of Study Procedures and Assessments .....	53
4. SELECTION AND WITHDRAWAL OF PATIENTS .....	65
4.1. Patient Inclusion Criteria.....	65

4.1.1.	Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072 .....	65
4.1.2.	New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072) .....	66
4.1.3.	Randomization Criteria for New Patients .....	68
4.2.	Patient Exclusion Criteria .....	68
4.2.1.	Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072 .....	68
4.2.2.	New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072) and Roll-Over Patients.....	69
4.3.	Withdrawal Criteria and Procedures for the Patient .....	70
4.3.1.	General Withdrawal Criteria .....	70
4.3.2.	Study-Specific Patient Withdrawal Criteria and Procedures .....	71
4.3.3.	Pharmacokinetic Sampling in Case of Patient Withdrawal .....	72
4.4.	Replacement of Patients .....	72
4.5.	Rescreening .....	72
4.6.	Screening Failure .....	73
5.	TREATMENTS .....	74
5.1.	Investigational Medicinal Products Used in the Study .....	74
5.1.1.	Test Investigational Medicinal Product .....	74
5.1.1.1.	Starting Dose and Dose Levels .....	74
5.1.1.2.	Dose Modification and Dose Stratification.....	75
5.1.2.	Placebo Investigational Medicinal Product.....	75
5.2.	Preparation, Handling, Labeling, Storage, and Accountability for IMPs .....	77
5.2.1.	Storage and Security .....	77
5.2.2.	Labeling.....	77
5.2.3.	Accountability .....	77
5.3.	Justification for Investigational Medicinal Products.....	78
5.3.1.	Justification for Dose of Test Investigational Medicinal Product.....	78
5.3.2.	Justification for Use of Placebo Investigational Medicinal Product.....	78
5.4.	Other Medicinal Products/Non-Investigational Medicinal Products .....	78
5.5.	Treatment after the End of the Study .....	79
5.6.	Restrictions.....	79
5.6.1.	Activity.....	79
5.6.2.	Specific Beverages .....	79

5.6.3.	Blood Donation .....	79
5.7.	Prior and Concomitant Medication or Therapy .....	80
5.8.	Procedures for Monitoring Patient Compliance.....	81
5.9.	Randomization and Blinding .....	82
5.10.	Maintenance of Randomization and Blinding.....	84
5.10.1.	Maintenance of Randomization .....	84
5.10.2.	Blinding and Unblinding.....	84
5.10.3.	Data Monitoring Committee .....	84
5.11.	Total Blood Volume.....	85
6.	ASSESSMENT OF EFFICACY .....	86
6.1.	Assessments of Efficacy .....	86
6.1.1.	Clinical Global Impression–Improvement (CGI-I).....	86
6.1.2.	Positive and Negative Syndrome Scale (PANSS) .....	86
6.2.	Other Assessments .....	86
6.2.1.	Structured Clinical Interview for DSM-5 (SCID-5) .....	86
6.2.2.	Quality of Life Scales.....	87
6.2.2.1.	Schizophrenia Quality of Life Scale (SQLS).....	87
6.2.2.2.	5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L).....	87
6.2.3.	Drug Attitudes Inventory 10-item Version (DAI-10) .....	87
6.2.4.	Personal and Social Performance Scale (PSP).....	87
6.2.5.	Healthcare Resource Utilization .....	87
6.2.6.	Clinical Global Impression of Severity (CGI-S).....	88
7.	ASSESSMENT OF SAFETY .....	89
7.1.	Adverse Events.....	89
7.1.1.	Definition of an Adverse Event.....	89
7.1.2.	Recording and Reporting of Adverse Events.....	90
7.1.3.	Severity of an Adverse Event.....	90
7.1.4.	Relationship of an Adverse Event to the Investigational Medicinal Product .....	91
7.1.5.	Serious Adverse Events.....	91
7.1.5.1.	Definition of a Serious Adverse Event.....	92
7.1.5.2.	Expectedness .....	92
7.1.5.3.	Reporting a Serious Adverse Event .....	93
7.1.6.	Protocol-Defined Adverse Events of Special Interest.....	95

7.1.7.	Protocol Deviations Because of an Adverse Event.....	95
7.2.	Pregnancy .....	95
7.3.	Medication Error and Special Situations Related to the Investigational Medicinal Products.....	96
7.4.	Clinical Laboratory Tests.....	96
7.4.1.	Serum Chemistry, Hematology, and Urinalysis.....	97
7.4.2.	Other Clinical Laboratory Tests.....	98
7.4.2.1.	Virology and Thyroid Screening Tests .....	98
7.4.2.2.	Human Chorionic Gonadotropin Tests .....	98
7.4.2.3.	Urine Drug Screen.....	98
7.4.2.4.	Prolactin .....	98
7.5.	Physical Examinations .....	98
7.6.	Vital Signs.....	99
7.7.	Electrocardiography .....	99
7.8.	Assessment of Local Tolerability and Pain.....	100
7.8.1.	Erythema and Edema Assessment .....	100
7.8.2.	Induration and Nodule Assessment.....	100
7.8.3.	Injection Pain Intensity Assessment.....	100
7.9.	Assessment of Suicidality .....	101
7.9.1.	Columbia Suicide Severity Rating Scale (C-SSRS) .....	101
7.9.2.	Clinical Global Impression-Severity of Suicidality (CGI-SS).....	101
7.10.	Study-Specific Assessments of Safety .....	102
7.10.1.	Abnormal Involuntary Movement Scale (AIMS) .....	102
7.10.2.	Barnes Akathisia Rating Scale (BARS).....	102
7.10.3.	Simpson-Angus Scale (SAS) .....	102
7.10.4.	Calgary Depression Scale for Schizophrenia (CDSS) .....	102
7.11.	Other Assessments .....	103
8.	ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/BIOMARKERS/ PHARMACOGENOMICS.....	104
8.1.	Pharmacokinetic Assessment.....	104
8.2.	Pharmacokinetic/Pharmacodynamics Assessment.....	105
8.3.	Assessment of Exploratory Biomarkers.....	105
8.4.	Pharmacogenetics.....	105

9.	STATISTICS .....	107
9.1.	Sample Size and Power Considerations .....	107
9.2.	Analysis Sets .....	107
9.2.1.	Intent-to-Treat Analysis Set .....	107
9.2.2.	Safety Analysis Set .....	107
9.2.3.	Per-Protocol Analysis Set .....	107
9.2.4.	Pharmacokinetics Analysis Set .....	107
9.2.5.	Enrolled Patients Set .....	108
9.2.6.	Additional Analysis Sets .....	108
9.3.	Data Handling Conventions .....	108
9.4.	Study Population .....	108
9.4.1.	Patient Disposition .....	108
9.4.2.	Demographic and Baseline Characteristics.....	108
9.5.	Efficacy Analysis .....	108
9.5.1.	Primary Endpoint .....	108
9.5.2.	Exploratory Endpoints .....	109
9.5.3.	Planned Method of Analysis .....	109
9.5.3.1.	Primary Efficacy Analysis .....	109
9.5.3.2.	Sensitivity Analysis.....	109
9.5.3.3.	Exploratory Efficacy Analysis .....	109
9.6.	Multiple Comparisons and Multiplicity.....	109
9.7.	Safety Analysis .....	109
9.8.	Tolerability Analysis.....	110
9.9.	Pharmacokinetic Analysis.....	110
9.10.	Pharmacodynamic Analysis.....	110
9.11.	Pharmacokinetic/Pharmacodynamic Analysis .....	110
9.12.	Biomarker and Pharmacogenetics Analysis.....	110
9.13.	Planned Interim Analysis .....	111
9.14.	Reporting Deviations from the Statistical Plan.....	111
10.	QUALITY CONTROL AND QUALITY ASSURANCE.....	112
11.	COMPLIANCE STATEMENT .....	112
12.	DATA MANAGEMENT AND RECORD KEEPING.....	112
13.	FINANCING AND INSURANCE .....	113

14.	PUBLICATION POLICY .....	113
15.	REFERENCES .....	114
16.	SUMMARY OF CHANGES .....	116
16.1.	Global Amendment 01 (Dated 03 June 2020).....	116
16.2.	Administrative Letter 02 (Dated 09 February 2020).....	129
16.3.	Letter of Clarification 01 (Dated 22 July 2019).....	131
APPENDIX A.	CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS .....	133
APPENDIX B.	STUDY PROCEDURES AND ASSESSMENTS BY VISIT .....	135
APPENDIX C.	QUALITY CONTROL AND QUALITY ASSURANCE .....	145
APPENDIX D.	ETHICS .....	147
APPENDIX E.	BIRTH CONTROL METHODS AND PREGNANCY TESTING.....	149
APPENDIX F.	LOST TO FOLLOW-UP .....	151
APPENDIX G.	LIST OF PROHIBITED MEDICATIONS .....	152
APPENDIX H.	TOTAL BLOOD VOLUME .....	154
APPENDIX I.	EXPLORATORY BIOMARKERS SAMPLES .....	156
APPENDIX J.	PHARMACOGENETIC ASSESSMENTS.....	157
APPENDIX K.	PRODUCT COMPLAINTS.....	158
APPENDIX L.	DATA MANAGEMENT AND RECORD KEEPING.....	160
APPENDIX M.	PUBLICATION POLICY .....	163
APPENDIX N.	MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 .....	164



**LIST OF TABLES**

Table 1:	Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) - For New Patients Only – Pre-Treatment Period (Screening and Stage 1) .....	54
Table 2:	Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – For New and Roll-Over Patients – Baseline, Double-Blind Maintenance Stage (Stage 2), End of Treatment, and Follow-Up.....	58
Table 3:	Conversion Table between Oral Risperidone and TV-46000 Doses .....	75
Table 4:	Investigational Medicinal Products Used in the Study .....	75
Table 5:	Other Medicinal Products Used in the Study .....	79
Table 6:	The Relationship of an Adverse Event to the Investigational Medicinal Product.....	91
Table 7:	Clinical Laboratory Tests .....	97
Table 8:	Questions for Unblinded Nurses Administering Study Drug to Patients (When Using Prefilled Syringes Only).....	103

## LIST OF FIGURES

Figure 1: Overall Study Schematic Diagram .....	50
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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Term</b>
β-HCG	Beta human chorionic gonadotropin
ADR	adverse drug reaction
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
CA	competent authority
CDMS	clinical data management system
CDSS	Calgary Depression Scale for Schizophrenia
CFR	Code of Federal Regulations (USA)
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression of Severity
CGI-SS	Clinical Global Impression-Severity of Suicidality
C <sub>max</sub>	maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DAI-10	Drug Attitudes Inventory 10-item version
DMSO	dimethyl sulfoxide
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition
ECG	electrocardiogram/electrocardiography
EoS	end of study
EoT	end-of-treatment
EPS	extrapyramidal symptoms
EQ-5D-5L	5-Level EuroQol Five Dimensions Questionnaire

<b>Abbreviation</b>	<b>Term</b>
ER	emergency room
ET	early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
im	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
LAI	long-acting injectable
LSO	local safety officer
NDA	New Drug Application
NOAEL	no observed adverse effect level
NPRS	Numeric Pain Rating Scale
OTC	over-the-counter
PANSS	Positive and Negative Syndrome Scale
PI	prescribing information
PopPK	population pharmacokinetic
PSP	Personal and Social Performance Scale
Q1	Quarter 1
Q4	Quarter 4
q1m	every month
q2m	every 2 months

<b>Abbreviation</b>	<b>Term</b>
q3m	every 3 months
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SAS	Simpson-Angus Scale
sc	subcutaneous
SCID-5	Structured Clinical Interview for DSM-5
SOP	Standard Operating Procedure
SQLS	Schizophrenia Quality of Life Scale
SUSAR	suspected unexpected serious adverse reaction
TC	telephone call/teleconference
ULN	upper limit of normal
US(A)	United States (of America)
VC	videoconference

## 1. INTRODUCTION AND BACKGROUND INFORMATION

### 1.1. Introduction

Schizophrenia is a severely debilitating psychotic disorder characterized by positive symptoms (eg, delusions, hallucinations, and grossly disorganized or catatonic behavior) and negative symptoms (eg, affective flattening, alogia, and avolition [[New York State Office of Mental Health 2011](#), [Stefan 2002](#)]). Cognitive deficits are common; they include impairment of executive functioning and attention, as well as difficulties with short- and long-term memory.

The worldwide lifetime morbidity risk of the disorder is about 1% across diverse geographic, cultural, and socio-economic regions. Since, in most patients, the disease follows a chronic course with long-lasting impairment, long-term treatment with antipsychotic agents is usually required. Noncompliance and high discontinuation rates are particularly problematic in patients with schizophrenia. Premature discontinuation of antipsychotic drug therapy is a common phenomenon; in the Clinical Antipsychotic Trials of Intervention Effectiveness study, 74% of patients discontinued their antipsychotic drug within 18 months due to either poor tolerability or lack of efficacy. Even among patients who do not explicitly discontinue drug therapy, nonadherence to long-term oral medication regimen is one of the most significant therapeutic issues in the therapy of schizophrenia and related disorders. As a result, many of these patients do not experience the full benefit of antipsychotic drug therapy and suffer frequent relapses or exacerbations that require rehospitalization, often in the context of psychiatric emergency ([Rainer 2008](#)). Thus, the use of a long-acting injectable (LAI) antipsychotic agent may increase compliance in patients with schizophrenia ([Barnes 1994](#), [Hughes 2007](#), [Keith 2003](#), [Walburn 2001](#)). In addition, recent evidence suggests that early use of LAI risperidone might carry advantages for clinical outcomes in patients with schizophrenia, further supported by neuroimaging ([Subotnik 2015](#)).

The underlying disease mechanisms and initial approach to the diagnosis and treatment of schizophrenia in adolescent patients aged 13 to 17 years and adult patients 18 years of age and older are essentially the same. Schizophrenia in children and adolescents is accepted to be clinically and biologically similar to adult-onset schizophrenia but with some differences in the presentation of the symptoms, relative frequency of core psychotic symptoms (eg, auditory hallucinations, delusions, and thought disorder), neurocognitive impairments, psychophysiological abnormalities, and the presence of structural brain abnormalities ([Asarnow 1995](#), [Bo 2016](#), [Rapoport 2005](#)). Pediatric patients display a more severe clinical prognosis and a greater neurodegenerative trajectory and can be less responsive to treatment compared to patients with adult-onset schizophrenia ([Bo 2016](#)). Children and adolescents who are diagnosed with schizophrenia display high stability with regard to the phenotypical expression of the disorder into adulthood ([Hollis 2000](#)). Studies of neuropsychological functions and brain structure in patients with schizophrenia have shown the same degenerative patterns, regardless of the patient's age at the onset of the disorder ([Weinberger 2011](#)).

The sponsor is developing a risperidone extended-release injectable suspension for subcutaneous (sc) use that will deliver therapeutic levels of risperidone over intervals of 1 month (TV-46000 every month [q1m]) or 2 months (TV-46000 every 2 months [q2m]) to patients with

schizophrenia. The product is a new sustained-delivery technology based on biocompatible block copolymers dissolved in organic solvents (dimethyl sulfoxide [DMSO] for TV-46000). TV-46000 is a new formulation of risperidone that uses this technology; the product is referred to as TV-46000 q1m and TV-46000 q2m to designate the 1- and 2-month duration products, respectively. There are 4 possible TV-46000 dose strengths for each duration product, comparable to 2, 3, 4, and 5 mg/day of oral risperidone. The sponsor will provide a single-concentration vial of TV-46000 or prefilled syringes; the dose and the volume administered will be comparable to the oral risperidone dose on which the patient will be stabilized.

[REDACTED]

The critical importance of optimal compliance with prescribed antipsychotic regimens has been repeatedly and convincingly demonstrated in patients with schizophrenia. Adherence increases the likelihood of positive outcomes in all aspects of a patient's life, including better symptom control, reduced risk of relapse and rehospitalization, and improved quality of life as well as social and occupational functioning. Despite their proven effectiveness, poor adherence to prescribed antipsychotic regimens remains the most important driver of suboptimal clinical outcomes in patients with schizophrenia ([Birnbaum 2008](#)).

The rationale for developing q1m and q2m risperidone products is to improve patient compliance and to offer greater convenience to the patient through a reduction in clinic visits in comparison to other risperidone products currently on the market. It is intended that therapeutic concentrations will be reached within 24 hours of injection. It is anticipated that these advantages will reduce the rate of relapse and concomitant impact on patients' well-being and healthcare costs. The efficacy, safety, and tolerability of different durations of TV-46000 administered sc versus placebo are currently being studied in the ongoing Phase 3 Study TV46000-CNS-30072 (the RISE Study).

The purpose of Study TV46000-CNS-30078 is to evaluate the safety and tolerability of different durations of TV-46000 administered sc. Experience with TV-46000 in humans is limited, and therefore, there are only limited data on adverse drug reactions (ADRs) associated with this formulation. However, the safety profile of the active ingredient, risperidone, administered in a different long-acting parenteral formulation, has been well characterized. The marketed intramuscular (im) risperidone long-acting injection (RISPERDAL CONSTA<sup>®</sup>, Janssen Pharmaceuticals) is generally well tolerated. The most commonly reported ADRs include insomnia, anxiety, headache, upper respiratory tract infection, parkinsonism, and depression. The occurrence of ADRs appears to be dose-related. Injection of TV-46000 is expected to result in less pain than the conventional (oil-based) antipsychotic im depot injections.

In addition, there is a paucity of data in relation to LAI use in children and adolescents with serious mental illness, and existing reports have substantial methodological limitations ([Lytle 2017](#)). Enrollment of adolescents in this study will provide data for evaluating the safety and tolerability of TV-46000 in this patient population.

The Investigator's Brochure (IB) provides detailed information on the background, pharmaceutical particulars, nonclinical experience, and clinical experience with TV-46000.

## 1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the IB.

### 1.2.1. Nonclinical Studies

The nonclinical pharmacology and toxicology of risperidone have been well established for oral and im administration both in vitro and in vivo. Nonclinical studies evaluating genotoxicity, carcinogenicity, chronic toxicology, and reproductive and developmental toxicology of risperidone are publicly available in published literature or prescribing information (PI) of approved oral or im risperidone products.

Injection of TV-46000 sc to rats and dogs elicited pharmacological signs typical of risperidone. In rats only, transient stress-related signs were detected in some of the animals. Pathological findings could be divided into systemic pharmacologically related changes [REDACTED]

[REDACTED] Local reaction in rats and dogs was a typical foreign body local absorptive reaction. Residual fibrotic capsules at the sites of injection were still evident [REDACTED] after injection in [REDACTED]

[REDACTED] but their size showed a trend toward reduction. In 3 single-dose pharmacokinetic and local tolerance non-Good Laboratory Practice (GLP) studies in mini pigs, TV-46000 was administered as a single dose [REDACTED]. In these studies, the sc lesions were milder than in rats or dogs; however, 2 cases of generalized erythema [REDACTED]

[REDACTED] Both cases were non-life-threatening, and 1 was self-limited.

[REDACTED] In single-dose GLP toxicology studies in both rats and dogs, a no observed adverse effect level (NOAEL), and therefore, a margin of safety, could not be determined under the experimental conditions of the studies performed because expected adverse reactions related to the pharmacological actions of risperidone were noted at all dose levels. Similarly, a NOAEL (and therefore, a margin of safety) could not be determined in the multiple-dose toxicity study in dogs because of decreased size and weight of male and female reproductive organs that were observed at all tested dose levels of the study drug. These changes are known risperidone pharmacological effects. Overall, TV-46000 [REDACTED] and its vehicle [REDACTED] were well tolerated locally and systemically in rats, dogs, and mini pigs at all doses tested. The mutagenic potential of the [REDACTED] in TV-46000 was tested in a GLP Ames test, and no increase in frequency of revertants was noted.

To summarize, nonclinical studies reported by Teva evaluated [REDACTED] TV-46000 [REDACTED] administered by sc injection.



Subsequent clinical investigations [REDACTED] have demonstrated that this formulation is more suited to a 1- and 2-month dosing interval; however, the nonclinical data that have been generated are still relevant for the ongoing clinical development program.

## **1.2.2. Clinical Studies**

### **1.2.2.1. Clinical Pharmacology Studies**

One pilot Phase 1 exploratory pharmacokinetic study (Study RISPE1ZG15EU) in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics of TV-46000 has been completed. The study demonstrated that TV-46000, administered at sub-therapeutic doses of 12.5 or 25 mg, was safe and well tolerated when administered as an sc injection to either the posterior upper arm or the abdomen. There was no overall change in the total exposure (area under the plasma concentration-time curve [AUC]), maximum observed concentration ( $C_{max}$ ), or rate of absorption irrespective of injection site (ie, arm or abdomen) or rubbing of the injection site following sc injection of TV-46000.

In a Phase 1 single and multiple ascending dose study (TV46000-SAD-10055) to evaluate the safety, tolerability, and pharmacokinetics of TV-46000 in patients with schizophrenia or schizoaffective disorder, a total of 99 patients with schizophrenia or schizoaffective disorder were allocated into 8 sequential cohorts of 12 patients each. Study participants were clinically stable patients who were currently on antipsychotic treatment of oral risperidone. The study included 5 single-dose cohorts (50 to 225 mg) and 2 multiple-dose cohorts (75 and 150 mg) administered once-monthly for 3 consecutive months. In addition, interchangeability of injection site was assessed via administration of a similar dose (225 mg) to the abdomen and to the upper arm.

All doses of TV-46000 attained therapeutic plasma concentrations within 24 hours. Study results supported TV-46000 dosing intervals for 4 to 8 weeks based on therapeutic total active moiety plasma concentration. Population pharmacokinetic (PopPK) modeling and simulation have been used to select the q1m and q2m doses of TV-46000 for the Phase 3 study, on the basis of matching the average exposure level of total active moiety for the 2, 3, 4, and 5 mg/day doses of oral risperidone.

[REDACTED]

The comparison between different sites of injection showed that either the abdomen or arm could be used for sc injection without significantly altering the controlled-release drug delivery of risperidone.

Additional information on TV-46000 and risperidone pharmacokinetics can be found in the IB.

#### **1.2.2.2. Clinical Safety and Efficacy Studies**

As of October 2017, the safety and efficacy of oral risperidone have been evaluated in clinical studies in a total of 9803 adult and pediatric patients exposed to 1 or more doses of risperidone for up to 3 years, including a total of 2687 patients who received oral risperidone in double-blind, placebo-controlled studies. The most common adverse events (reported in  $\geq 5\%$  of risperidone-treated patients and with a frequency twice that of placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain (see [RISPERIDONE tablets, Teva Pharmaceuticals, US PI, 2014](#)).

The safety and efficacy of risperidone long-acting injection have been evaluated in clinical studies in a total of 2392 patients exposed to 1 or more doses of risperidone for up to 4 years, including a total of 332 patients who were treated with 25 or 50 mg risperidone LAI while participating in a 12-week, double-blind, placebo-controlled study. The most common ADRs in patients with schizophrenia ( $\geq 5\%$  of risperidone-treated patients) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth (see [RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI, 2014](#)).

Limited efficacy data for TV-46000 in patients are available. Furthermore, human safety data on TV-46000 are also limited; to date, doses up to 225 mg have been tested. However, the safety profile is expected to be generally similar to that of risperidone LAI. To date, the only new safety signals that were identified in the TV-46000 Phase 1 program were some types of injection site reactions such as injection site pain, erythema, induration, pruritus, and swelling. The majority of these adverse events were mild to moderate in severity and resolved quickly. To date, there is no efficacy or safety data available from the ongoing, blinded Phase 3 Study TV46000-CNS-30072.

### **1.3. Known and Potential Benefits and Risks to Patients**

#### **1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)**

Experience with TV-46000 in humans is limited, and therefore, there are only limited data on ADRs associated with this formulation. However, the safety profile of the active ingredient, risperidone, administered in a different long-acting parenteral formulation, has been well characterized. The marketed im risperidone long-acting injection is generally well tolerated. The most commonly reported ADRs include insomnia, anxiety, headache, upper respiratory tract infection, parkinsonism, and depression. The occurrence of ADRs appears to be dose-related. Injection of TV-46000 is expected to result in less pain than the conventional (oil-based) antipsychotic im depot injections. Additional information regarding benefits and risks to patients can be found in the IB.

Based on the limited data from the clinical program, injection site erythema, injection site edema, injection site pain, and injection site nodules appear to be ADRs of TV-46000.

In summary, the benefit and risk assessment for TV-46000 is favorable following review of the available data.

Additional information regarding benefits and risks to patients may be found in the IB.

### **1.3.2. Overall Benefit and Risk Assessment for This Study**

In completed clinical studies, oral and im administration of risperidone demonstrated superiority over placebo in assessments such as Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms, and Positive and Negative Syndrome Scale (PANSS). This superiority was generally dose dependent, with oral doses ranging from 2 to 16 mg/day on a once per day or twice per day schedule. On a longer term, risperidone treatment resulted in a significantly longer time to relapse over a 2-year period compared to treatment with an active comparator.

Intramuscular risperidone was generally well tolerated over the dose range of 12.5 to 50 mg. The most common adverse events in clinical studies ( $\geq 5\%$  of risperidone-treated patients and with a frequency twice that of placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain. The most common ADRs in clinical studies of risperidone LAI in patients with schizophrenia ( $\geq 5\%$  of risperidone-treated patients) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth.

To date, Teva has evaluated TV-46000 safety data from 99 patients and 53 healthy volunteers at doses of 12.5 to 225 mg. Study TV46000-CNS-30072 was only recently initiated and is therefore not included in the above total. Limited efficacy data for TV-46000 in patients are available. Furthermore, human safety data on TV-46000 are also limited. However, the safety profile is expected to be generally similar to that of risperidone LAI. To date, the only new safety signals that were identified in the TV-46000 Phase 1 program were some types of injection site reactions. They have not significantly impacted TV-46000's benefit-risk profile nor have they presented a significant burden to the patients.

Thus, the safety profile emerging from these data is consistent with other formulations of risperidone, with the exception of the identification of some types of injection site reactions.

With regard to the adolescent patient population, nonclinical studies with TV-46000 in young and mature animals did not identify a particular concern for treatment of the targeted adolescent population aged 13 years and above.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. 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 <b>primary objective</b> 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.

#### 2.1.1. Justification of Primary Endpoint

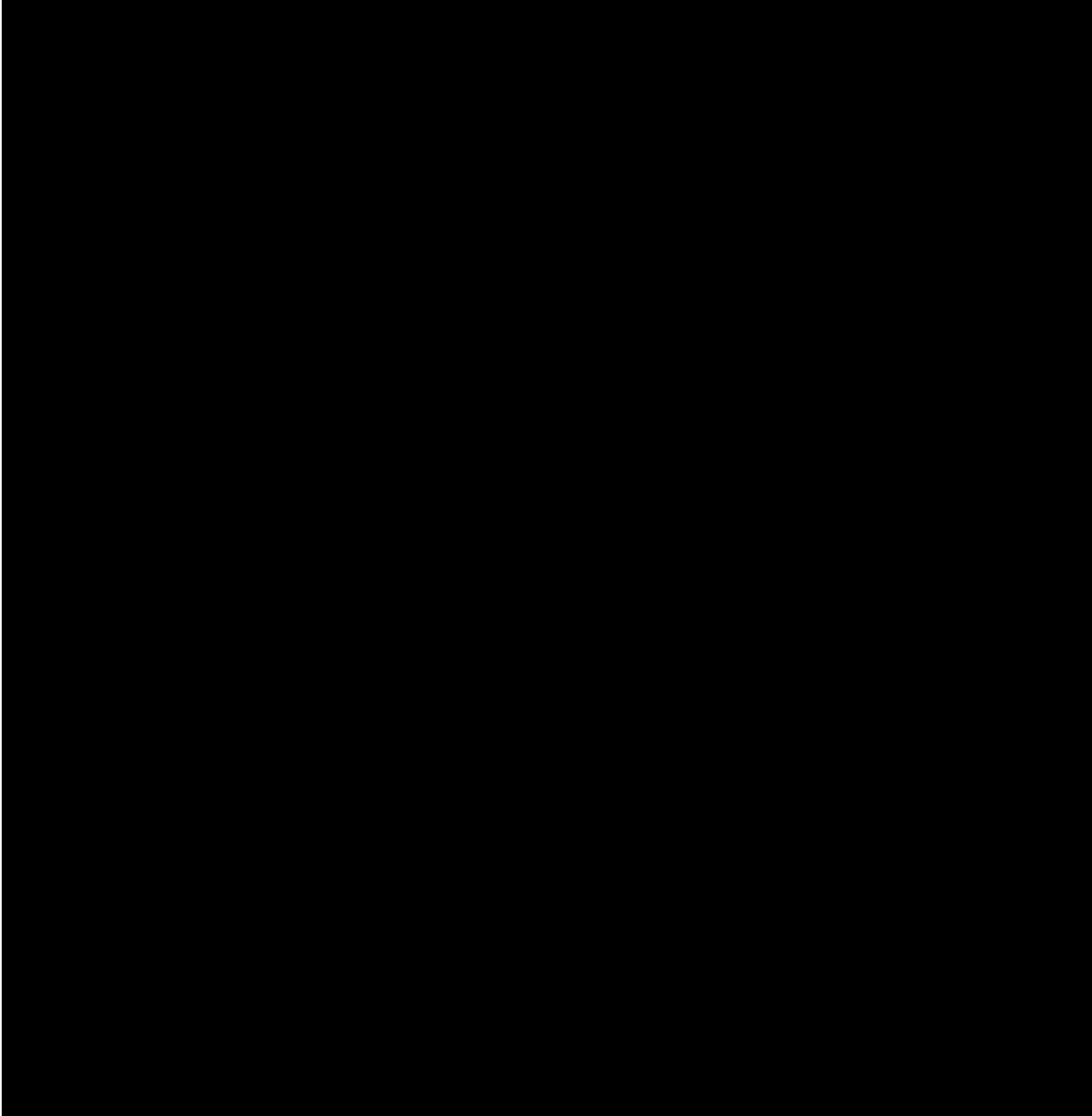
The primary endpoint is the frequency of all adverse events, including serious adverse events. This is compatible with the recommendations of the Food and Drug Administration (FDA), which requested during the End-of-Phase 1 interaction that safety data be collected for at least 100 patients exposed to TV-46000 for a minimum of 12 months.

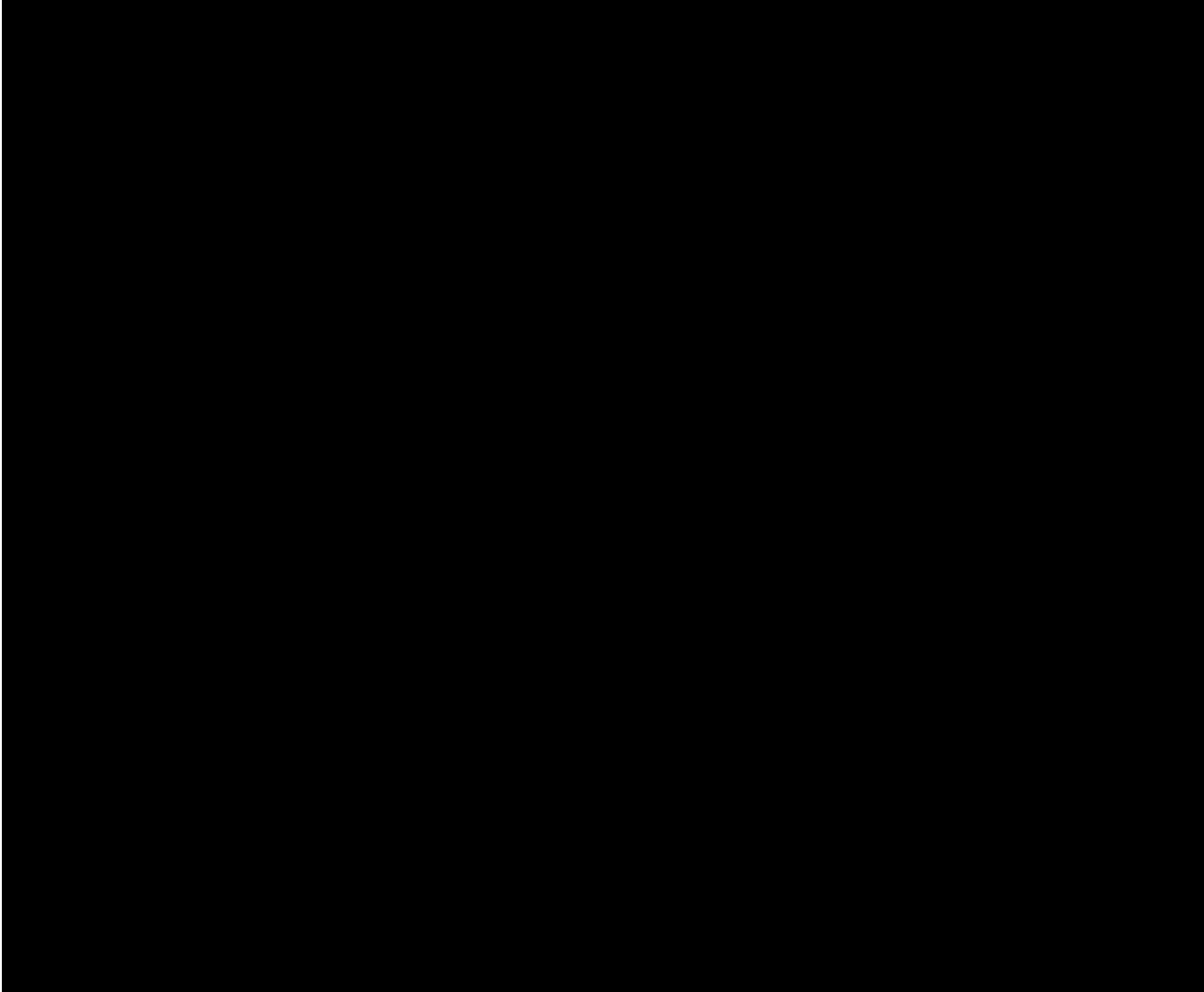
### 2.2. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are as follows:

Objectives	Endpoints

Objectives	Endpoints

Objectives	Endpoints
	

Objectives	Endpoints
	

### 3. STUDY DESIGN

#### 3.1. General Study Design and Study Schematic Diagram

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 adolescent patients, it is mandatory that a parent/caregiver accompanies the patient to each visit and serves as a reliable informant. It is recommended that a caregiver is identified for each adult patient. Local requirements should be followed. The caregiver may be contacted in case of loss of contact with the patient or to provide additional information about the patient, if needed. Adult patients could be accompanied by caregivers to visits.

##### **A. New Patients: Screening through beginning of Stage 2**

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).

**Screening:** These patients will undergo screening procedures/assessments within 4 weeks before the start of Stage 1. Adult patients (aged 18-65) should have had a diagnosis of schizophrenia for >1 year, and adolescent patients (aged 13-17) should have had a diagnosis of schizophrenia for >6 months (diagnosis must be reconfirmed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition [DSM-5] [SCID-5]), and have been generally responsive to antipsychotics in the past year based on discussions with family members or healthcare professionals. Adult patients should also have had  $\geq 1$  episode of relapse in the last 24 months. Patients will provide informed consent or assent, as applicable, at the screening visit, before any study-related procedures or assessments are performed.

**Stage 1 (12-week oral conversion and stabilization stage):** New patients on any antipsychotic (other than clozapine) who can benefit from conversion to oral risperidone based on the investigator's judgment will be converted to oral risperidone to stabilize the patients on the treatment. Oral risperidone (at a dose of 2 to 5 mg/day, based on clinical judgment) will be given for 12 weeks to ensure that the patients can tolerate risperidone and that the doses are adequate to treat their positive symptoms. Adolescent patients will receive a maximal dose of 4 mg/day. Patients will come to the clinic for 4 visits (weeks -12, -10, -8, and -4) for various assessments and dose adjustments (Table 1). Additional visits may be required for dose adjustments. Patients will be evaluated using the PANSS, Clinical Global Impression of Severity (CGI-S), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus



Scale (SAS), Columbia Suicide Severity Rating Scale (C-SSRS), Calgary Depression Scale for Schizophrenia (CDSS), Clinical Global Impression-Severity of Suicidality (CGI-SS), and Clinical Global Impression-Improvement (CGI-I). Additionally, telephone contact will take place at weeks -6 and -2, or more frequently if required in the judgment of the investigator.

Stability (as assessed at the baseline visit) is defined as meeting all of the following criteria for at least 4 consecutive weeks prior to the baseline visit:

- outpatient status

■ [REDACTED]  
■ [REDACTED]  
■ [REDACTED]  
■ [REDACTED]

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.

If a patient withdraws from the study prior to the randomization (baseline) visit (Visit 6), the case report form (CRF) for the patient's last visit will be marked as "Not Continuing", and the reason for discontinuation will be recorded. No extra testing or procedures will be required in addition to the regular visits.

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) described below.

#### **B. Roll-Over Patients: Screening through beginning of Stage 2**

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 (see [Table 2](#) and Appendix B, Section 3).

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.

**C. New and Roll-Over Patients: Stage 2**

After 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. All patients will attend in-clinic visits q1m (ie, the dosing visits) and will undergo various procedures and assessments as detailed in [Table 2](#). Throughout the duration of the study, telephone contact will take place weekly between clinic visits.

Patients who complete all scheduled visits will have EoT/early termination (ET) procedures and assessments performed at week 56 and follow-up procedures and assessments performed at weeks 60 and 64.

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

Patients who withdraw from the study before completing the 56-week maintenance stage will have follow-up procedures and assessments performed at their follow-up visits. During the follow-up period, patients will be treated according to the investigator's judgment.

For new patients (ie, patients not rolling over from the pivotal efficacy study), the total duration of patient participation in the study is planned to be up to 80 weeks (including a screening period of up to 4 weeks, a 12-week oral conversion/stabilization stage [Stage 1], a 56-week maintenance stage [Stage 2], and a follow-up period [8 weeks]).

For patients rolling over from the pivotal efficacy Study TV46000-CNS-30072, the total duration of patient participation in the study is planned to be up to 64 weeks (including up to 56 weeks in the maintenance stage [Stage 2] and a follow-up period [8 weeks]).

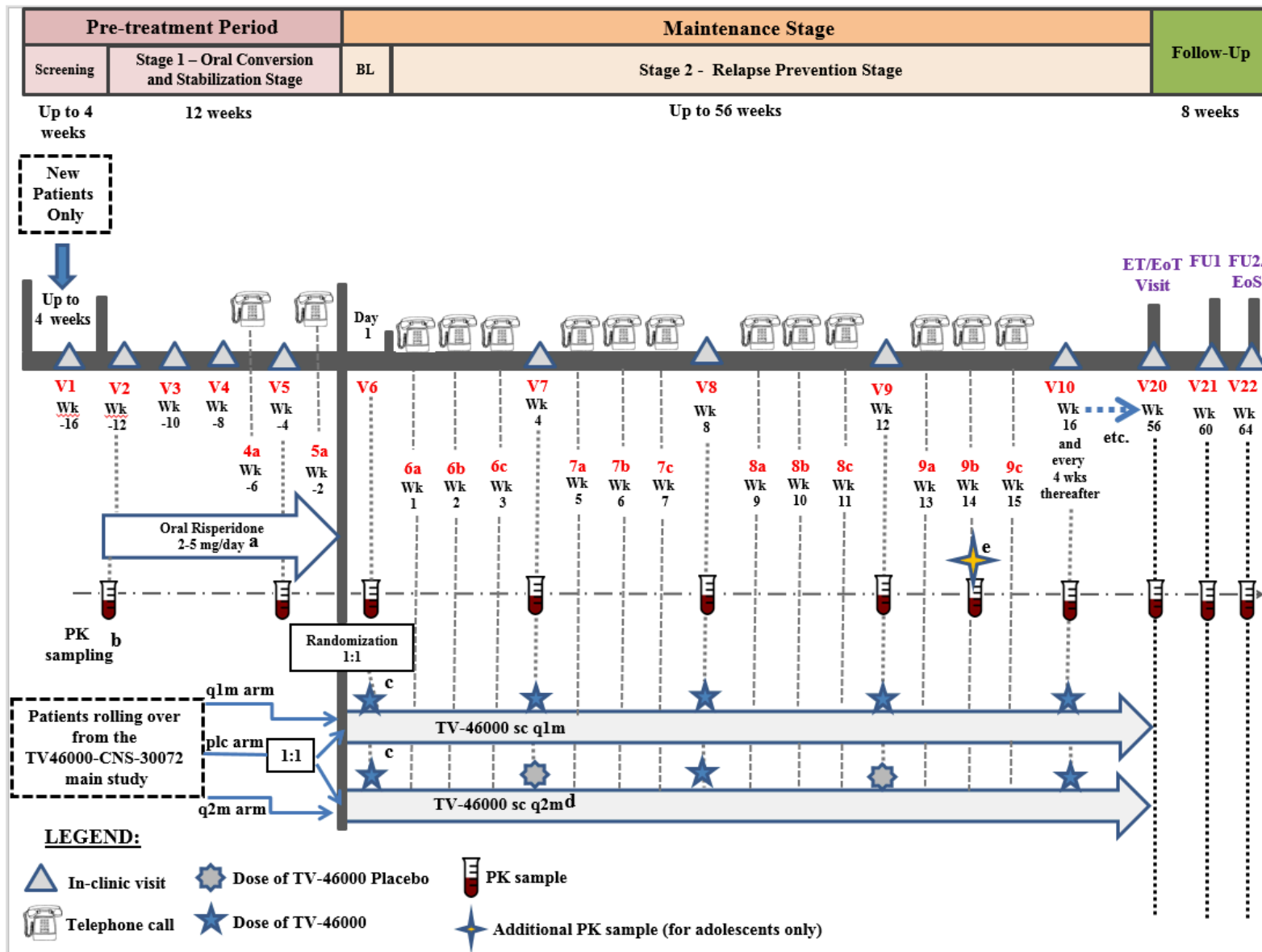
End of study (EoS) is defined as the date when the last patient in Stage 2 has completed all efficacy and safety assessments at the final visit per protocol (Follow-up Visit 2).

The study duration will be approximately 25 months, from Quarter 1 (Q1) 2019 to Quarter 1 (Q1) 2021.

Study procedures and assessments with their time points are shown in [Table 1](#) and [Table 2](#). The study schematic diagram is shown in [Figure 1](#).

For Coronavirus disease 2019 (COVID-19) updates, refer to [Appendix N](#).

Figure 1: Overall Study Schematic Diagram



[REDACTED]

BL=baseline; EoS=end of study; EoT=end of treatment; ET=early termination; FU=follow-up; PK=pharmacokinetics; plc=placebo; q1m=every month; q2m=every 2 months; q4w=every 4 weeks; sc=subcutaneous; V=visit; Wk=week; IMP=investigational medicinal product.

### **3.2. Planned Number of Patients and Countries**

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.

Assuming that at least 90% of patients in Study TV46000-CNS-30072 roll over into this study, then about 225 patients will roll over, and approximately 143 new patients will be screened to achieve enrollment of approximately 107 new patients in Stage 1. This is expected to achieve an overall number of approximately 300 enrolled patients in Stage 2, including approximately 75 new patients and approximately 225 roll-over patients.

In case the assumption about the number of patients rolling over from Study TV46000-CNS-30072 is found to not be valid at a later stage (ie, at the time of interim analysis), the number of new patients may be modified to meet the requirement to follow 100 patients for at least 1 year.

The study is planned to be conducted in the United States (US) and Bulgaria in approximately 100 investigational centers (new centers and those that participated in Study TV46000-CNS-30072). The study is expected to start in Q1 2019 and last until approximately Q1 2021.

Adolescent patients will only be enrolled in the US; any enrolled adolescents will be in addition to the aforementioned total.

### **3.3. Justification for Study Design and Selection of Population**

Long-term use of antipsychotic agents has been shown to be effective in preventing relapse in patients with schizophrenia, but carries the risk of side effects (including weight gain, hyperglycemia/diabetes, and metabolic syndrome) and must be justified for each new agent or new formulation. Therefore, the sponsor is conducting a scientifically valid study that supports the use of TV-46000 at the proposed clinical dosage regimen (Study TV46000-CNS-30072). This study comprises the safety extension of Study TV46000-CNS-30072, to further evaluate the safety, tolerability, and efficacy of TV-46000.

The population for this study consists of adult and adolescent patients with chronic schizophrenia and excludes patients with acute disease. Only new patients who have been stabilized on oral therapy with risperidone, or stable roll-over patients from Study TV46000-CNS-30072, will be enrolled into the double-blind maintenance stage of the study.

The doses of randomized investigational medicinal product (IMP) to be evaluated in this double-blind study (50 to 125 mg q1m sc and 100 to 250 mg q2m sc) were selected on the basis of Study TV46000-SAD-10055 and Study TV46000-CNS-30072.

Based on the pharmacokinetic performance and the safety profile of TV-46000 in Study TV46000-SAD-10055 and the PopPK model-derived simulations, it is expected that TV-46000 will provide sufficient coverage throughout 28 days (for q1m) and 56 days (for q2m) in 4 doses (50, 75, 100, and 125 mg and 100, 150, 200, and 250 mg, respectively) equivalent to 2, 3, 4, and 5 mg/day oral risperidone based on the total active moiety ([Table 3](#)). The maximal TV-46000 dose administered to adolescents will be equivalent to 4 mg/day oral risperidone.

A Phase 3 safety study will allow the establishment of an adequate safety database for long-term exposure to TV-46000. Maintaining patients on TV-46000 following their completion of the

placebo-controlled Phase 3 pivotal efficacy study or switching patients from placebo to either the q1m product or the q2m product will simplify this study design and will provide additional safety data for the higher doses (100 to 250 mg).

### **3.4. Stopping Rules for the Study**

There are no formal rules for ET of this study. During the conduct of the study, serious adverse events will be reviewed (Section [7.1.5](#)) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of the following:

- new toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

### **3.5. Schedule of Study Procedures and Assessments**



For COVID-19 updates, refer to [Appendix N](#).

**Table 1: Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) - For New Patients Only – Pre-Treatment Period (Screening and Stage 1)**

Study Period	Pre-Treatment Period <sup>a</sup>							N/A
	Screening	Stage 1: Oral Conversion and Stabilization Stage <sup>b</sup>						Unscheduled Visit
Visit number	V1	V2	V3	V4	V4a	V5	V5a	
Time point Procedures and assessments	Wk-16	Wk -12	Wk -10	Wk -8	Wk -6	Wk -4 <sup>c</sup>	Wk -2	As deemed necessary by the investigator <sup>d</sup>
Allowed time window	+4 weeks	±3 days						N/A
In-clinic visit	X	X	X	X		X		X
Telephone call <sup>e,f</sup>					X		X	
Informed consent (and assent, as applicable)	X							
Medical and psychiatric history	X							
SCID-5	X							
Prior medication history	X							
Inclusion and exclusion criteria	X							
Clinical laboratory tests <sup>g,h</sup>	X			X				
Virology and thyroid screening tests <sup>i</sup>	X							
Urine drug screen	X							
Concomitant medication inquiry	X	X	X	X		X		X
Full physical examination, including weight	X <sup>j</sup>	X						
Vital sign measurements <sup>k</sup>	X	X	X	X		X		X
12-lead ECG <sup>l</sup>	X							
FSH test <sup>m</sup>	X							
Serum β-HCG test for women of childbearing potential	X							

Study Period	Pre-Treatment Period <sup>a</sup>							N/A
	Screening	Stage 1: Oral Conversion and Stabilization Stage <sup>b</sup>						Unscheduled Visit
Visit number	V1	V2	V3	V4	V4a	V5	V5a	
Time point Procedures and assessments	Wk -16	Wk -12	Wk -10	Wk -8	Wk -6	Wk -4 <sup>c</sup>	Wk -2	As deemed necessary by the investigator <sup>d</sup>
Allowed time window	+4 weeks	±3 days						N/A
In-clinic visit	X	X	X	X		X		X
Telephone call <sup>e,f</sup>					X		X	
Urine β-HCG test for women of childbearing potential <sup>n</sup>		X	X	X		X		
Inquiry about pregnancy status (for women of childbearing potential)					X		X	
PANSS	X	X	X	X		X		X
CGI-S	X	X	X	X		X		
CGI-SS <sup>o</sup>	X	X	X	X		X		
CGI-IP		X	X	X		X		
AIMS	X	X	X	X		X		
BARS	X	X	X	X		X		
SAS	X	X	X	X		X		
C-SSRS <sup>q</sup>	X	X	X	X	X	X	X	X
PSP (for adult patients only)	X							
SQLS (for adult patients only)	X							
EQ-5D-5L (for adults patients only)	X							
CDSS	X	X	X	X		X		
Healthcare resource utilization	X							
DAI-10 (for adult patients only)	X							
Blood samples for plasma drug concentration <sup>r</sup>		X				X		



Clinical Study Protocol with Amendment 01

Study Period	Pre-Treatment Period <sup>a</sup>							N/A
	Screening	Stage 1: Oral Conversion and Stabilization Stage <sup>b</sup>						Unscheduled Visit
Visit number	V1	V2	V3	V4	V4a	V5	V5a	
Time point Procedures and assessments	Wk -16	Wk -12	Wk -10	Wk -8	Wk -6	Wk -4 <sup>c</sup>	Wk -2	As deemed necessary by the investigator <sup>d</sup>
Allowed time window	+4 weeks	±3 days						N/A
In-clinic visit	X	X	X	X		X		X
Telephone call <sup>e,f</sup>					X		X	
Oral risperidone dispensing (for qd intake) <sup>g</sup>		X	X	X		X		
Dosage review and adjustment <sup>h</sup>		X	X	X		X		
Adverse event inquiry (including SAE reporting)	X	X	X	X	X	X	X	X
Inquiry regarding alcohol consumption/illicit drug use	X	X	X	X	X	X	X	X
Brief set of clinical questions to detect psychotic symptoms <sup>u</sup>					X		X	

<sup>a</sup> If a patient withdraws from the study prior to the randomization (baseline) visit (Visit 6), the CRF for the patient's last visit will be marked as "Not Continuing", and the reason for discontinuation will be recorded. No extra testing or procedures will be required in addition to the regular visits.

<sup>b</sup> Visits 3 through 5a should be scheduled relative to Visit 2 (and not relative to screening). For example, Visit 3 should be scheduled 2 weeks (±3 days) after Visit 2, regardless of when the screening visit took place.

<sup>c</sup> Patients whose symptoms have stabilized at this visit will be required to meet the specified stability criteria for at least 4 consecutive weeks, until the baseline visit at which they will be assessed.

<sup>d</sup> Other procedures may be performed at the discretion of the investigator.

<sup>e</sup> Telephone contact will occur at week -6 and week -2 in the oral conversion and stabilization stage (Stage 1) (or more frequently if required in the judgement of the investigator). These contacts will be referred to by the previous visit number and a letter (for example, the telephone contact that takes place 2 weeks after Visit 4 will be referred to as "Visit 4a").

<sup>f</sup> Each contact will include inquiries about suicidal ideation and behavior (C-SSRS), adverse events, alcohol consumption, and pregnancy status (for women of childbearing potential). Patients will also be asked a brief set of clinical questions in order to detect psychotic symptoms (see relevant assessment).

<sup>g</sup> Clinical laboratory tests (serum chemistry, hematology, and urinalysis) may also be performed at any time if clinically indicated.

<sup>h</sup> Glomerular filtration rate (GFR) will be calculated based on plasma creatinine levels, weight, gender, and age using the Cockcroft-Gault equation.

<sup>i</sup> Includes HIV, HBsAg, hepatitis C antibody, TSH, T<sub>3</sub>, and T<sub>4</sub>.

<sup>j</sup> Height will be measured at the screening visit only.

<sup>k</sup> Vital sign measurements will include blood pressure [systolic/diastolic], respiratory rate, tympanic temperature, and pulse.

Clinical Study Protocol with Amendment 01

- <sup>l</sup> At screening, ECG measurements will be done in triplicate. The mean of the 3 measurements will be used to determine study eligibility.
- <sup>m</sup> The FSH test will only be performed for women with no menses for 12 months in order to confirm postmenopausal status.
- <sup>n</sup> Urine  $\beta$ -HCG (dipstick) test will be performed at all visits where oral risperidone is administered prior to study drug administration. A negative result must be obtained before study drug can be administered.
- <sup>o</sup> In Stage 1, for new patients, Part 2 of the CGI-SS will be compared to screening.
- <sup>p</sup> CGI-I during Stage 1 will be relative to screening.
- <sup>q</sup> 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.
- <sup>r</sup> During the in-clinic visits in Stage 1 (V2 and V5) where the blood samples for pharmacokinetic assessment are taken, samples should be taken within an hour prior to dosing, if possible. In any case, the hour of the last dose taken prior to collection of the pharmacokinetic sample will be recorded on the CRF.
- <sup>s</sup> Patients will be advised to take the oral risperidone at approximately the same hour every day (morning or evening, at their convenience). The hour of the last dose taken prior to collection of the pharmacokinetic sample will be recorded on the CRF.
- <sup>t</sup> Adolescent patients will receive a maximal dose of 4 mg/day oral risperidone.
- <sup>u</sup> The specific questions asked will be at the discretion of the investigator. A list of suggested questions will be provided to the investigator. Psychiatric adverse events or suspicion of psychiatric deterioration prompted by the telephone contact will trigger an invitation of the patient to an unscheduled visit where psychiatric scales will be administered to rule out an impending relapse at the discretion of the investigator.
- $\beta$ -HCG=beta human chorionic gonadotropin; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; 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; CRF=case report form; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitudes Inventory 10-item version; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition; ECG=electrocardiogram; EQ-5D-5L=5-Level EuroQol Five Dimensions Questionnaire; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; N/A=not applicable; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance Scale; qd=every day; SAE=serious adverse event; SAS=Simpson-Angus Scale; SCID-5=Structured Clinical Interview for DSM-5; SQLS=Schizophrenia Quality of Life Scale; T<sub>3</sub>=triiodothyronine; T<sub>4</sub>=thyroxine; TSH=thyroid-stimulating hormone; Wk=week; V=visit.

**Table 2: Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – For New and Roll-Over Patients – Baseline, Double-Blind Maintenance Stage (Stage 2), End of Treatment, and Follow-Up**

Study Period	Double-Blind Maintenance Stage <sup>a</sup>															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention Stage														FU1	FU2/ EoS	Unscheduled Visit
		The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).													ET/ EoT			
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c	V20	V21	V22	As deemed necessary by the investigator <sup>b</sup>
Time point Procedures and assessments	Day 1	Wks 1- 3	Wk 4	Wks 5-7	Wk 8	Wks 9- 11	Wk 12	Wks 13-15	Wk 16	Wks 17-19	Wk 20	Wks 21-23	Wk 24	Wks 25-27	Wk 56	Wk 60	Wk 64	
Allowed window	±3 days																	N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call <sup>c, d</sup>		X		X		X		X		X		X		X				
Informed consent (and assent, as applicable) (for roll-over patients only)	X																	
Inclusion and exclusion criteria	X <sup>e</sup>																	
Clinical laboratory tests <sup>f, g</sup>	X <sup>h</sup>				X				X				X		X	X	X	
Virology and thyroid screening tests <sup>i</sup>	X																	
Urine drug screen	X <sup>h</sup>														X			
Concomitant medication inquiry	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	X
Full physical examination, including weight	X <sup>h, j</sup>														X	X	X	
Vital sign measurements <sup>k</sup>	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	X
12-lead ECG <sup>l</sup>	X				X				X				X		X <sup>m</sup>	X	X	

Study Period	Double-Blind Maintenance Stage <sup>a</sup>															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention Stage														FU1	FU2/ EoS	Unscheduled Visit
			The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).												ET/ EoT			
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c	V20	V21	V22	As deemed necessary by the investigator <sup>b</sup>
Time point Procedures and assessments	Day 1	Wks 1- 3	Wk 4	Wks 5-7	Wk 8	Wks 9- 11	Wk 12	Wks 13-15	Wk 16	Wks 17-19	Wk 20	Wks 21-23	Wk 24	Wks 25-27	Wk 56	Wk 60	Wk 64	
Allowed window	±3 days																	N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call <sup>c, d</sup>		X		X		X		X		X		X		X				
Serum β-HCG test for women of childbearing potential	X															X	X	
Urine β-HCG test for women of childbearing potential <sup>n</sup>	X <sup>h</sup>		X		X		X		X		X		X		X			
Inquiry about pregnancy status (for women of childbearing potential)		X		X		X		X		X		X		X				
PANSS <sup>o</sup>	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	X
CGI-S	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
CGI-SSP <sup>p</sup>	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
CGI-I <sup>q</sup>			X		X		X		X		X		X		X	X	X	
AIMS	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
BARS	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
SAS	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
C-SSRS <sup>r</sup>	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Double-Blind Maintenance Stage <sup>a</sup>															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention Stage														FU1	FU2/ EoS	Unscheduled Visit
			The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).												ET/ EoT			
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c	V20	V21	V22	As deemed necessary by the investigator <sup>b</sup>
Time point Procedures and assessments	Day 1	Wks 1- 3	Wk 4	Wks 5-7	Wk 8	Wks 9- 11	Wk 12	Wks 13-15	Wk 16	Wks 17-19	Wk 20	Wks 21-23	Wk 24	Wks 25-27	Wk 56	Wk 60	Wk 64	
Allowed window	±3 days																	N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call <sup>c, d</sup>		X		X		X		X		X		X		X				
PSP (for adult patients only)	X <sup>h</sup>						X <sup>s</sup>						X		X		X	
SQLS (for adult patients only)	X <sup>h</sup>						X <sup>s</sup>						X		X		X	
EQ-5D-5L (for adult patients only)	X <sup>h</sup>						X <sup>s</sup>						X		X		X	
CDSS	X <sup>h</sup>		X		X		X		X		X		X		X	X	X	
Healthcare resource utilization	X <sup>h</sup>						X <sup>s</sup>						X		X		X	
DAI-10 (for adult patients only)	X <sup>h</sup>														X		X	
Blood samples for pharmacogenetic analysis	X <sup>t</sup>																	
Blood samples for biomarker analysis <sup>u</sup>	X				X				X				X		X	X	X	
Blood samples for plasma drug concentration <sup>v</sup>	X		X		X		X		X		X		X		X	X	X	X <sup>w</sup>

Study Period	Double-Blind Maintenance Stage <sup>a</sup>															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention Stage														FU1	FU2/ EoS	Unscheduled Visit
			The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).												ET/ EoT			
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c	V20	V21	V22	As deemed necessary by the investigator <sup>b</sup>
Time point Procedures and assessments	Day 1	Wks 1- 3	Wk 4	Wks 5-7	Wk 8	Wks 9- 11	Wk 12	Wks 13-15	Wk 16	Wks 17-19	Wk 20	Wks 21-23	Wk 24	Wks 25-27	Wk 56	Wk 60	Wk 64	
Allowed window	±3 days																	N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call <sup>c, d</sup>		X		X		X		X		X		X		X				
Additional blood samples for adolescent pharmacokinetic analysis (for adolescents only)							X <sup>x</sup>											
Assessment of stability	X <sup>y</sup>																	
Randomization <sup>z</sup>	X																	
TV-46000 q1m sc administration	X <sup>aa</sup> (new patients only)		X		X		X		X		X		X		X <sup>bb</sup>			
TV-46000 q2m sc administration <sup>cc</sup> (to maintain the blind, patients will be injected q4w, but will alternate between TV-46000 and placebo sc injections)	X <sup>aa</sup> (new patients only)		X		X		X		X		X		X		X <sup>bb</sup>			
Questions to assess ease of study drug administration (for new patients only) <sup>dd</sup>	X		X		X													

Study Period	Double-Blind Maintenance Stage <sup>a</sup>															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention Stage														FU1	FU2/ EoS	Unscheduled Visit
			The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).															
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c	V20	V21	V22	As deemed necessary by the investigator <sup>b</sup>
Time point Procedures and assessments	Day 1	Wks 1- 3	Wk 4	Wks 5-7	Wk 8	Wks 9- 11	Wk 12	Wks 13-15	Wk 16	Wks 17-19	Wk 20	Wks 21-23	Wk 24	Wks 25-27	Wk 56	Wk 60	Wk 64	
Allowed window	±3 days																	N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call <sup>c, d</sup>		X		X		X		X		X		X		X				
Adverse event inquiry (including SAE reporting, injection site-related events including pain) <sup>ee</sup>	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inquiry regarding alcohol consumption/illicit drug use	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief set of clinical questions to detect psychotic symptoms <sup>ff</sup>		X		X		X		X		X		X		X				

<sup>a</sup> The double-blind maintenance stage will be up to 56 weeks in length, with patients continuing until they experience a relapse event (and complete all EoS assessments); meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free until study completion. Patients will continue study visits and assessments as shown in the table (ie, the same assessments performed at Visits 7 and 8 will be repeated at Visits 9 and 10, respectively, unless otherwise specified). The functional measures (PSP, SQLS, and EQ-5D-5L) and the healthcare resource utilization will be performed every 12 weeks (Visits 9, 12, 15, and 18).

<sup>aa</sup> 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).

<sup>b</sup> Other procedures may be performed at the discretion of the investigator.

<sup>bb</sup> Applicable only for the EoT visit (ie, not ET). If in the judgment of the investigator, the patient will not come to 1 or both follow-up visits, then a dose of study drug should not be given at this EoT visit.

Clinical Study Protocol with Amendment 01

- <sup>c</sup> Telephone contact will occur weekly between clinic visits in the double-blind maintenance stage (Stage 2). These contacts will be referred to by the previous visit number and a letter (for example, the telephone contacts that take place 1, 2, and 3 weeks after Visit 6 will be referred to as “Visit 6a,” “Visit 6b,” and “Visit 6c,” respectively).
- <sup>cc</sup> New patients randomized to this arm will receive TV-46000 at baseline and q8w thereafter and placebo at week 4 and q8w thereafter (between the TV-46000 q2m injections) to maintain the blind. Roll-over patients who were assigned to placebo during Study TV46000-CNS-30072 and are randomized to receive TV 46000 q2m in this study will receive TV 46000 at week 4 and q8w thereafter, and a placebo sc injection at week 8 and q8w thereafter. For roll-over patients who were assigned to TV-46000 q2m during Study TV46000-CNS-30072, 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).
- <sup>d</sup> Each contact will include inquiries about injection site pain, suicidal ideation and behavior (C-SSRS), adverse events, alcohol consumption, and pregnancy status (for women of childbearing potential). Patients will also be asked a brief set of clinical questions in order to detect psychotic symptoms (see relevant assessment).
- <sup>dd</sup> This will be completed by the unblinded nurse who administers the study drug to the patients following the first 3 injections (using prefilled syringes) to each patient (ie, Visits 6, 7 and 8). In the event that prefilled syringes of TV-46000 become unavailable during the study, the unblinded nurse responsible for study drug administration will use vials (instructions on how to use vials can be found in the Pharmacy Manual).
- <sup>e</sup> New patients must meet randomization criteria in addition to other relevant inclusion criteria before randomization. Roll-over patients must meet specific inclusion/exclusion criteria (Section 4.1 and Section 4.2).
- <sup>ee</sup> Injection site pain and other injection site reactions will only be assessed during Stage 2 of the study, in which the sc injections are administered. Pain may be assessed periodically using the NPRS until resolution.
- <sup>f</sup> Clinical laboratory tests (serum chemistry, hematology, and urinalysis) may also be performed at any time if clinically indicated.
- <sup>ff</sup> The specific questions asked will be at the discretion of the investigator. A list of suggested questions will be provided to the investigator. Psychiatric adverse events or suspicion of psychiatric deterioration prompted by the telephone contact will trigger an invitation of the patient to an unscheduled visit where psychiatric scales will be administered to rule out an impending relapse at the discretion of the investigator.
- <sup>g</sup> Glomerular filtration rate (GFR) will be calculated based on plasma creatinine levels, weight, gender, and age using the Cockcroft-Gault equation.
- <sup>h</sup> For roll-over patients, this procedure will be performed as part of the TV46000-CNS-30072 EoT visit, and the results will be transferred to this study's clinical database.
- <sup>i</sup> For roll-over patients only; includes HIV, HBsAg, hepatitis C antibody, TSH, T3, and T4.
- <sup>j</sup> For adult roll-over patients, height will be obtained from the patient's record in Study TV46000-CNS-30072. For adolescent roll-over patients, height will be measured again at the baseline visit. New patients will have height recorded at screening and therefore do not need to be measured again for height at the baseline visit.
- <sup>k</sup> Vital sign measurements will include blood pressure [systolic/diastolic], respiratory rate, tympanic temperature, and pulse.
- <sup>l</sup> At baseline, measurements will be done in triplicate. The mean of the 3 measurements will be used to determine study eligibility. Single measurements will be performed at all other in-clinic visits where ECG recordings are taken.
- <sup>m</sup> During the ET/EoT visit, if in the judgment of the investigator the patient will not come to 1 or both of the follow-up visits, an ECG should be performed.
- <sup>n</sup> Urine  $\beta$ -HCG (dipstick) test will be performed at all visits where study drug is administered prior to study drug administration. A negative result must be obtained before study drug can be administered.
- <sup>o</sup> The PANSS will be relative to randomization for new patients. For roll-over patients, the PANSS will be relative to randomization in Study TV46000 CNS-30072.



Clinical Study Protocol with Amendment 01

- <sup>p</sup> In Stage 2, for new patients, Part 2 of the CGI-SS will be compared to baseline; for roll-over patients, it will be compared to baseline of Study TV46000 CNS 30072.
- <sup>q</sup> For new patients, CGI-I during Stage 2 will be relative to the baseline visit; for roll-over patients, it will be relative to the patient's baseline visit in Study TV46000-CNS-30072.
- <sup>r</sup> 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.
- <sup>s</sup> As of Visit 9, inclusive, this assessment will be performed every 12 weeks (Visits 9, 12, 15, and 18), at ET/EoT visit, and at Follow-up Visit 2.
- <sup>t</sup> For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.
- <sup>u</sup> Blood samples for biomarker analyses will be collected as follows: 6 mL for serum, 6 mL for plasma, and 2.5 mL for PAXgene RNA, unless the patient declines testing or local regulations prohibit testing.
- <sup>v</sup> Blood samples for pharmacokinetic assessment should be taken within an hour prior to dosing, where possible and as applicable.
- <sup>w</sup> During Stage 2, unscheduled pharmacokinetic samples will be aimed to be collected in the event of relapse as defined per the study's relapse criteria, any serious adverse event, patient withdrawal, and/or need for potential TV-46000 depot excision. Every effort should be made to obtain the additional pharmacokinetic sample at the closest time possible to the occurrence of the event.
- <sup>x</sup> Another pharmacokinetic sample will be collected from adolescent patients at a supplementary in-clinic visit at week 14 (2 weeks after Visit 9). It is highly preferable to collect the sample at week 14. However, if this is not possible, it may be collected 2 weeks after another in-clinic visit. Up to 2 additional samples may also be collected from adolescent patients at week 15 and week 13 (3 weeks and 1 week post-injection at Visit 9, respectively) at the sponsor's discretion. The additional samples, if taken following another in-clinic visit, will be collected at the same intervals. If more than 1 additional sample is taken, they do not need to be collected after the same injection (ie, 1 sample can be taken 3 weeks after Visit X, and another can be taken 1 week after Visit Y). These additional pharmacokinetic samples will be taken from new adolescent patients or adolescent roll over patients from whom additional pharmacokinetic blood samples were not obtained during Study TV46000-CNS-30072.
- <sup>y</sup> For new patients only. Stability is defined as meeting all of the following criteria for at least 4 consecutive weeks prior to the baseline visit: outpatient status; PANSS total score  $\leq 80$ ; minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of  $\leq 4$  on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; CGI-S score  $\leq 4$  (moderately ill); and CGI-SS score  $\leq 2$  (mildly suicidal) on Part 1 and  $\leq 5$  (minimally worsened) on Part 2.
- <sup>z</sup> New patients, and roll-over patients who were assigned to the placebo arm in Study TV46000-CNS-30072, will be randomized to receive TV-46000 q1m or q2m. Roll-over patients who were randomized to the TV-46000 q1m or q2m treatment arms in Study TV46000-CNS-30072 will continue on the same dosing regimen.

$\beta$ -HCG=beta human chorionic gonadotropin; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BL=baseline; 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; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitudes Inventory 10-item version; ECG=electrocardiogram; EQ-5D-5L=5-Level EuroQol Five Dimensions Questionnaire; EoS=end of study; EoT=end of treatment; ET=early termination; FU=follow-up; GFR=glomerular filtration rate; HbsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; IMP=investigational medicinal product; N/A=not applicable; NPRS=Numeric Pain Rating Scale; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance Scale; q1m=every month; q2m=every 2 months; q8w=every 8 weeks; RNA=ribonucleic acid; SAE=serious adverse event; SAS=Simpson-Angus Scale; sc=subcutaneous; SQLS=Schizophrenia Quality of Life Scale; T<sub>3</sub>=triiodothyronine; T<sub>4</sub>=thyroxine; TSH=thyroid-stimulating hormone; V=visit; Wk=week.

## 4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva ([Appendix C](#)).

### 4.1. Patient Inclusion Criteria

Patients may participate in this study only if they meet all of the following criteria:

#### 4.1.1. Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072

- a. The patient must sign and date the informed consent document. For adolescent patients, written informed consent will be obtained from each patient's parent or legal guardian, and written assent will be obtained from each patient.
- b. The patient must have participated in the pivotal efficacy study (Study TV46000-CNS-30072) without experiencing relapse events and without important protocol deviations ([Appendix C](#)).
- c. If the patient was taking antidepressants or mood stabilizers (including the cytochrome P450 [CYP] 2D6 inhibitors fluoxetine, paroxetine, and duloxetine) in Study TV46000-CNS-30072, no dose changes or initiation of treatment with these medications will be permitted.
- d. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the required visits throughout the duration of the study period, including for the follow-up procedures and assessments as specified in this protocol.
- e. The patient, in the investigator's judgment, requires chronic treatment with an antipsychotic medication.
- f. The patient, in the investigator's judgment, can benefit from participation in this study.
- g. The patient is able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens (oral and sc administration) and non-use of prohibited concomitant medications; can read and understand the written word in order to complete patient-reported outcomes measures; and can be reliably rated on assessment scales.
- h. The patient has had a stable place of residence for the previous 3 months before the baseline visit in this study, and changes in residence are not anticipated over the course of study participation.
- i. The patient has no significant life events (such as pending loss of housing, family status change, long travel abroad, surgery, etc) that could affect study outcomes expected throughout the period of study participation.
- j. The patient is a male or female of any ethnic origin, 13 through 65 years of age (note the exception for roll-over patients who may have exceeded 65 years of age during the course of Study TV46000-CNS-30072; these patients will still be permitted to participate in this study).
- k. The patient is in adequate health as determined by medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, urinalysis, and serology.

- l. Women of childbearing potential and sexually active female adolescents must agree not to try to become pregnant, and, unless they have exclusively same-sex partners, must agree to use a highly effective method of contraception and agree to continue use of this method beginning 1 month before the first administration of study drug and for the duration of the study and for 120 days after the last injection of study drug. Highly effective methods of contraception include the following:
  - combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - intrauterine device (IUD) and intrauterine hormone-releasing system in place at least 2 months before screening
  - bilateral tubal occlusion
  - vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process
  - Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- m. The patient, if adult or adolescent male, is surgically sterile, or, if capable of producing offspring, has exclusively same-sex partners or is currently using an approved method of birth control and agrees to the continued use of this method for the duration of the study (and for 120 days after the last dose of study drug). Male patients with sex partners who are women of childbearing potential (see [Appendix E](#)) must use condoms even if surgically sterile. In addition, male patients may not donate sperm for the duration of the study and for 120 days after taking the study drug.

**4.1.2. New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072)**

- a. [Revision 01] The patient is an adult (age 18-65) and has a diagnosis of schizophrenia according to the DSM-5 for >1 year (diagnosis must be reconfirmed by SCID-5) and ≥1 episode of relapse in the last 24 months, **OR** the patient is an adolescent (age 13-17) with a diagnosis of schizophrenia according to the DSM-5 for > 6 months (diagnosis must be reconfirmed by SCID-5).
- b. The patient has been responsive to an antipsychotic treatment (other than clozapine) in the past year based on investigator judgment (and discussions with family members, caregivers, or healthcare professionals as applicable).
- c. The patient has provided written informed consent and is competent to do so. For adolescent patients, written informed consent will be obtained from each patient's parent or legal guardian, and written assent will be obtained from each patient.

- d. The patient, in the investigator's judgment, requires chronic treatment with an antipsychotic medication.
- e. The patient, in the investigator's judgment, can benefit from participation in this study.
- f. The patient is able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens (oral and sc administration) and non-use of prohibited concomitant medications; can read and understand the written word in order to complete patient-reported outcomes measures; and can be reliably rated on assessment scales.
- g. The patient has a PANSS total score lower than 100 at screening.
- h. The patient has had a stable place of residence for the previous 3 months before screening, and changes in residence are not anticipated over the course of study participation.
- i. The patient has no significant life events (such as pending loss of housing, family status change, long travel abroad, surgery, etc) that could affect study outcomes expected throughout the period of study participation.
- j. The patient is a male or female of any ethnic origin, 13 through 65 years of age.
- k. The patient has a body mass index between 18.0 and 38.0 kg/m<sup>2</sup>, inclusive.
- l. The patient is in adequate health as determined by medical and psychiatric history, medical examination, ECG, serum chemistry, hematology, urinalysis, and serology.
- m. Women of childbearing potential and sexually active female adolescents must agree not to try to become pregnant, and, unless they have exclusively same-sex partners, must agree to use a highly effective method of contraception and agree to continue use of this method beginning 1 month before the first administration of study drug and for the duration of the study and for 120 days after the last injection of study drug. Highly effective methods of contraception include the following:
  - combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 month before the first dose of IMP.
  - IUD and intrauterine hormone-releasing system in place at least 2 months before screening
  - bilateral tubal occlusion
  - vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process
  - Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- n. The patient, if adult or adolescent male, is surgically sterile, or, if capable of producing offspring, has exclusively same-sex partners or is currently using an

approved method of birth control and agrees to the continued use of this method for the duration of the study (and for 120 days after the last dose of study drug). Male patients with sex partners who are women of childbearing potential (see [Appendix E](#)) must use condoms even if surgically sterile. In addition, male patients may not donate sperm for the duration of the study and for 120 days after taking the study drug.

- o. The patient must be willing and able to comply with study restrictions and willing to return to the investigational center for the required visits throughout the duration of the study period, including for the follow-up procedures and assessments as specified in this protocol.

#### **4.1.3. Randomization Criteria for New Patients**

The following criteria are randomization criteria and must be fulfilled at the baseline visit before randomization in addition to other relevant inclusion criteria:

- a. The patient has not experienced mental or physical deterioration, which prevents participation in the study per investigator judgement.
- b. The patient has demonstrated good compliance in following protocol requirements during Stage 1 of the study.
  - 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 in the double-blind period (Stage 2).
- c. The patient has been stabilized per the following criteria for at least 4 consecutive weeks prior to the baseline visit:
  - outpatient status
  - PANSS total score  $\leq 80$
  - minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of  $\leq 4$  on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
  - CGI-S score  $\leq 4$  (moderately ill)
  - CGI-SS score  $\leq 2$  (mildly suicidal) on Part 1 and  $\leq 5$  (minimally worsened) on Part 2

#### **4.2. Patient Exclusion Criteria**

Patients may not participate in this study if they meet any of the following criteria:

##### **4.2.1. Patients Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072**

- a. The patient has a finding in the baseline 12-lead ECG that is considered clinically significant in the judgment of the investigator.
- b. Poor compliance with study procedures (in the opinion of the investigator or sponsor) during the pivotal efficacy Study TV46000-CNS-30072. This should be discussed on a case-by-case basis.

**4.2.2. New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072) and Roll-Over Patients**

- a. The patient has a current clinically significant DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, or amnesic or other cognitive disorders, or borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.
- b. The patient is currently on clozapine or has received electroconvulsive therapy in the last 12 months.
- c. The patient has a history of epilepsy or seizures, neuroleptic malignant syndrome, tardive dyskinesia, or other medical condition that would expose the patient to undue risk.
- d. The patient has a positive serology for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen, and/or hepatitis C. If serology is positive for hepatitis C but the ribonucleic acid test is negative and the patient has no history of liver disease, enrollment will be considered following discussion between the investigator and the medical monitor as needed.
- e. The patient has current or a history of known hypersensitivity to risperidone or any of the excipients of TV-46000 or the oral formulation of risperidone used in the stabilization phase.
- f. The patient has a substance use disorder, including alcohol and benzodiazepines but excluding nicotine and caffeine.
- g. The patient has a significant risk of violent behavior based on the patient's medical history or the investigator's judgement.
- h. The patient has a significant risk of committing suicide based on the patient's medical history or the investigator's judgement and/or the C-SSRS (lifetime). Patients with a C-SSRS (current) positive response to suicidal ideation items 3, 4, or 5 are not eligible.
- i. The patient has a clinically significant deviation from normal in the physical examination.
- j. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results.
- k. If the patient has a prolonged QTcF interval (defined as a QTcF interval of >450 msec for males and >470 msec for females) at screening or baseline, calculated as the mean of the triplicate ECG measurements, eligibility will be decided on a case-by-case basis following discussion between the investigator and the sponsor.
- l. The patient has any clinically significant uncontrolled medical condition (treated or untreated). The investigator may discuss with the medical monitor as needed.
- m. The patient is a pregnant or lactating female.
- n. The patient has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery).
- o. The patient has any other disease or condition that, in the opinion of the investigator, would make participation not in the best interest of the patient or that could prevent, limit, or confound the protocol-specified assessments.
- p. The patient has used an investigational drug other than TV-46000 within 3 months prior to screening or has participated in a non-drug clinical trial within 30 days prior to screening.

- q. The patient is using or consuming medications prohibited in this study.
- r. Vulnerable patients (eg, people kept in detention).

### **4.3. Withdrawal Criteria and Procedures for the Patient**

#### **4.3.1. General Withdrawal Criteria**

Patients are expected to participate in the study for its entire duration and to perform the scheduled visits and procedures.

Each patient is free to withdraw from the study or discontinue treatment with IMP at any time, without prejudice to their continued care, but every effort should be undertaken to determine the reason for discontinuation.

Every effort should be made to ensure that the patients comply with study visits and procedures as detailed in the protocol. Patients must be withdrawn from the study if any of the following events occur:

1. The patient withdraws consent or requests discontinuation from the IMP or withdrawal from the study for any reason.
2. The patient develops an illness that would interfere with his or her continued participation.
3. The patient is noncompliant with the study procedures and assessments or with administration of IMPs in the opinion of the investigator.
4. The patient takes prohibited concomitant medications as defined in this protocol.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. The patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.

See [Appendix F](#) for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

If the reason for withdrawal from the study or discontinuation from IMP is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

The investigator must inform the study contact person as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include also adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be “need to take a prohibited medication,” not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient’s medical records and transcribed to the CRF.

All assessments should be performed according to the protocol on the last day the patient takes IMP, or as soon as possible thereafter.

#### **4.3.2. Study-Specific Patient Withdrawal Criteria and Procedures**

Patients must be withdrawn from the study if any of the following events occur:

1. The patient withdraws consent to continue in the study for any reason. Every effort should be undertaken to identify the reason for discontinuation.
2. The patient develops a serious or intolerable adverse event that necessitates discontinuation at the discretion of the investigator.
3. The investigator believes that continued participation is not in the best interest of the patient.
4. The investigator believes that the patient has not adhered to the study procedures or restrictions. A protocol deviation occurs that, in the opinion of the investigator, warrants discontinuation from the study.
5. The patient requires concomitant medication that may interfere with the pharmacokinetics of the study drug.
6. The patient relapses, as defined by the study’s relapse criteria.
7. The patient demonstrates a significant clinical deterioration that cannot be managed with rescue medication, as judged by the investigator based on any relevant history or observation made by the investigative site, including rating scales.
8. A patient has a mean increase of  $\geq 30$  msec from baseline in triplicate QTcF (interval corrected for heart rate using Fridericia’s formula) values at any visit, pending discussion between the sponsor and the investigator.
9. The patient exhibits an event of possible drug-induced liver injury that requires immediate study treatment cessation and is defined as follows:
  - a. alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 8 \times$  the upper limit of normal (ULN)
  - b. ALT or AST  $> 5 \times$  ULN for more than 2 weeks
  - c. ALT or AST  $> 3 \times$  ULN and total bilirubin level  $> 2 \times$  ULN or international normalized ratio  $> 1.5$



- d. ALT or AST  $>3 \times \text{ULN}$  with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>5\%$ )

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.

#### **4.3.3. Pharmacokinetic Sampling in Case of Patient Withdrawal**

Note: Withdrawal under the above criteria will be discussed by the investigator and the sponsor. For patients who withdraw from the study, every effort will be made to follow safety after withdrawal, including pharmacokinetic sampling when applicable, unless consent is withdrawn. For pharmacokinetics, the sample date and time will be recorded both on the source documentation and the CRF.

If a patient is withdrawn from the study or there is occurrence of a serious adverse event that in the judgement of the investigator would be best managed by immediate cessation of treatment, the possibility to excise the IMP depot should be discussed with the sponsor to draw on learnings of this procedure gained during pre-clinical studies. In this case, 2 consecutive pharmacokinetic samples will be obtained: 1 immediately before the excision procedure and 1 several hours after the procedure and prior to patient discharge. Additional pharmacokinetic samples may be obtained if judged to be required by the sponsor. The sample date and time as well as the date and time of the excision procedure will be recorded both on the source documentation and the CRF.

#### **4.4. Replacement of Patients**

The sponsor intends to follow up on a meaningful number of patients with an adequate exposure to TV-46000 and has committed to follow 100 patients for at least 1 year, who can be either patients rolling over from Study TV46000-CNS-30072 or new patients. The assumptions about the number of new patients to be enrolled into this study are based on the proportion of new patients who will not be eligible for randomization at the end of Stage 1 and the overall number and timing of withdrawals of the study patients enrolled during Stage 2. The sponsor will follow the recruitment and completion rates periodically against the original assumptions and warrants the right to increase the proportion of new patients in this study in case the assumptions are not met.

#### **4.5. Rescreening**

A patient who is screened but not enrolled, eg, because enrollment inclusion and exclusion criteria were not met or enrollment did not occur within the specified window, may be considered for screening again if, eg, there is a change in the patient's medical condition or a modification of study inclusion and exclusion criteria.

Patients may have individual parameters retested at the discretion of both the investigator and the sponsor.

Patients may be rescreened once if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator or if repeated values show normalization of the out-of-range values, but their initial screening period has expired.

If the patient is rescreened, an informed consent form (ICF) or assent form, as applicable, will need to be re-signed.

#### **4.6. Screening Failure**

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. For these patients, minimal information must be obtained, including but not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

## 5. TREATMENTS

### 5.1. Investigational Medicinal Products Used in the Study

IMPs are defined as the test IMP and placebo IMP.

#### 5.1.1. Test Investigational Medicinal Product

TV-46000 will be supplied as a ready-to-use, extended-release injectable product in a single-use 2-mL vial or as a 1 mL Luer lock prefilled syringe containing 50, 75, 100, 125, 150, 200, or 250 mg of risperidone. [REDACTED]

[REDACTED]

[REDACTED]

For COVID-19 updates, refer to [Appendix N](#).

[REDACTED]

##### 5.1.1.1. Starting Dose and Dose Levels

For new patients, TV-46000 will be administered in the abdomen (except as indicated below) by sc injection, at intervals of q1m or q2m, at a dose equivalent to the oral risperidone (2 to 5 mg/day) on which they were stabilized in Stage 1, per the conversion table below ([Table 3](#)) and per their assigned treatment arm. The maximal dose administered will be equivalent to an oral risperidone dose of 5 mg/day (adolescent patients will receive a maximal dose equivalent to oral risperidone 4 mg/day). As a precautionary measure, adolescent patients who will require a stabilization dose of more than 4 mg/day (oral risperidone) during the stabilization stage will not be randomized. Patients who would require a stabilization dose below 2 mg/day will not be randomized in the study.

Roll-over patients who were randomized to the q1m or q2m treatment arms in Study TV46000-CNS-30072 will continue to receive TV-46000 at the same frequency and dose. Patients randomized to the placebo arm in Study TV46000-CNS-30072 will be re-randomized to either the q1m or q2m arms and will receive TV-46000 at the dose equivalent to the oral dose on which they were stabilized in Stage 1 of Study TV46000-CNS-30072.

Several investigational centers may be selected by the sponsor (based on the sponsor's considerations, and the centers' capabilities and prior clinical experience with injectable medication) for injection of study drug into the back of the upper arm instead of the abdomen for all or some of the enrolled patients at these sites (approximately 20% of the study patient population).

The injection site that is chosen for an individual patient should remain consistent throughout the study. If the chosen site is the arm, the injection will be administered in an alternating manner between the right and the left arm. If the chosen site is the abdomen, the injection will be administered in an alternating manner to the right and to the left of the umbilicus. Further details will be provided in the Pharmacy Manual.

**Table 3: Conversion Table between Oral Risperidone and TV-46000 Doses**

Corresponding TV-46000 Dose	Oral Risperidone Dose			
	2 mg/day	3 mg/day	4 mg/day	5 mg/day (Adults Only)
at q1m	50 mg	75 mg	100 mg	125 mg
at q2m	100 mg	150 mg	200 mg	250 mg

q1m=every month; q2m=every 2 months.

#### 5.1.1.2. Dose Modification and Dose Stratification

The dose of test IMP will not be modified for a given patient during the study.

#### 5.1.2. Placebo Investigational Medicinal Product

TV-46000 Placebo is available as an extended-release injectable product [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Additional details about sc injection administration can be found in the Pharmacy Manual.

For COVID-19 updates, refer to [Appendix N](#).

**Table 4: Investigational Medicinal Products Used in the Study**

[REDACTED]	[REDACTED]	[REDACTED]
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Note: For COVID-19 updates, refer to [Appendix N](#).

## **5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs**

### **5.2.1. Storage and Security**

The investigator or designee must confirm appropriate temperature conditions have been maintained for all medicinal products received and any discrepancies must be reported and resolved before their use.

The IMPs (TV-46000 and TV-46000 Placebo) must be stored according to the storage conditions specified on the label and must be securely locked [REDACTED] and kept in the outer carton until use.

For COVID-19 updates, refer to [Appendix N](#).

### **5.2.2. Labeling**

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

### **5.2.3. Accountability**

Each IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and are used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs, and only authorized staff at each investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at each investigational center.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. All test or placebo IMP supplies (used, partially used, and unused) will be returned to the sponsor or its designee according to local and national regulations and the site's standard operating procedures (SOPs), following written authorization from the sponsor.

The sponsor's or designee's monitor will review all relevant drug-related information for accountability purposes prior to any drug destruction. Documented evidence of destruction should be made available to the sponsor and/or its designees. The investigator, pharmacist, or drug administrator must verify that no TV-46000 drug supplies remain in the study centers' possession at the end of the study.

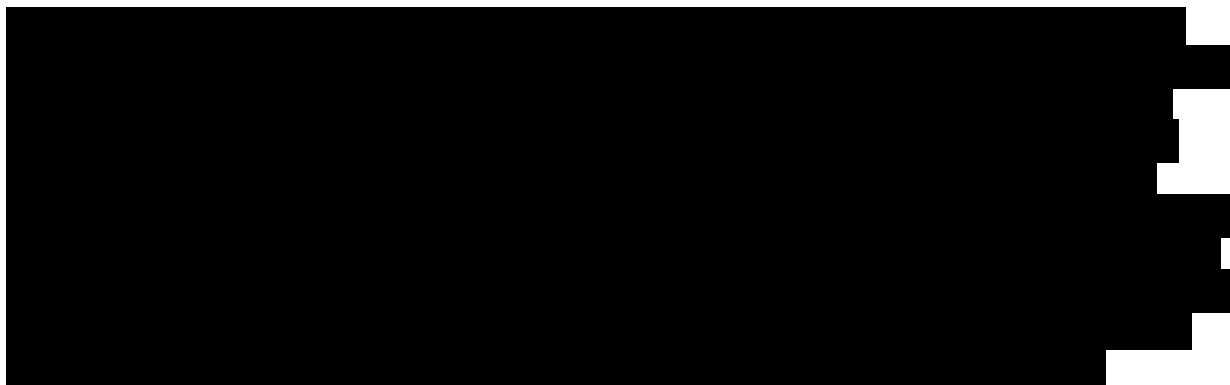
Further guidance and information are provided in the Pharmacy Manual.

For COVID-19 updates, refer to [Appendix N](#).

### **5.3. Justification for Investigational Medicinal Products**

#### **5.3.1. Justification for Dose of Test Investigational Medicinal Product**

The doses of randomized IMP to be evaluated in this double-blind study (50 to 125 mg q1m sc and 100 to 250 mg q2m sc) were selected on the basis of Study TV46000-SAD-10055 (see Section [1.2.2.1](#)).



Based on the pharmacokinetic performance and the safety profile of TV-46000 in Study TV46000-SAD-10055 and the PopPK model-derived simulations, it is expected that TV-46000 will provide sufficient coverage throughout 28 days (for q1m) and 56 days (for q2m) in 4 doses (50, 75, 100, and 125 mg and 100, 150, 200, and 250 mg, respectively) equivalent to 2, 3, 4, and 5 mg/day oral risperidone based on the total active moiety ([Table 3](#)). The maximal TV-46000 dose administered to adolescents will be equivalent to 4 mg/day oral risperidone.

#### **5.3.2. Justification for Use of Placebo Investigational Medicinal Product**

TV-46000 Placebo is administered in this study to patients in the TV-46000 q2m treatment group in order to maintain the blind. There is no placebo arm in this study.

### **5.4. Other Medicinal Products/Non-Investigational Medicinal Products**

Oral risperidone used for stabilization ([Table 5](#)) will be a commercial product supplied either via a hybrid approach (by the study center and centrally) or a completely centralized manner to allow 1 process for all sites and system integration. The brand name of the oral risperidone supplied will be recorded on the source documentation.

Note that oral risperidone is mandated for use in this study (for new patients); however, for the purposes of this study, it is not considered an IMP.

**Table 5: Other Medicinal Products Used in the Study**

Medicinal product name	Stabilization
Trade name and INN, if applicable, or company-assigned number	Risperidone
Formulation	Tablets, oral solution, or orally disintegrating tablets <sup>a</sup>
Unit dose strengths/dosage levels	Multiple strengths commercially available
Route of administration	Oral; self-administered by patient
Dosing instructions	2 to 5 mg/day
Packaging	Various (commercial product)
Manufacturer	Various (commercial product)

<sup>a</sup> The brand name of the oral risperidone supplied will be recorded on the source documentation.  
INN=international nonproprietary name.

## 5.5. Treatment after the End of the Study

In cases where the patient is withdrawn from this study, no further treatment is planned by the sponsor after the patient completes their participation in this study. In addition, continued access to IMP will not be provided to study participants once the study ends. Investigators should advise the study participants to return to the care of their primary physicians. Patients may be treated in the meantime per investigator judgment and instruction as applicable.

## 5.6. Restrictions

Patients will be required to comply with the following restrictions:

### 5.6.1. Activity

There are no specific restrictions in this study regarding normal daily activities, unless otherwise advised by the investigator.

### 5.6.2. Specific Beverages

Patients should not consume excessive amounts of alcoholic beverages, defined as more than 2 units per day (1 unit = 1/2 pint [8 ounces] of beer, 1 small glass [5 ounces] of wine, or 1 measure of spirits), during the course of the study, including the follow-up period. Patients should be advised regarding potential risk of drowsiness, dizziness, and other side effects of alcohol on risperidone treatment.

### 5.6.3. Blood Donation

Patients may not donate blood from 30 days prior to the first IMP administration until 6 months after the last IMP administration.



## 5.7. Prior and Concomitant Medication or Therapy

[REDACTED]

[REDACTED]

1 [REDACTED]

1 [REDACTED]

1 [REDACTED]

1 [REDACTED]

1 [REDACTED]

1 [REDACTED]

1 [REDACTED]

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#### **5.8. Procedures for Monitoring Patient Compliance**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study.

## 5.9. 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 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.

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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.

[REDACTED]

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.

For COVID-19 updates, refer to [Appendix N](#).

## **5.10. Maintenance of Randomization and Blinding**

### **5.10.1. Maintenance of Randomization**

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes.

### **5.10.2. Blinding and Unblinding**

Pharmacokinetic data will be assessed during the study.

For information about investigational site personnel who may be aware of IMP assignments, see Section [5.9](#). These individuals will not be involved in the conduct of any study procedures or assessments of any adverse events.

In cases of a serious adverse event or a pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code.

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

### **5.10.3. Data Monitoring Committee**

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

### **5.11. Total Blood Volume**

[REDACTED]

[REDACTED]

[REDACTED]

## **6. ASSESSMENT OF EFFICACY**

For each assessment, where applicable, every effort should be made to retain the same rater for each patient throughout the course of the study, except under exceptional circumstances.

For COVID-19 updates, refer to [Appendix N](#).

### **6.1. Assessments of Efficacy**

#### **6.1.1. Clinical Global Impression–Improvement (CGI-I)**

The CGI-I scale permits a global evaluation of the patient's overall improvement in symptoms. 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) ([Guy 1976a](#)).

The CGI-I will be administered by the investigator/trained rater at all in-clinic visits during the study (except for the screening and baseline visits). For new patients, CGI-I during Stage 1 will be relative to screening; CGI-I during Stage 2 will be relative to the baseline visit. For roll-over patients, the CGI-I during Stage 2 will be relative to the patient's baseline visit in Study TV46000-CNS-30072.

#### **6.1.2. Positive and Negative Syndrome Scale (PANSS)**

The PANSS ([Kay 1987](#)) is a 30-item instrument used in patients with schizophrenia to identify the presence and severity of psychopathology symptoms, the relationship of these symptoms to one another, and the global psychopathology. Each item is scored on a 7-point scale ranging from 1 (absent) to 7 (extreme). The positive symptom scale includes 7 items with a maximum score of 49; the negative symptom scale includes 7 items with a maximum score of 49; and the general psychopathology scale includes 16 items with a maximum score of 112.

The PANSS will be administered by the investigator at screening and all visits during the study.



### **6.2. Other Assessments**

#### **6.2.1. Structured Clinical Interview for DSM-5 (SCID-5)**

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

The SCID-5 can be used to ensure that the major DSM-5 diagnoses are systematically evaluated and that all the study patients have symptoms that meet the DSM-5 criteria for inclusion and exclusion, and to characterize a study population in terms of current and previous psychiatric diagnoses ([First 2015](#)).

### **6.2.2. Quality of Life Scales**

The quality of life scales used in this study will include the 2 measures described below.

#### **6.2.2.1. Schizophrenia Quality of Life Scale (SQLS)**

The Schizophrenia Quality of Life Scale (SQLS) will be administered to adult patients only at the time points specified in [Table 1](#) and [Table 2](#), and will be used to capture quality of life. The 33-item measure yields 3 subscale scores: psychosocial, motivation/energy, and symptoms/side effects ([Wilkinson 2000](#)). Higher scores on the scales indicate worse quality of life.

#### **6.2.2.2. 5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L)**

The 5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L) will be administered to adult patients only at the time points specified in [Table 1](#) and [Table 2](#), and is a standardized questionnaire that assesses overall state of health. The EQ-5D-5L consists of 2 parts. In Part 1, patients rate their health state in 5 domains (mobility, self-care, usual activities, pain/discomfort, and mood) using a scale of 1 to 5, where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. In Part 2, patients rate their health state on a 100-mm visual analog scale; a rating of 0 represents the worst imaginable health state, and a rating of 100 represents the best imaginable health state ([EuroQol Group 1990](#), [Rabin 2001](#)).

### **6.2.3. Drug Attitudes Inventory 10-item Version (DAI-10)**

The Drug Attitudes Inventory 10-item Version (DAI-10) will be administered to adult patients only at the time points specified in [Table 1](#) and [Table 2](#), and measures subjective responses and attitudes toward maintenance of antipsychotic drug therapy that may affect compliance. There are 2 versions: the DAI-10 and the DAI-30, which correlate very closely ( $r=0.93$ ). Only the shorter DAI-10 will be used in this study. The DAI-10 consists of 10 items covering 3 domains (subjective positive, subjective negative, and attitude toward medication), although only a single composite score is computed ([Hogan 1983](#), [Nielsen 2012](#)). A positive total score indicates a compliant response and a negative total score indicates a non-compliant response.

### **6.2.4. Personal and Social Performance Scale (PSP)**

The Personal and Social Performance Scale (PSP) will be administered to adult patients only at the time points specified in [Table 1](#) and [Table 2](#), and is a clinician-rated instrument that measures personal and social functioning in patients with schizophrenia ([Morosini 2000](#)). 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: 1) socially useful activities, 2) personal and social relationships, 3) self-care, and 4) disturbing and aggressive behaviors. Higher scores represent better personal and social functioning, with ratings from 91 to 100 indicating more than adequate functioning, while scores under 30 indicate functioning so poor that intensive supervision is required.

### **6.2.5. Healthcare Resource Utilization**

Healthcare resource utilization will be assessed for hospitalizations, emergency room (ER) visits, and outpatient visits (ie, not including protocol-mandated outpatient visits) at the time points



specified in [Table 1](#) and [Table 2](#). Hospitalizations will be assessed as the percentage of patients with hospitalizations over the past 4 weeks, the associated length of stay, and the number of hospitalizations among patients who were hospitalized. In addition, the percentage of patients with ER visits and their number of ER visits over the past 4 weeks and the percentage of patients with outpatient visits and their number of outpatient visits over the past 4 weeks will be evaluated at all study visits.

This should be completed by the site investigator/coordinator through patient interviews. Verification against medical records should be performed whenever possible. The family member or caregiver may also need to provide input.

#### **6.2.6. Clinical Global Impression of Severity (CGI-S)**

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) ([Guy 1976a](#)).

The CGI-S will be administered by the investigator/trained rater at all in-clinic visits.

## **7. ASSESSMENT OF SAFETY**

In this study, safety will be assessed by qualified study personnel by evaluating the reported adverse events, clinical laboratory test results, vital sign measurements, ECG findings, physical examination findings (including body weight measurements), use of concomitant medication, and local injection site tolerance. Additional assessments of safety of specific interest to the use of medicinal products in schizophrenia include assessments of suicidality, depression, and abnormal movements (eg, tardive dyskinesia, akathisia, and parkinsonism).

For COVID-19 updates, refer to [Appendix N](#).

### **7.1. Adverse Events**

#### **7.1.1. Definition of an Adverse Event**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the IMP. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant

(Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

Worsening of the disease under study, schizophrenia, will be assessed using PANSS and should be recorded as an adverse event only if the presentation or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

### **7.1.2. Recording and Reporting of Adverse Events**

For recording of adverse event, the study period is defined for each patient as the time period from signature of the ICF or assent form, as applicable, to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 120 days after the last dose of IMP. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP in this study is administered and until 120 days after the last dose of IMP.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events, the serious adverse event form must be completed, and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a healthcare professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in cases of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to the IMP and study procedures and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the Serious Adverse Event Management Plan (SMP).

### **7.1.3. Severity of an Adverse Event**

The severity of each adverse event must be recorded as one of the following:

**Mild:** No limitation of usual activities

**Moderate:** Some limitation of usual activities

**Severe:** Inability to carry out usual activities

#### 7.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP is characterized in [Table 6](#).

**Table 6: The Relationship of an Adverse Event to the Investigational Medicinal Product**

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	<p>The relationship of an adverse event may be considered “no reasonable possibility” if it is clearly due to extraneous causes or if at least 2 of the following apply:</p> <ul style="list-style-type: none"> <li>• It does not follow a reasonable temporal sequence from the administration of the IMP.</li> <li>• It could readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.</li> <li>• It does not follow a known pattern of response to the IMP.</li> <li>• It does not reappear or worsen when the IMP is re-administered.</li> </ul>
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	<p>The relationship of an adverse event may be considered “reasonable possibility” if at least 2 of the following apply:</p> <ul style="list-style-type: none"> <li>• It follows a reasonable temporal sequence from administration of the IMP.</li> <li>• It cannot be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.</li> <li>• It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists.</li> <li>• It follows a known pattern of response to the IMP.</li> </ul>

IMP=investigational medicinal product.

#### 7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the ICF or assent form, as applicable, to the end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

[REDACTED]

**7.1.5.1. Definition of a Serious Adverse Event**

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event  
Hospitalizations scheduled before the patient signed the ICF or assent form, as applicable, will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

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  $>3 \times$  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 nonserious adverse event.

**7.1.5.2. Expectedness**

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the RSI section of the current version of the IB for TV-46000. For the purpose of suspected unexpected serious adverse

reaction (SUSAR) reporting, the version of the RSI at the time of occurrence of the SUSAR applies.

The sponsor's Global Patient Safety and Pharmacovigilance (GPSP) team will determine the expectedness for all serious adverse events.

### **7.1.5.3. Reporting a Serious Adverse Event**

#### **7.1.5.3.1. Investigator Responsibility**

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event including seriousness criteria
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)
- the date of awareness about the event

Additional information includes the following:

- age and sex of patient
- date of first dose of IMP
- date of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness

- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP, study procedures, and to underlying disease.



Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities (CAs), Independent Ethics Committee/Institutional Review Boards (IEC/IRBs), and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

#### **7.1.5.3.2. Sponsor Responsibility**

If a serious unexpected adverse event is believed to be related to the IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of IMP and the appropriate CAs (and IEC/IRB, as appropriate).

In addition to notifying the investigators and CAs (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to IMP

### **7.1.6. Protocol-Defined Adverse Events of Special Interest**

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

### **7.1.7. Protocol Deviations Because of an Adverse Event**

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

## **7.2. Pregnancy**

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable, that occur during the study, or within at least 120 days after the last dose of study drug, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no protocol-related procedures have been applied.

All female patients (or female partners of men participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or a serious adverse event, as appropriate.

Since there is lack of data on human teratogenicity, genotoxicity, fetotoxicity, or spermatotoxicity for this IMP, female partners of men participating in the study who become pregnant will be asked to sign an ICF or assent form, as applicable.

If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.



### **7.3. Medication Error and Special Situations Related to the Investigational Medicinal Products**

Any administration of IMP that is not in accordance with the study protocol should be reported as a deviation in the patient's source documents, regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

### **7.4. Clinical Laboratory Tests**

All clinical laboratory test results outside the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of the IMP or medical treatment, or further diagnostic work-up per investigator's judgement. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

### Table 7: Clinical Laboratory Tests

Country	Year	Value
Algeria	2010	1.0
Algeria	2011	1.0
Algeria	2012	1.0
Algeria	2013	1.0
Algeria	2014	1.0
Algeria	2015	1.0
Algeria	2016	1.0
Algeria	2017	1.0
Algeria	2018	1.0
Algeria	2019	1.0
Algeria	2020	1.0
Algeria	2021	1.0
Algeria	2022	1.0
Algeria	2023	1.0
Algeria	2024	1.0
Algeria	2025	1.0
Algeria	2026	1.0
Algeria	2027	1.0
Algeria	2028	1.0
Algeria	2029	1.0
Algeria	2030	1.0
Algeria	2031	1.0
Algeria	2032	1.0
Algeria	2033	1.0
Algeria	2034	1.0
Algeria	2035	1.0
Algeria	2036	1.0
Algeria	2037	1.0
Algeria	2038	1.0
Algeria	2039	1.0
Algeria	2040	1.0
Algeria	2041	1.0
Algeria	2042	1.0
Algeria	2043	1.0
Algeria	2044	1.0
Algeria	2045	1.0
Algeria	2046	1.0
Algeria	2047	1.0
Algeria	2048	1.0
Algeria	2049	1.0
Algeria	2050	1.0
Algeria	2051	1.0
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Algeria	2061	1.0
Algeria	2062	1.0
Algeria	2063	1.0
Algeria	2064	1.0
Algeria	2065	1.0
Algeria	2066	1.0
Algeria	2067	1.0
Algeria	2068	1.0
Algeria	2069	1.0
Algeria	2070	1.0
Algeria	2071	1.0
Algeria	2072	1.0
Algeria	2073	1.0
Algeria	2074	1.0
Algeria	2075	1.0
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Algeria	2080	1.0
Algeria	2081	1.0
Algeria	2082	1.0
Algeria	2083	1.0
Algeria	2084	1.0
Algeria	2085	1.0
Algeria	2086	1.0
Algeria	2087	1.0
Algeria	2088	1.0
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Algeria	2100	1.0
Algeria	2101	1.0
Algeria	2102	1.0
Algeria	2103	1.0
Algeria	2104	1.0
Algeria	2105	1.0
Algeria	2106	1.0
Algeria	2107	1.0
Algeria	2108	1.0
Algeria	2109	1.0
Algeria	2110	1.0
Algeria	2111	1.0
Algeria	2112	1.0
Algeria	2113	1.0
Algeria	2114	1.0
Algeria	2115	1.0
Algeria	2116	1.0
Algeria	2117	1.0
Algeria	2118	1.0
Algeria	2119	1.0
Algeria	2120	1.0
Algeria	2121	1.0
Algeria	2122	1.0
Algeria	2123	1.0
Algeria	2124	1.0
Algeria	2125	1.0
Algeria	2126	1.0
Algeria	2127	1.0
Algeria	2128	1.0
Algeria	2129	1.0
Algeria	2130	1.0
Algeria	2131	1.0
Algeria	2132	1.0
Algeria	2133	1.0
Algeria	2134	1.0
Algeria	2135	1.0
Algeria	2136	1.0
Algeria	2137	1.0
Algeria	2138	1.0
Algeria	2139	1.0
Algeria	2140	1.0</

[REDACTED]

[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

Table 7.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 7.5. Physical Examinations

Full 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](#). 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 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.

## 7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, tympanic temperature, and pulse) will be measured at the time points detailed in [Table 1](#) and [Table 2](#). All vital sign results outside the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a supine or seated position for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and on the CRF as an adverse event and will be monitored as described in Section 7.1.2.

For COVID-19 updates, refer to [Appendix N](#).

## 7.7. Electrocardiography

A standard 12-lead ECG will be recorded at the time points detailed in [Table 1](#) and [Table 2](#). Triplicate measurements will be performed at screening and baseline, and single measurements will be performed at all other in-clinic visits where ECG recordings are taken. A qualified physician at a central diagnostic center will interpret the ECG.

All ECG results outside the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit [new patients]) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

For COVID-19 updates, refer to [Appendix N](#).

## **7.8. Assessment of Local Tolerability and Pain**

In cases where 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 below as applicable.

### **7.8.1. Erythema and Edema Assessment**

Scoring of erythema and edema will be done using 5-point scales:

#### **Erythema:**

- None = 0
- Very slight = 1
- Well defined = 2
- Moderate to severe = 3
- Severe = 4

#### **Edema:**

- None = 0
- Very slight = 1
- Slight = 2
- Moderate = 3
- Severe = 4

### **7.8.2. Induration and Nodule Assessment**

The presence and size (length and width) of any palpable induration/nodule at the injection site will be assessed and recorded. Scoring of nodules will be done using a 4-point scale:

- No induration/nodule = 0
- Discernible induration/small nodule <0.5 cm = 1
- Marked induration/medium size nodule of 0.5 to 1 cm = 2
- Severe induration/significant size nodule >1 cm = 3

### **7.8.3. Injection Pain Intensity Assessment**

In cases where an adverse event related to an injection site reaction is reported, the intensity of injection pain will be assessed by patients using an 11-point Numeric Pain Rating Scale (0 [no pain] to 10 [worst pain]) ([Williamson 2005](#)). Pain measurement will be evaluated during visits and telephone calls until resolution. The exact timing will be captured in the source documentation.

## **7.9. Assessment of Suicidality**

Risperidone is considered to be central nervous system-active. In addition, there is increased risk of suicide attempts in patients with schizophrenia or bipolar disorder. The sponsor considers it important to monitor for such events before and during this clinical study.

Risperidone is considered to be an atypical antipsychotic medicinal product. Although risperidone or other similar medicinal products in this class are not known to be associated with an increased risk of suicidal thinking or behavior when given to patients with schizophrenia, the sponsor considers it important to monitor for such events before and during this clinical study.

The study population should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing the test IMP in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with test IMP should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the C-SSRS and CGI-SS scales.

### **7.9.1. 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 ([Posner 2011](#)). There are required items that address suicidal ideation and potential additional items related to intensity of ideation and suicidal behavior if there are any positive responses to a required item. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

The minimum requirements determined by the scale author, Dr. Kelly Posner Gerstanhaber, MD, state that anyone can administer the C-SSRS for clinical trials, regardless of education level, as long as the administrator views the C-SSRS training video and gets a training certificate. Thus, the C-SSRS interview and rating will be performed by raters with appropriate prior clinical trial experience with C-SSRS administration, who meet the minimum requirements outlined by the scale author, after review and approval by the Teva clinical project physician or designee.

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.

### **7.9.2. Clinical Global Impression-Severity of Suicidality (CGI-SS)**

The CGI-SS scale provides an overall clinician-rated assessment of the risk of suicidality ([Lindenmayer 2003](#)). 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. In Stage 1, for new patients, Part 2 of the CGI-SS will be compared to screening. In Stage 2, for new patients, Part 2 of the CGI-SS will be compared to baseline; for roll-over patients, it will be compared to baseline of Study TV46000-CNS-30072.

## **7.10. Study-Specific Assessments of Safety**

### **7.10.1. Abnormal Involuntary Movement Scale (AIMS)**

The AIMS will be performed at the time points specified in [Table 1](#) and [Table 2](#). The AIMS scores the occurrence of tardive dyskinesia in patients receiving neuroleptic medications ([Guy 1976b](#)). 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.

### **7.10.2. Barnes Akathisia Rating Scale (BARS)**

The BARS will be performed at the time points specified in [Table 1](#) and [Table 2](#). The BARS is an instrument that assesses the severity of drug-induced akathisia ([Barnes 1989](#)). 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.

### **7.10.3. Simpson-Angus Scale (SAS)**

The SAS will be performed at the time points specified in [Table 1](#) and [Table 2](#). The SAS is a 10-item instrument for the assessment of neuroleptic-induced parkinsonism ([Simpson 1970](#)). 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.

### **7.10.4. Calgary Depression Scale for Schizophrenia (CDSS)**

The CDSS will be performed at the time points specified in [Table 1](#) and [Table 2](#). The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and EPS in schizophrenia ([Addington 1993](#)). This clinician-administered instrument consists of 9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe).

**7.11. Other Assessments**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]					
[REDACTED]					
[REDACTED]					
[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]					



### 8.1.

[illegible]

104

[REDACTED]

[REDACTED]

**8.2.**

[REDACTED]

[REDACTED]

### **8.3.      Assessment of Exploratory Biomarkers**

[REDACTED]

### **8.4.      Pharmacogenetics**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **9. STATISTICS**

This section describes the statistical analysis as foreseen at the time of planning the study. The changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

Note that for new patients, baseline or screening data from the current study (after signing the ICF or assent form, as applicable) will be used. For roll-over patients, unless otherwise specified, data from Study TV46000-CNS-30072 will be used as baseline.

### **9.1. 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.

### **9.2. Analysis Sets**

#### **9.2.1. 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 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.

#### **9.2.2. Safety Analysis Set**

The safety analysis set will include all patients who receive at least 1 dose of TV-46000 during this 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.

#### **9.2.3. 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.

#### **9.2.4. Pharmacokinetics Analysis Set**

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

**9.2.5. 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.

**9.2.6. Additional Analysis Sets**

Additional analysis sets will be defined in the statistical analysis plan.

**9.3. Data Handling Conventions**

For all variables, only the observed data from the patients will be used in the statistical analyses (ie, there is no plan to estimate missing data, unless otherwise specified). Ad hoc imputation for safety presentation may be conducted and will be detailed in the statistical analysis plan.

**9.4. Study Population**

The safety analysis set (Section 9.2.2) will be used for study population summaries and efficacy endpoints 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). Select summary tables will be presented using the ITT analysis set.

**9.4.1. Patient Disposition**

The numbers and percentages of new patients screened and enrolled in Stage 1 of this study; new patients who were enrolled in Stage 1 of this study but were not randomized for the double-blind maintenance stage (Stage 2) and their reason for not being randomized; all (new and roll-over) patients who were assigned treatment; all patients who were assigned treatment but not treated; all patients in the ITT, safety, and pharmacokinetics analysis sets; all patients who completed the study; and all patients who withdrew from the study will be summarized. Data from patients who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics.

**9.4.2. Demographic and Baseline Characteristics**

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

The ITT analysis set and the safety analysis set will be used for the summary, as applicable.

**9.5. Efficacy Analysis**

Efficacy analysis will be descriptive and will be described in the statistical analysis plan.

**9.5.1. Primary Endpoint**

As this is a safety-oriented study, there is no primary efficacy endpoint for this study [REDACTED]

### 9.5.2. Exploratory Endpoints

### 9.5.3. Planned Method of Analysis

[REDACTED]. Summaries will be presented by treatment group and by source of patients (new patients and roll-over patients).

#### 9.5.3.1. Primary Efficacy Analysis

There is no primary efficacy analysis for this study.

#### 9.5.3.2. Sensitivity Analysis

No sensitivity analyses are planned.

#### 9.5.3.3. Exploratory Efficacy Analysis

[REDACTED]  
For COVID-19 updates, refer to [Appendix N](#).

### 9.6. Multiple Comparisons and Multiplicity

No adjustments will be made for the preplanned multiple comparisons/endpoints.

### 9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section [9.2.2](#)).

Safety assessments and time points are provided in [Table 1](#) and [Table 2](#).

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class 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 the test IMP (ie, reasonable possibility [see Section [7.1.4](#)], defined as related or with missing relationship), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by source of patients (new patients and roll-over patients) and by treatment group as well as total. Summaries will include both incidence and person-time incidence (number of events divided by the total exposure to drug). A summary table of adverse events that includes adverse events from Study TV46000-CNS-30072 for roll-over patients will be presented as well. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory, ECG, and vital sign measurement data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

Descriptive statistics for allowed rescue medications (Section 5.7) will be presented by treatment group.

Safety outcomes, including changes from baseline in EPS scale scores (BARS, AIMS, and SAS) and CDSS during Stage 2, will be presented using descriptive statistics by treatment group.

The incidence of treatment-emergent adverse events related to EPS will be summarized by the following event categories: akathisia, dyskinesia, dystonia, parkinsonism, and tremor. The C-SSRS and CGI-SS will be used to assess the risk of suicide events during the study.

Descriptive statistics will be presented by treatment group.

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.

Selected safety data will also be presented by site of injection (abdomen versus arm) and by age group (adolescents [ages 13 through 17] and adults [18 years of age or older]), as applicable.

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. For categorical variables, patient counts and percentages will be provided.

Safety data collected in Stage 1 will also be summarized using descriptive statistics for new patients.

## **9.8. Tolerability Analysis**

In cases where 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 and summarized using descriptive statistics.

## **9.9. Pharmacokinetic Analysis**

Pharmacokinetic analysis will be descriptive and will be described in the statistical analysis plan.

## **9.10. Pharmacodynamic Analysis**

Not applicable.

## **9.11. Pharmacokinetic/Pharmacodynamic Analysis**

The results of the pharmacokinetic/pharmacodynamic analysis (if relevant data permit) will be presented in a separate report.

## **9.12. Biomarker and Pharmacogenetics Analysis**

Genetic variation in CYP2D6, and corresponding metabolizer status, will be assessed using descriptive statistics for an association with pharmacokinetic endpoints.

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

### **9.13. Planned Interim Analysis**

There will be a planned data cut with statistical output produced before the New Drug Application submission.

### **9.14. Reporting Deviations from the Statistical Plan**

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.



## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to [Appendix C](#) for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

For COVID-19 updates, refer to [Appendix N](#).

Refer to [Appendix K](#) for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

## 11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national CAs in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study and with the properties of the IMPs as described in the IB or PI.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with CAs.

See [Appendix D](#) for the ethics expectations of informed consent or assent, CAs and IEC/IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

## 12. DATA MANAGEMENT AND RECORD KEEPING

See [Appendix L](#) for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

### **13. FINANCING AND INSURANCE**

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete the FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

### **14. PUBLICATION POLICY**

See [Appendix M](#) for information regarding the publication policy.

## 15. REFERENCES

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## 16. SUMMARY OF CHANGES

### 16.1. Global Amendment 01 (Dated 03 June 2020)

The primary reason for this amendment is to clarify various aspects related to study conduct. For example, to avoid duplication and reduce patient burden, many of the baseline procedures and assessments outlined in this protocol related to the roll-over patients, will be performed in the end-of-treatment (EoT) visit of the TV46000-CNS-30072 study, and the results will be transferred to this study's clinical database. The volume of collected blood samples was corrected accordingly. Other modifications include the biomarker sample collection (which is now optional) and gender was removed as a stratification factor for randomization of new patients and roll-over patients previously assigned to placebo. In addition, various clarifications were made, eg, blinding of personnel to the IMP treatment assignments in the TV46000-CNS-30072 and TV46000-CNS-30078 studies (especially with regard to those also involved in the conduct of the TV46000-CNS-30072 study).

Also, since pin-pointing the onset of schizophrenia in adolescents is difficult, the time since the diagnosis of schizophrenia in the inclusion criterion for adolescents (aged 13-17) was reduced to 6 months to better align with the DSM-5 criteria, and the requirement for relapse in the last 24 months was removed due to the short time since diagnosis.

Administrative issues were added or corrected (eg, study name, sponsor address, personnel changes, etc), and other issues tracked during the course of the study were revised as applicable.

The 2 existing administrative letters (dated 22 July 2019 and 09 February 2020) that have not yet been incorporated into a protocol amendment, were implemented in this one.

Additionally, COVID-19 pandemic-related operational updates were added to the study as a new appendix ([Appendix N](#)). Administrative changes have been applied, including updating the Table of Contents.

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. [Table 2](#) (Study Procedures and Assessments) has also been revised to reflect the changes described below.

Minor grammatical and editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
<b>TITLE PAGE</b>		
NDA number: <del>Not applicable</del> <u>213586</u>	NDA number: 213586	New Drug Application number assigned. [Other sections affected by this change: Investigator Agreement and Coordinating Investigator Agreement]
See New wording column.	(The SHINE Study – <u>S</u> afety in <u>H</u> umans of TV-46000 sc <u>I</u> njection <u>E</u> valuation)	Addition of study name to protocol. [Other section affected by this change: Investigator Agreement and Coordinating Investigator Agreement]
Teva Branded Pharmaceutical Products R&D, Inc. <del>41 Moores Road</del> <u>145 Brandywine Parkway</u> <del>Frazer, Pennsylvania 19355</del> <u>West Chester, Pennsylvania 19380</u> United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, Pennsylvania 19380 United States of America	Per Administrative Letter 02, new address following relocation of sponsor offices.
<b>COORDINATING INVESTIGATOR AGREEMENT</b>		
See New wording column.	Executed signature pages are maintained within the Trial Master File.	Clarification.
<b>LIST OF ABBREVIATIONS</b>		
See New wording column	Added: COVID-19 = Coronavirus disease 2019 TC = telephone call/teleconference VC = videoconference	Newly-introduced abbreviations
<b>1. INTRODUCTION AND BACKGROUND</b>		
<b>1.1. Introduction</b>		
... TV-46000 incorporates risperidone and 2 copolymers, specifically poly(D,L-lactide)-co-poly(ethylene glycol)-co-	... TV-46000 incorporates risperidone and 2 copolymers, specifically poly(D,L-lactide)-co-poly(ethylene glycol)-co-	Clarification and simplification.

Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
poly(D,L-lactide) and methoxy-poly(ethylene glycol)- <i>co</i> -poly(D,L-lactide), dissolved in DMSO. <del>Exposure to aqueous environments causes the formulation to gel.</del> Therefore, after sc administration, the q1m and q2m products form a depot under the skin <del>due to the insolubility of the copolymers in an aqueous environment. The copolymers are designed to degrade by hydrolysis, ultimately leading to the resorption of the depot at the injection site.</del> The depot is expected to be fully degraded following the complete release of the drug substance. ...	poly(D,L-lactide) and methoxy-poly(ethylene glycol)- <i>co</i> -poly(D,L-lactide), dissolved in DMSO. Therefore, after sc administration, the q1m and q2m products form a depot under the skin. The depot is expected to be fully degraded following the complete release of the drug substance. ...	
<b>3. STUDY DESIGN</b>		
<b>3.1. General Study Design and Study Schematic Diagram</b>		
<b>Screening:</b> These patients will undergo screening procedures/assessments within 4 weeks before the start of Stage 1. <del>They</del> <u>Adult patients (aged 18-65)</u> should have had a diagnosis of schizophrenia for >1 year, <u>and adolescent patients (aged 13-17) should have had a diagnosis of schizophrenia for &gt;6 months</u> (diagnosis must be reconfirmed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition [DSM-5] [SCID-5]), and have been generally responsive to antipsychotics in the past year based on discussions with family members or healthcare professionals. <del>Patients</del> <u>Adult patients</u> should also have had ≥1 episode of relapse in the last 24 months. Patients will provide informed consent or assent, as applicable, at the screening visit, before any study-related procedures or assessments are performed.	<b>Screening:</b> These patients will undergo screening procedures/assessments within 4 weeks before the start of Stage 1. Adult patients (aged 18-65) should have had a diagnosis of schizophrenia for >1 year, and adolescent patients (aged 13-17) should have had a diagnosis of schizophrenia for >6 months (diagnosis must be reconfirmed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition [DSM-5] [SCID-5]), and have been generally responsive to antipsychotics in the past year based on discussions with family members or healthcare professionals. Adult patients should also have had ≥1 episode of relapse in the last 24 months. Patients will provide informed consent or assent, as applicable, at the screening visit, before any study-related procedures or assessments are performed.	Clarification following revision of adolescent inclusion criterion.
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. <u>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 (see Table 2 and Appendix B, Section 3).</u>	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 (see Table 2 and Appendix B, Section 3).	Clarification.  Cross-references to relevant protocol sections added.
The study duration will be approximately <del>22</del> <u>25</u> months, from	The study duration will be approximately 25 months, from	Correction due to updated

Original text with changes shown	New wording	Reason/Justification for change
Quarter 1 (Q1) 2019 to <del>Quarter 4</del> <u>Quarter 1 (Q1) 2021</u> .	Quarter 1 (Q1) 2019 to Quarter 1 (Q1) 2021.	timeline projections.
<b>3.2. Planned Number of Patients and Countries</b>		
The study is planned to be conducted in the United States (US), <del>Canada, and</del> Bulgaria, <del>and France (and possibly other countries as well)</del> in approximately 100 investigational centers (new centers and those that participated in Study TV46000-CNS-30072). The study is expected to start in Q1 2019 and last until approximately <del>Q4 2020</del> <u>Q1 2021</u> .	The study is planned to be conducted in the United States (US) and Bulgaria in approximately 100 investigational centers (new centers and those that participated in Study TV46000-CNS-30072). The study is expected to start in Q1 2019 and last until approximately Q1 2021.	Updated study countries and timelines.
<b>3.5. Schedule of Study Procedures and Assessments</b>		
<b>Table 2: Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – For New and Roll-Over Patients – Baseline, Double-Blind Maintenance Stage (Stage 2), End of Treatment, and Follow-Up</b>		
See New wording column.	h. For roll-over patients, this procedure will be performed as part of the TV46000-CNS-30072 EoT visit, and the results will be transferred to this study's clinical database.	Newly-added footnote for clarification.  Subsequent footnotes were re-labeled.
See New wording column.	The footnote was added for clarification to the X denoting the 30078 baseline visit for the following procedures: <ul style="list-style-type: none"> <li>• clinical laboratory tests (serum chemistry, hematology, and urinalysis)</li> <li>• urine drug screen</li> <li>• inquiry of concomitant medication</li> <li>• full physical examination</li> <li>• vital sign measurements</li> <li>• urine <math>\beta</math>-HCG tests (for women of childbearing potential)</li> <li>• PANSS</li> <li>• CGI-S</li> <li>• CGI-SS</li> <li>• AIMS</li> <li>• BARS</li> <li>• SAS</li> <li>• C-SSRS</li> <li>• PSP (for adult patients only)</li> </ul>	To avoid duplication and reduce patient burden, some procedures for roll-over patients will be performed as part of the EoT visit in the TV46000-CNS-30072 study.



Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
	<ul style="list-style-type: none"> <li>• SQLS (<b>for adult patients only</b>)</li> <li>• EQ-5D-5L (<b>for adult patients only</b>)</li> <li>• CDSS</li> <li>• healthcare resource utilization</li> <li>• DAI-10 (<b>for adult patients only</b>)</li> <li>• inquiry about adverse events (including serious adverse event reporting and injection site-related events including pain)</li> <li>• inquiry about alcohol consumption and illicit drug use since previous visit</li> </ul>	
s. t. For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, <u>unless the patient declines testing or local regulations prohibit testing.</u>	t. For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.	PGx sample collection is now optional and not mandatory.  Other sections affected by this change: Appendix B.
†. u. Blood samples for biomarker analyses will be collected as follows: 6 mL for serum, 6 mL for plasma, and 2.5 mL for PAXgene RNA, <u>unless the patient declines testing or local regulations prohibit testing.</u>	u. Blood samples for biomarker analyses will be collected as follows: 6 mL for serum, 6 mL for plasma, and 2.5 mL for PAXgene RNA, unless the patient declines testing or local regulations prohibit testing.	Biomarker sample collection is now optional and not mandatory.
<b>4. SELECTION AND WITHDRAWAL OF PATIENTS</b>		
<b>4.1.2. New Patients (Not Rolling Over from the Pivotal Efficacy Study TV46000-CNS-30072)</b>		
a. [Revision 01] The patient is an adult (age 18-65) and has a diagnosis of schizophrenia according to the DSM-5 for >1 year (diagnosis must be reconfirmed by SCID-5) and ≥1 episode of relapse in the last 24 months, <b>OR</b> the patient is an adolescent (age 13-17) with a diagnosis of schizophrenia according to the DSM-5 for > 6 months (diagnosis must be reconfirmed by SCID-5).	a. [Revision 01] The patient is an adult (age 18-65) and has a diagnosis of schizophrenia according to the DSM-5 for >1 year (diagnosis must be reconfirmed by SCID-5) and ≥1 episode of relapse in the last 24 months, <b>OR</b> the patient is an adolescent (age 13-17) with a diagnosis of schizophrenia according to the DSM-5 for > 6 months (diagnosis must be reconfirmed by SCID-5).	Adolescent inclusion criterion was revised to better align with the DSM-5, and the requirement for relapse was removed due the short time since diagnosis.
<b>5. TREATMENTS</b>		
<b>5.7. Prior and Concomitant Medication or Therapy</b>		
In general, <del>a</del> Antidepressants, antipsychotics (other than study drug), and mood stabilizers will not be permitted as concomitant medications. However, <u>some</u> antidepressants and mood	In general, antidepressants, antipsychotics (other than study drug), and mood stabilizers will not be permitted as concomitant medications. However, some antidepressants and mood	Clarification that exceptions are allowed for some

Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
stabilizers (including the CYP2D6 inhibitors fluoxetine, paroxetine, and duloxetine) will be permitted if the patient is on a stable dose for at least 3 months prior to screening.	stabilizers (including the CYP2D6 inhibitors fluoxetine, paroxetine, and duloxetine) will be permitted if the patient is on a stable dose for at least 3 months prior to screening.	antidepressants under the conditions listed.
<b>5.9. Randomization and Blinding</b>		
<b>New patients</b> 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 <del>gender (male or female) and</del> the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg/day).	<b>New patients</b> 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).	Gender was removed as a stratification factor for randomization.
<b>Roll-over patients who were assigned to placebo during Study TV46000-CNS-30072</b> 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 <del>gender (male or female) and</del> the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg/day).	<b>Roll-over patients who were assigned to placebo during Study TV46000-CNS-30072</b> 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).	Gender was removed as a stratification factor for randomization.
... 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 <u>new patients in Study TV46000-CNS-30072 and</u> during the course of this study. <u>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 TV46000-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.</u> ...	... 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 TV46000-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. ...	Correction per Admin Letter 02 (dated Feb 2020).  Clarification regarding unblinding of study personnel in the TV46000-CNS-30072 and TV46000-CNS-30078 studies.

Original text with changes shown	New wording	Reason/Justification for change
<b>5.11. Total Blood Volume (Other sections affected by this change: Appendix H)</b>		
<p>The total blood volume to be collected for each patient in this study is variable, since the duration of participation will be up to either approximately 80 weeks in duration (for new patients) or 64 weeks in duration (for roll-over patients). The maximum total blood volume to be collected in this study is approximately 320 mL for each new patient and approximately <del>298</del> <u>277</u> mL for each roll-over patient (including the ET/EoT visit and assuming that the patient completes the follow-up visits).</p> <p>Up to 3 additional samples will be collected from adolescent patients for pharmacokinetic analysis (see Section 8.1). These additional pharmacokinetic samples will be taken from new adolescent patients or adolescent roll-over patients from whom additional pharmacokinetic blood samples were not obtained during Study TV46000-CNS-30072. Therefore, the maximum total blood volume to be collected is approximately 332 mL for each new adolescent patient and approximately <del>340</del> <u>289</u> mL for each roll-over adolescent patient.</p>	<p>The total blood volume to be collected for each patient in this study is variable, since the duration of participation will be up to either approximately 80 weeks in duration (for new patients) or 64 weeks in duration (for roll-over patients). The maximum total blood volume to be collected in this study is approximately 320 mL for each new patient and approximately 277 mL for each roll-over patient (including the ET/EoT visit and assuming that the patient completes the follow-up visits).</p> <p>Up to 3 additional samples will be collected from adolescent patients for pharmacokinetic analysis (see Section <u>8.1</u>). These additional pharmacokinetic samples will be taken from new adolescent patients or adolescent roll-over patients from whom additional pharmacokinetic blood samples were not obtained during Study TV46000-CNS-30072. Therefore, the maximum total blood volume to be collected is approximately 332 mL for each new adolescent patient and approximately 289 mL for each roll-over adolescent patient.</p>	Correction of blood volume for roll-over patients since, to avoid duplication, some procedures will be performed as part of the EoT visit in the TV46000-CNS-30072 study.
<b>6. ASSESSMENT OF EFFICACY</b>		
<b>6.1.1. Clinical Global Impression - Improvement</b>		
The CGI-I will be administered by the investigator/trained rater at all <u>in-clinic</u> visits during the study (except for the screening and baseline visits).	The CGI-I will be administered by the investigator/trained rater at all in-clinic visits during the study (except for the screening and baseline visits).	Clarification.
<b>7. ASSESSMENT OF SAFETY</b>		
<b>7.4.2.2. Human Chorionic Gonadotropin Tests</b>		
<p>A serum beta human chorionic gonadotropin (<math>\beta</math>-HCG) test will be performed for all women of child bearing potential at screening (new patients only), baseline, and the follow-up visits (see Table 1 and Table 2). At baseline, both a serum and a urine <math>\beta</math>-HCG test will be performed <u>for new and roll-over patients</u>.</p> <p>...</p>	<p>A serum beta human chorionic gonadotropin (<math>\beta</math>-HCG) test will be performed for all women of child bearing potential at screening (new patients only), baseline, and the follow-up visits (see Table 1 and Table 2). At baseline, both a serum and a urine <math>\beta</math>-HCG test will be performed for new and roll-over patients.</p> <p>...</p>	Clarification.
<b>7.11. Other Assessments</b>		
The unblinded nurses who administer study drug to patients will	The unblinded nurses who administer study drug to patients will	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
complete the following set of questions after drug administration (for new patients only) in order to assess the ease of administration when using the prefilled syringes. For each patient, this set of questions (Table 8) will be completed only for the first 3 injections. <u>The responses will only be captured in the site's source documentation, not in the clinical database.</u> ...	complete the following set of questions after drug administration (for new patients only) in order to assess the ease of administration when using the prefilled syringes. For each patient, this set of questions (Table 8) will be completed only for the first 3 injections. The responses will only be captured in the site's source documentation, not in the clinical database. ...	
<b>8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS/BIOMARKERS/PHARMACOGENOMICS</b>		
<b>8.3. Assessment of Exploratory Biomarkers</b>		
<b>8.4. Pharmacogenetics</b>		
... For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, <u>unless the patient declines testing or local regulations prohibit testing.</u>	... For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.	Collection of PGx samples is now optional for new and roll-over patients.
<b>9. STATISTICS</b>		
<b>9.2.5. Enrolled Patients Set</b>		
See New wording column.	<b>9.2.5. Enrolled Patients Set</b> 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.	This definition was added for consistency with the TV46000-CNS-30072 protocol.
<b>APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS</b>		
<b>Sponsor's Authorized Representative</b> [REDACTED] Specialty Clinical Development	<b>Sponsor's Authorized Representative</b> [REDACTED] Specialty Clinical Development	Updated to reflect change of responsibilities at Teva.  Other sections affected by this change: Sponsor

Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
Teva Branded Pharmaceutical Products R&D, Inc. Tel: + [REDACTED] Cell: + [REDACTED] Email: [REDACTED]	Teva Branded Pharmaceutical Products R&D, Inc. Tel: + [REDACTED] Cell: + [REDACTED] Email: [REDACTED]	Protocol Approval page.
<b>Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study</b> [REDACTED] Teva Branded Pharmaceutical Products R&D, Inc. Tel: + [REDACTED] Cell: + [REDACTED] Email: [REDACTED]	<b>Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study</b> [REDACTED] Teva Branded Pharmaceutical Products R&D, Inc. Tel: + [REDACTED] Cell: + [REDACTED] Email: [REDACTED]	Updated to reflect change of responsibilities at Teva.
<b>Medical Monitors:</b> [REDACTED] ICON PLC Mobile: [REDACTED] Email: [REDACTED] <b><u>Back up: Lead Medical Monitor (MM) and Regional MM for Bulgaria:</u></b> [REDACTED] ICON PLC Tel: + [REDACTED] Mobile: [REDACTED] E-Mail: [REDACTED] <b>Regional MM for US:</b> [REDACTED] ICON PLC External Tel: [REDACTED] Mobile: [REDACTED] Email: [REDACTED] <b>MM General E-Mail:</b> STUDY-MA-DL-0075-0112-MedicalReview@iconplc.com	<b><u>Medical Monitors:</u></b> <b><u>Lead Medical Monitor (MM) and Regional MM for Bulgaria:</u></b> [REDACTED] ICON PLC Tel: + [REDACTED] Mobile: + [REDACTED] E-Mail: [REDACTED] <b>Regional MM for US:</b> [REDACTED] ICON PLC External Tel: [REDACTED] Mobile: [REDACTED] Email: [REDACTED] <b><u>MM General E-Mail:</u></b> STUDY-MA-DL-0075-0112-MedicalReview@iconplc.com	Updated due to change of responsibilities.  General email added.

Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
<b>Rater Training for Clinical Scales and Utilization Measures</b> <del>Bracket-Signant Health (formerly Bracket)</del> 575 E. Swedesford Road, Ste 200 Wayne, PA 19087 United States	<b>Rater Training for Clinical Scales and Utilization Measures</b> Signant Health (formerly Bracket) 575 E. Swedesford Road, Ste 200 Wayne, PA 19087 United States	Update of vendor name following the merge between Bracket and CRF Health. Other contact information remains unchanged.
<b>Bioassay and Pharmacokinetic Sample Analysis</b> <del>Please refer to the study Trial Master File.</del> Teva Pharmaceutical Works P. Ltd. Co. (TPW) Bioanalytical Laboratory Pallagi St. 13 Debrecen 4042 Hungary	<b>Bioassay and Pharmacokinetic Sample Analysis</b> Teva Pharmaceutical Works P. Ltd. Co. (TPW) Bioanalytical Laboratory Pallagi St. 13 Debrecen 4042 Hungary	Updated with the details of the laboratory that will perform the analysis.
<b>APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT</b>		
The following procedures will be performed at Visit 6 <u>for new and roll-over patients, unless otherwise specified.</u> <b>Note: For roll-over patients, the procedures marked with an asterisk (*) 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.</b>	The following procedures will be performed at Visit 6 for new and roll-over patients, <b>unless otherwise specified.</b> <b>Note: For roll-over patients, the procedures marked with an asterisk (*) 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.</b>	To avoid duplication and to reduce patient burden, some procedures will be performed as part of the EoT visit in the TV46000-CNS-30072 study.
See new wording column	The following procedures were marked with an asterisk: <ul style="list-style-type: none"> <li>clinical laboratory tests (serum chemistry, hematology, and urinalysis)</li> <li>urine drug screen</li> <li>inquiry of concomitant medication</li> <li>full physical examination (including weight; <b>height to be measured for adolescent roll-over patients only</b>)</li> <li>vital sign measurements</li> <li>urine <math>\beta</math>-HCG tests (for women of childbearing potential)</li> <li>PANSS</li> <li>CGI-S</li> <li>CGI-SS</li> <li>AIMS</li> <li>BARS</li> <li>SAS</li> </ul>	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
	<ul style="list-style-type: none"> <li>• C-SSRS</li> <li>• PSP (<b>for adult patients only</b>)</li> <li>• SQLS (<b>for adult patients only</b>)</li> <li>• EQ-5D-5L (<b>for adult patients only</b>)</li> <li>• CDSS</li> <li>• healthcare resource utilization</li> <li>• DAI-10 (<b>for adult patients only</b>)</li> <li>• inquiry about adverse events (including serious adverse event reporting and injection site-related events including pain)</li> <li>• inquiry about alcohol consumption and illicit drug use since previous visit</li> </ul>	
<ul style="list-style-type: none"> <li>• blood samples for biomarker analysis - <u>unless the patient declines testing or local regulations prohibit testing</u></li> </ul>	<ul style="list-style-type: none"> <li>• blood samples for biomarker analysis - unless the patient declines testing or local regulations prohibit testing</li> </ul>	<p>Biomarker sample collection is now optional and not mandatory.</p> <p>Updated for all relevant time points in the appendix.</p>
See New wording column.	<p>Unscheduled Visits:</p> <p>...</p> <p>In addition, to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether the aforementioned procedures (which are currently marked in Table 1 and Table 2 as mandatory) actually need to be performed during the unscheduled visit in the case that:</p> <p>(i) the unscheduled visit is one of multiple in-clinic visits, that are deemed necessary in close proximity (2 or more visits within 1 week), <b>and</b></p> <p>(ii) when the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event or impending/current relapse), and <b>not</b> due to a potential relapse or a change in the patient's medical status per clinical judgement. Notwithstanding, it is hereby emphasized that the above refers <b>only</b> to unscheduled visits, and not to any other scheduled in-</p>	<p>Clarification regarding procedures to be performed during unscheduled visits, per Letter of Clarification 01.</p>

Original text with changes shown	New wording	Reason/Justification for change
	clinic visits or telephone contacts.	
<b>APPENDIX G. LIST OF PROHIBITED MEDICATIONS (Other sections affected by this change: Section 5.7)</b>		
... In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-OH risperidone, may be associated with a significant drug interaction with risperidone, or may pose a significant risk to patients' participation in the study ( <u>eg, chloroquine, which is a QTc prolongator</u> ) are prohibited.	... In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-OH risperidone, may be associated with a significant drug interaction with risperidone, or may pose a significant risk to patients' participation in the study (eg, chloroquine, which is a QTc prolongator) are prohibited.	Clarification due to COVID-19 pandemic.
<b>APPENDIX H. TOTAL BLOOD VOLUME</b>		
See New wording column.	Table of Maximum Total Blood Volumes for Roll-Over Patients has been revised to reflect the changes described below: <ul style="list-style-type: none"> <li>• The number of clinical laboratory samples was updated from 10 to 9, and the total blood volume for these samples was updated from 70 mL to 63 mL;</li> <li>• The number of biomarkers samples was updated from 10 to 9, and the total blood volume for these samples was updated from 145 mL to 130.5 mL;</li> <li>• Total number of samples in the study was updated from 42 to 40;</li> <li>• Maximum total blood volume collected in the study for adults patients was updated from 298 mL to 277mL;</li> <li>• Maximum total blood volume collected in the study for adolescents was updated from 310 mL to 289 mL;</li> </ul>	Correction of blood volume for roll-over patients since, to avoid duplication, some procedures will be performed as part of the EoT visit in the 30072 study.
d. Biomarker blood samples will be collected as follows: 6 mL each for plasma and serum, and 2.5 mL for RNA (PAXgene), <u>unless the patient declines testing or local regulations prohibit testing.</u>	d. Biomarker blood samples will be collected as follows: 6 mL each for plasma and serum, and 2.5 mL for RNA (PAXgene), unless the patient declines testing or local regulations prohibit testing.	Collection of biomarker samples is now optional for new and roll-over patients.
<b>APPENDIX I. EXPLORATORY BIOMARKERS SAMPLES</b>		



Clinical Study Protocol with Amendment 01

Original text with changes shown	New wording	Reason/Justification for change
<b>APPENDIX J. PHARMACOGENETIC ASSESSMENTS</b>		
For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, <u>unless the patient declines testing or local regulations prohibit testing.</u>	For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.	Collection of PGx samples is now optional for new and roll-over patients.
<b>APPENDIX N. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19</b>		
New appendix and text.	Additional text too numerous to include in this table; refer to Appendix N of this protocol.	Created to manage study conduct during the COVID-19 pandemic.
<b>Section 3.1. General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments; Section 5.1.1. Test Investigational Medicinal Product; Section 5.1.2. Placebo Investigational Medicinal Product; Table 4. Investigational Medicinal Products Used in the Study; Section 5.2.1. Storage and Security; Section 5.2.3. Accountability; Section 5.9. Randomization and Blinding; Section 6. Assessment of Efficacy; Section 7. Assessment of Safety; Section 7.4. Clinical Laboratory Tests; Section 7.6. Vital Signs; Section 7.7. Electrocardiography; Section 8.1. Pharmacokinetic Assessment; Section 9.5.3.3. Exploratory Efficacy Analysis; Section 10. Quality Control and Quality Assurance; Appendix C. Quality Control and Quality Assurance; Appendix F. Lost to Follow-Up</b>		
See New wording column.	For COVID-19 updates, refer to Appendix N.	Updated sections to cross-reference the addition of Appendix N.

## 16.2. Administrative Letter 02 (Dated 09 February 2020)



### ADMINISTRATIVE LETTER 02

Study number: TV46000-CNS-30078

Clinical Study Protocol

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

Dated 29 January 2019

IND number: 124384; EudraCT number: 2019-000063-24

09 February 2020

Dear Investigator:

The purpose of this letter is to notify you regarding a few administrative issues related to the study, and to correct and clarify a statement in the protocol pertaining to unblinding of study personnel and delegates.

#### **a. Appointment of New Clinical Study Physician**

[REDACTED] was the clinical study physician (CSP) and served as the Sponsor's Medical Expert for the study since its initiation in 2019. Following a change in responsibilities at Teva, he was appointed as Vice President, Therapeutic Area Head of Neurology and Psychiatry instead of [REDACTED], PhD (see Appendix A of the protocol). However, he continued to serve concomitantly as the medical expert and contact point for the study until another physician was chosen to replace him in this capacity.

I recently joined the study team and replaced [REDACTED] as the CSP. My contact details are provided below:

[REDACTED]

Teva Branded Pharmaceutical Products R&D, Inc.

[REDACTED]

#### **b. Addition of New Study Name**

Following the issuance of the protocol, an official name was chosen for this clinical study:

The **SHINE** Study – **S**afety in **H**umans of TV-46000 sc **IN**jection **E**valuation (TV46000-CNS-30078)

This name will be used hereinafter in formal communications in conjunction with the study number.



**c. Correction of Typographical Error in Protocol**

In the synopsis and in Section 5.9 of the protocol, it is stated that "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 patients in ~~Study TV46000-CNS-30072 and~~ during the course of this study."

The sponsor hereby clarifies that the text shown in strikethrough should be deleted. Namely, the sponsor's clinical personnel and delegates are blinded to the identity and dosing regimens of the IMPs received in the TV46000-CNS-30072 clinical study, but not in this study.

**d. Relocation of Teva Offices in Pennsylvania**

The Teva offices in Pennsylvania, United States (US) have moved from Frazer to their new location in West Chester. The new address is provided in the footer of this letter.

These changes will be incorporated into the protocol during the next amendment, as applicable.

Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

[Redacted signature block]

Sincerely,

[Redacted signature block]

Teva Branded Pharmaceutical Products R&D, Inc.

Cc: [Redacted] Study File.

**16.3. Letter of Clarification 01 (Dated 22 July 2019)****LETTER OF CLARIFICATION 01**

Study number: TV46000-CNS-30078

Clinical Study Protocol

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

(The SHINE Study – Safety in Humans of TV-46000 sc Injection Evaluation)

Dated 29 January 2019

IND number: 124384; EudraCT number: 2019-000063-24

22 July 2019

Dear Investigator:

The purpose of this letter is to clarify and provide guidance to the investigator and site staff regarding unscheduled visits and conduct of various procedures and assessments during these visits.

The sub-section titled "Unscheduled Visits" in Appendix B of the protocol currently states that the procedures performed during unscheduled visits will include the following:

- inquiry of concomitant medication
- vital sign measurements
- PANSS
- C-SSRS
- blood samples for plasma drug concentration
- adverse event inquiry (including serious adverse event reporting and injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit

These assessments are marked with an "X" in Table 1 and Table 2 of the protocol (besides the pharmacokinetic sample, which is marked only in Table 2). In addition, as stated in the appendix and in the corresponding table footnotes, other procedures may be performed at the discretion of the investigator.

To reduce patient burden and to avoid unnecessary data collection, the sponsor hereby clarifies that the investigator will also have discretion in determining whether procedures, which are currently marked as mandatory **during unscheduled visits**, actually need to be performed in the case that:



- (i) the unscheduled visit is one of multiple in-clinic visits, that are deemed necessary in close proximity (2 or more visits within 1 week), **and**
- (ii) when the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event or impending/current relapse), and **not** due to a potential relapse or a change in the patient's medical status per clinical judgement.

Notwithstanding, the sponsor hereby emphasizes that the above refers **only** to unscheduled visits, and not to any other scheduled in-clinic visits or telephone contacts.

This change is **not considered substantial** and will be incorporated into the protocol during the next amendment, as applicable.

Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement as applicable.

Please feel free to contact the ICON Medical Monitor, [REDACTED]

[REDACTED] if you have any questions or concerns regarding this letter.

Sincerely, [REDACTED]

Teva Branded Pharmaceutical Products R&D Inc.

Cc: [REDACTED] Study File.

**APPENDIX A. CLINICAL LABORATORIES AND OTHER  
DEPARTMENTS AND INSTITUTIONS**

<b>Sponsor's Authorized Representative</b>	<div>[REDACTED]</div> <div>Teva Branded Pharmaceutical Products R&amp;D, Inc.</div> <div>[REDACTED]</div>
<b>Legal Representative of the Sponsor in the European Union</b>	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
<b>Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study</b>	<div>[REDACTED]</div> <div>Teva Branded Pharmaceutical Products R&amp;D, Inc.</div> <div>[REDACTED]</div>
<b>Coordinating Investigator</b>	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
<b>Medical Monitors</b>	<b><u>Lead Medical Monitor (MM) and Regional MM for Bulgaria:</u></b> <div>[REDACTED]</div> <b><u>Regional MM for US:</u></b> <div>[REDACTED]</div> <b><u>MM General E-Mail:</u></b> <div>[REDACTED]</div>

<b>Sponsor's Representative of Global Patient Safety and Pharmacovigilance</b> <b>For serious adverse events:</b> Send by email to the local safety officer/contract research organization. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	<div style="background-color: black; width: 100px; height: 20px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 150px; height: 20px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 100px; height: 20px; margin-bottom: 5px;"></div> Teva Pharmaceutical Industries, Ltd. <div style="background-color: black; width: 100px; height: 20px; margin-bottom: 5px;"></div>
<b>Contract Research Organization</b>	ICON Clinical Research LLC 2100 Pennbrook Parkway North Wales, PA 19454 United States
<b>Central Clinical Laboratory</b>	ICON Clinical Research Ltd South County Business Park Leopardstown, Dublin 18 D18 X5R3 Ireland
<b>Rater Training for Clinical Scales and Utilization Measures</b>	Signant Health (formerly Bracket) 575 E. Swedesford Road, Ste 200 Wayne, PA 19087 United States
<b>Electronic Data Capture</b>	ICON Clinical Research LLC 2100 Pennbrook Parkway North Wales, PA 19454 United States
<b>Central Electrocardiogram Evaluation</b>	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA, 19103 United States
<b>Interactive Response Technology</b>	ICON Clinical Research LLC 2100 Pennbrook Parkway North Wales, PA 19454 United States
<b>Bioassay and Pharmacokinetic Sample Analysis</b>	Teva Pharmaceutical Works P. Ltd. Co. (TPW) Bioanalytical Laboratory Pallagi St. 13 Debrecen 4042 Hungary

**APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT****1. Procedures for Screening (Visit 1, Week -16+4 weeks) – New Patients Only**

The screening visit (Visit 1) will take place within 4 weeks of Stage 1 (Visit 2, Week -12). The following procedures will be performed at Visit 1:

- obtain written informed consent (and assent, as applicable) before any study-related procedures are performed
- review medical and psychiatric history
- Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (SCID-5)
- review prior medication history
- review inclusion and exclusion criteria
- clinical laboratory tests (ie, serum chemistry, hematology, and urinalysis)
- virology and thyroid screening tests
- urine drug screen
- inquiry about concomitant medication
- full physical examination (including height and weight)
- vital sign measurements
- 12-lead electrocardiogram (ECG) (in triplicate)
- follicle-stimulating hormone test (for women with no menses for 12 months)
- serum beta human chorionic gonadotropin ( $\beta$ -HCG) pregnancy test (for women of childbearing potential)
- Positive and Negative Syndrome Scale (PANSS)
- Clinical Global Impression of Severity (CGI-S)
- Clinical Global Impression-Severity of Suicidality (CGI-SS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Personal and Social Performance Scale (PSP) **(for adult patients only)**
- Schizophrenia Quality of Life Scale (SQLS) **(for adult patients only)**
- 5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L) **(for adult patients only)**



- Calgary Depression Scale for Schizophrenia (CDSS)
- healthcare resource utilization
- Drug Attitudes Inventory 10-item version (DAI-10) (**for adult patients only**)
- inquiry about adverse events (including serious adverse event reporting)
- inquiry about alcohol consumption and illicit drug use

**2. Procedures Before Administration of Investigational Medicinal Product (Stage 1: Oral Conversion and Stabilization Stage) – New Patients Only**

- a. Stage 1: Oral Conversion and Stabilization (Visit 2, Week -12±3 days; Visit 3, Week -10±3 days; Visit 4, Week -8±3 days; and Visit 5, Week -4±3 days)**

The following procedures will be performed at Visits 2, 3, 4, and 5 (unless otherwise specified):

- clinical laboratory tests (serum chemistry, hematology, and urinalysis) – **at Visit 4 only**
- inquiry of concomitant medication
- full physical examination, including weight - **at Visit 2 only**
- vital sign measurements
- urine  $\beta$ -HCG test (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-SS
- Clinical Global Impression–Improvement (CGI-I)
- AIMS
- BARS
- SAS
- C-SSRS
- CDSS
- blood samples for plasma drug concentration - if possible, should be taken within an hour prior to dosing – **at Visit 2 and Visit 5 only**
- oral risperidone dispensing (for qd intake)
- dosage review and adjustment
- inquiry about adverse events (including serious adverse event reporting)
- inquiry about alcohol consumption and illicit drug use since previous visit

**b. Stage 1: Oral Conversion and Stabilization (Telephone Contacts [Visit 4a, Week -6±3 days and Visit 5a, Week -2±3 days])**

The following procedures and assessments will be performed at Visits 4a and 5a (telephone contacts):

- inquiry about pregnancy status (for women of childbearing potential)
- C-SSRS
- adverse event inquiry (including serious adverse event reporting)
- inquiry about alcohol consumption and illicit drug use since previous visit
- brief set of clinical questions to detect psychotic symptoms – the specific questions asked will be at the discretion of the investigator.

Psychiatric adverse events or suspicion of psychiatric deterioration prompted by the telephone contact will trigger an invitation of the patient to an unscheduled visit where psychiatric scales will be administered to rule out an impending relapse at the discretion of the investigator.

**3. Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Baseline [Visit 6, Day 1 ±3 days])**

The following procedures will be performed at Visit 6 for new and roll-over patients, **unless otherwise specified**.

**Note: For roll-over patients**, the procedures marked with an asterisk (\*) 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.

- obtain written informed consent (and assent, as applicable) before any study-related procedures are performed (**roll-over patients only**)
- review inclusion and exclusion criteria (including randomization-specific criteria **for new patients**)
- clinical laboratory tests (serum chemistry, hematology, and urinalysis)\*
- virology and thyroid screening tests (**roll-over patients only**)
- urine drug screen\*
- inquiry of concomitant medication\*
- full physical examination (including weight; **height to be measured for adolescent roll-over patients only**)\*
- vital sign measurements\*
- 12-lead ECG (in triplicate)
- serum  $\beta$ -HCG tests (for women of childbearing potential)
- urine  $\beta$ -HCG tests (for women of childbearing potential)\*
- PANSS\*

- CGI-S\*
  - CGI-SS\*
  - AIMS\*
  - BARS\*
  - SAS\*
  - C-SSRS\*
  - PSP (for adult patients only)\*
  - SQLS (for adult patients only)\*
  - EQ-5D-5L (for adult patients only)\*
  - CDSS\*
  - healthcare resource utilization\*
  - DAI-10 (for adult patients only)\*
  - blood samples for pharmacogenetic analysis (**new patients and roll-over patients for whom a sample was not collected in Study TV46000-CNS-30072**) - unless the patient declines testing or local regulations prohibit testing.
  - blood samples for biomarker analysis - unless the patient declines testing or local regulations prohibit testing
  - blood samples for plasma drug concentration - if possible, should be taken within an hour prior to dosing
  - assessment of stability (based on the defined criteria) (**new patients only**)
  - randomization (**new patients and roll-over patients who were assigned to placebo in Study TV46000-CNS-30072**)
  - TV-46000 every month (q1m) administration– for patients in that treatment group (**new patients only**)
  - TV-46000 every 2 months (q2m) administration – for patients in that treatment group (**new patients only**)
  - questions to assess ease of study drug administration – **to be performed only when using prefilled syringes (assessed following the first 3 injections for each patient) (new patients only)**
  - inquiry about adverse events (including serious adverse event reporting and injection site-related events including pain)\*
  - inquiry about alcohol consumption and illicit drug use since previous visit\*
4. **Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Stage 2: Relapse Prevention)**

**Note: The 24-week series from Visit 7 to Visit 12c repeats (Visit 13-18c, 19-19c), until patient completion, relapse, or early termination (Visits 19-19c are identical to Visits 7-7c).**

- a. Stage 2: Relapse Prevention (Telephone Contacts [Visit 6a, Week 1±3 days; Visit 6b, Week 2±3 days; and Visit 6c, Week 3±3 days; and so forth after each in-clinic visit in Stage 2 until the ET/EoT visit])**

**Note:** Telephone contact will occur **weekly** between in-clinic visits during the double-blind maintenance stage (Stage 2) (see [Table 2](#)). These contacts will be referred to by the previous visit number and a letter (for example, the telephone contacts that take place 1, 2, and 3 weeks after Visit 6 will be referred to as “Visit 6a,” “Visit 6b,” and “Visit 6c,” respectively).

The following procedures and assessments will be performed at all telephone contacts between the in-clinic visits:

- inquiry about pregnancy status (for women of childbearing potential)
- C-SSRS
- adverse event inquiry (including serious adverse event reporting and injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit
- brief set of clinical questions to detect psychotic symptoms – the specific questions asked will be at the discretion of the investigator.

Psychiatric adverse events or suspicion of psychiatric deterioration prompted by the telephone contact will trigger an invitation of the patient to an unscheduled visit where psychiatric scales will be administered to rule out an impending relapse at the discretion of the investigator.

- b. Stage 2: Relapse Prevention (Visit 7, Week 4±3 days; Visit 9, Week 12±3 days; Visit 11, Week 20±3 days)**

The following procedures and assessments will be performed at Visits 7, 9, and 11:

- inquiry of concomitant medication
- vital sign measurements
- urine  $\beta$ -HCG test (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-SS
- CGI-I
- AIMS
- BARS

- SAS
- C-SSRS
- PSP (for adult patients only) – Visit 9 only
- SQLS (for adult patients only) - Visit 9 only
- EQ-5D-5L (for adult patients only) - Visit 9 only
- CDSS
- healthcare resource utilization – Visit 9 only
- blood samples for plasma drug concentration - if possible, should be taken within an hour prior to dosing

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- vital sign measurements
- 12-lead ECG
- urine  $\beta$ -HCG test (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-SS
- CGI-I
- AIMS
- BARS

- SAS
- C-SSRS
- PSP (for adult patients only) – Visit 12 only
- SQLS (for adult patients only) - Visit 12 only
- EQ-5D-5L (for adult patients only) - Visit 12 only
- CDSS
- healthcare resource utilization – Visit 12 only
- blood samples for biomarker analysis - unless the patient declines testing or local regulations prohibit testing
- blood samples for plasma drug concentration - if possible, should be taken within an hour prior to dosing
- TV-46000 q1m administration – for patients in that treatment group
- TV-46000 q2m administration – for patients in that treatment group (to maintain the blind, patients will be injected q4w, but will alternate between TV-46000 sc and placebo injections)
- questions to assess ease of study drug administration – **to be performed only when using prefilled syringes (assessed following the first 3 injections for each patient) (new patients only) – Visit 8 only**
- adverse event inquiry (including serious adverse event reporting and injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit

**Note:** Another pharmacokinetic sample will be collected from **adolescent patients only** at a supplementary in-clinic visit at week 14 (2 weeks after Visit 9 [week 12]). It is highly preferable to collect the sample at week 14. However, if this is not possible, it may be collected 2 weeks after another in-clinic visit. Up to 2 additional samples may also be collected from adolescent patients at week 15 and week 13 (3 weeks and 1 week post-injection at Visit 9, respectively) at the sponsor's discretion. The additional samples, if taken following another in-clinic visit, will be collected at the same intervals. If more than 1 additional sample is taken, they do not need to be collected after the same injection (ie, 1 sample can be taken 3 weeks after Visit X, and another can be taken 1 week after Visit Y). These additional pharmacokinetic samples will be taken from new adolescent patients or adolescent roll-over patients from whom additional pharmacokinetic blood samples were not obtained during Study TV46000-CNS-30072.

**d. Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT) (Visit 20, Week 56±3 days)**

The following procedures and assessments will be performed at the ET/EoT visit:

- clinical laboratory tests (serum chemistry, hematology, and urinalysis)

- urine drug screen
- inquiry of concomitant medication
- full physical examination, including weight
- vital sign measurements
- urine  $\beta$ -HCG test (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-SS
- CGI-I
- AIMS
- BARS
- SAS
- C-SSRS
- PSP (**for adult patients only**)
- SQLS (**for adult patients only**)
- EQ-5D-5L (**for adult patients only**)
- CDSS
- healthcare resource utilization
- DAI-10 (**for adult patients only**)
- blood samples for biomarker analysis - unless the patient declines testing or local regulations prohibit testing
- blood samples for plasma drug concentration - if possible, should be taken within an hour prior to dosing
- TV-46000 q1m administration – for patients in that treatment group (**this is applicable only for the EoT visit, not the ET visit**)
- TV-46000 q2m administration – for patients in that treatment group (to maintain the blind, patients will be injected q4w, but will alternate between TV-46000 sc and placebo injections) (**this is applicable only for the EoT visit, not the ET visit**)
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit

**Note:** If per the investigator's judgement, the patient is at risk of not appearing at one or both of the follow-up visits, the investigator may perform an ECG at this visit. Likewise, if in the

judgment of the investigator, the patient will not come to 1 or both follow-up visits, then a dose of study drug should not be given at this EoT visit.

#### **5. Follow-up (Visit 21, Week 60±3 days; Visit 22, Week 64±3 days)**

The following procedures and assessments will be performed at Follow-up Visit 1 (Visit 21) and Follow-up Visit 2 (Visit 22):

- clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- inquiry of concomitant medication
- full physical examination (including weight)
- vital sign measurements
- 12-lead ECG
- serum  $\beta$ -HCG tests (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-SS
- CGI-I
- AIMS
- BARS
- SAS
- C-SSRS
- PSP (for adult patients only) – Follow-up Visit 2 only
- SQLS (for adult patients only) - Follow-up Visit 2 only
- EQ-5D-5L (for adult patients only) - Follow-up Visit 2 only
- CDSS
- healthcare resource utilization – Follow-up Visit 2 only
- DAI-10 (for adult patients only) - Follow-up Visit 2 only
- blood samples for biomarker analysis - unless the patient declines testing or local regulations prohibit testing
- blood samples for plasma drug concentration
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit

#### **6. Unscheduled Visits**



An unscheduled visit may be performed at any time during the study as deemed necessary by the investigator (eg, in cases of psychiatric adverse events or suspicion of psychiatric deterioration). The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits will include the following:

- inquiry of concomitant medication
- vital sign measurements
- PANSS
- C-SSRS
- blood samples for plasma drug concentration
- adverse event inquiry (including serious adverse event reporting and injection site-related events including pain)
- inquiry about alcohol consumption and illicit drug use since previous visit

Other procedures may be performed at the discretion of the investigator.

In addition, to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether the aforementioned procedures (which are currently marked in [Table 1](#) and [Table 2](#) as mandatory) actually need to be performed during the unscheduled visit in the case that:

- (i) the unscheduled visit is one of multiple in-clinic visits, that are deemed necessary in close proximity (2 or more visits within 1 week), **and**
- (ii) when the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event or impending/current relapse), and **not** due to a potential relapse or a change in the patient's medical status per clinical judgement.

Notwithstanding, it is hereby emphasized that the above refers **only** to unscheduled visits, and not to any other scheduled in-clinic visits or telephone contacts.

During Stage 2, unscheduled pharmacokinetic samples will be aimed to be collected in the event of relapse as defined per the study's relapse criteria, any serious adverse event, patient withdrawal, and/or need for potential TV-46000 depot excision. Every effort should be made to obtain the additional pharmacokinetic sample at the closest time possible to the occurrence of the event.

## **APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE**

### **Protocol Amendments and Protocol Deviations**

#### **Protocol Amendments**

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and national and local competent authorities (CAs), as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

#### **Important Protocol Deviations**

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; use of prohibited medications. Important protocol deviations will be identified and recorded in the patient's source. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

For COVID-19 updates, refer to [Appendix N](#).

#### **Information to Study Personnel**

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

**Study Monitoring**

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form or assent form, as applicable, and the study is conducted according to applicable Standard Operating Procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent or assent, as applicable, is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (case report forms and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

For COVID-19 updates, refer to [Appendix N](#).

**Audit and Inspection**

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that CAs and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

## **APPENDIX D. ETHICS**

### **Informed Consent and Assent**

The investigator, or a qualified person designated by the investigator, should fully inform the patient (and the parent/legally acceptable representative, as applicable) of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient and the parent/legally acceptable representative, as applicable. The patient and the parent/legally acceptable representative, as applicable, should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

For adolescent patients, a personally signed and dated ICF will be provided by the parent/legally acceptable representative, and a signed and dated assent form will be provided by each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and the parent/legally acceptable representative). It will also be explained to the patients (and the parent/legally acceptable representative) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

### **Competent Authorities and Independent Ethics Committees/Institutional Review Boards**

Before this study starts, the protocol will be submitted to the national competent authority (CA) and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and CA (as applicable) for the investigational center give written approval or a favorable opinion.

### **Confidentiality Regarding Study Patients**

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In case report forms (CRFs) and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or CAs. Personal medical information will always be treated as confidential.

**Registration of the Clinical Study**

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

## **APPENDIX E. BIRTH CONTROL METHODS AND PREGNANCY TESTING**

Contraception recommendations and pregnancy testing should encompass all investigational medicinal products (IMPs) as well as non-IMPs, eg, background therapy, and the measures to be followed should be based on the medicinal product with the highest risk.

Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, cytochrome P450 4A inducers. In cases of suspected interaction, hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered.

### **Women/girls of childbearing potential are defined as:**

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- not postmenopausal

### **Postmenopausal women are defined as:**

- one year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy

### **Recommendations for application of birth control methods:**

- IMP with possible human teratogenicity/fetotoxicity
  - Highly effective method of contraception
  - Contraception during treatment and until the end of relevant systemic exposure
  - Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure
  - In each case of delayed menstrual period (over 1 month between menstruations), confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles.

### **Description of highly effective birth control methods:**

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, are considered. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, and transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP.
- Progestogen-only hormonal contraception (oral, injectable, and implantable) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP.
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening.
- Bilateral tubal occlusion
- Vasectomized partner, provided he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, and post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

**Male contraception**

Male patients must always use a condom.

**Vasectomy:**

Use of contraceptive methods applies also to vasectomized men because of the risk associated with transfer of a drug via seminal fluid.

**Pregnancy tests in women of childbearing potential:**

Consider additional pregnancy testing, but at least at the end of relevant systemic exposure, in case of possible human teratogenicity/fetotoxicity. This refers to IMPs for which human data on pregnancies is limited or not available, there is no suspicion of human teratogenicity based on class effects or genotoxic potential, and nonclinical reproductive toxicity studies of relevance for early human pregnancy show positive findings that do not generate a strong suspicion of human teratogenicity/fetotoxicity.

**Pregnant female partners of male study participants:**

Male study participants must use condoms during intercourse if their female partners are pregnant.

## **APPENDIX F. LOST TO FOLLOW-UP**

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and/or caregiver and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient and/or caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical records and transcribed to the CRF.
- Should the patient and/or caregiver continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

For COVID-19 updates, refer to [Appendix N](#).



**APPENDIX G. LIST OF PROHIBITED MEDICATIONS****List of Prohibited Medications Affecting Cytochrome P450**

A partial list of prohibited drugs that are either strong/moderate inhibitors of cytochrome P450 (CYP) 2D6 or strong inducers of CYP3A4 and/or P-glycoprotein is presented below:

**List of Prohibited Medications Affecting Cytochrome P450**

Therapeutic class	Strong and moderate CYP2D6 inhibitors <sup>a</sup>	Strong CYP3A4 and/or P-gp inducers <sup>b</sup>
Anti-arrhythmics	Quinidine, dronedarone	
Antidepressants <sup>c</sup>	Fluoxetine, paroxetine, duloxetine	
Kinase inhibitors	Dacomitinib	
Recreational drugs/psychostimulants	Ecstasy	
Calcimimetic agents	Cinacalcet	
Protease inhibitors	Tipranavir/ritonavir	
Antifungals	Terbinafine	
Monoamine oxidase inhibitors	Moclobemide	
Beta 3-adrenoreceptor agonists	Mirabegron	
Fusion inhibitors	AMD070	
Glucosylceramide synthase inhibitors	Eliglustat	
Anti-emetics	Rolapitant	
Antibiotics		Rifampin, rifabutin
Antineoplastics		Mitotane
Antilipemics		Avasimibe
Anticonvulsants		Phenytoin, carbamazepine, phenobarbital
Anti-androgens		Enzalutamide
Dopamine-Norepinephrine reuptake inhibitors	Bupropion	
Others		Lumacaftor
Herbal medications		St John's Wort

<sup>a</sup> The use of strong or moderate inhibitors of CYP2D6 is prohibited within 14 days or 5 half-lives (whichever occurs last) prior to first oral risperidone dose and throughout the study.

<sup>b</sup> The use of strong inducers of CYP3A4 and/or P-glycoprotein is prohibited within 30 days prior to first oral risperidone dose and throughout the study.

<sup>c</sup> These antidepressants are permitted if the patient was on a stable dose for at least 3 months prior to screening (no dose changes or initiation of treatment with these medications will be permitted during the study).  
CYP=cytochrome P450; P-gp=P-glycoprotein.

Moreover, the use of the following medications is prohibited throughout the study:

- risperidone (except when given according to the study protocol)
- antipsychotics other than the study treatments
  - except during the conversion and stabilization stage (Stage 1) and only if required for conversion from a previous antipsychotic to oral risperidone
- dopamine reuptake inhibitors or prescription psychostimulants within 30 days prior to first oral risperidone dose
- opiates or opiate-containing analgesics within 14 days prior to first oral risperidone dose

In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-OH risperidone, may be associated with a significant drug interaction with risperidone, or may pose a significant risk to patients' participation in the study (eg, chloroquine, which is a QTc prolongator) are prohibited.

**APPENDIX H. TOTAL BLOOD VOLUME**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[illegible]

## APPENDIX J. PHARMACOGENETIC ASSESSMENTS

A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent or assent form, as applicable, for pharmacogenetic assessments at the time point detailed in [Table 2](#).

For new patients, a blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter, unless the patient declines testing or local regulations prohibit testing. For roll-over patients, if a sample was not collected during Study TV46000-CNS-30072 for any reason, it will be collected at the baseline visit or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.

[REDACTED]

A blood sample for DNA extraction will be collected at baseline, or any visit thereafter, in one 6.0 mL tripotassium ethylenediaminetetraacetic acid (K3EDTA) vacutainer plastic tubes.

Blood samples for DNA extraction will be stored at approximately  $-70^{\circ}\text{C}$  (if  $-70^{\circ}\text{C}$  storage is not possible at the site, store at  $-20^{\circ}\text{C}$ ) before shipment.

Details on processes for collection, labeling, and shipment of these samples can be found in the procedural manual.

Samples will be stored for a period of up to 15 years from the last patient last visit in the main study and then will be destroyed.

## **APPENDIX K. PRODUCT COMPLAINTS**

### **Clinical Product Complaints**

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical investigational medicinal product (IMP) supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [clinical.productcomplaints@tevapharm.com](mailto:clinical.productcomplaints@tevapharm.com) within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

#### **1. Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

## **2. Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

## **3. Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

## **4. Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.



## **APPENDIX L. DATA MANAGEMENT AND RECORD KEEPING**

### **Direct Access to Source Data and Documents**

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data), the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee/Institutional Review Board (IEC/IRB), and inspectors from competent authority (CA) (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, and videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

### **Data Collection**

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21 Code of Federal Regulations Part 11 (USA) and documents of other concerned CAs. Before using the CDMS, it will be fully validated, and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent or assent, as applicable. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, and electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent or assent, as applicable, will be entered in the CRF.

### **Data Quality Control**

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's Standard Operating Procedures (SOPs) for clinical studies. Day-to-day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS, and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

### **Archiving of Case Report Forms and Source Documents**

#### Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

#### Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to the following:

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, and electronic diary)
- safety reports
- financial disclosure reports/forms

- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any CA

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the contract research organization or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome and sponsor has not provided written notification of destruction, then the investigator may submit a written request to the sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

## **APPENDIX M. PUBLICATION POLICY**

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

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

The sponsor will comply with the requirements for publication of study results: “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” ([www.ICMJE.org](http://www.ICMJE.org)). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

## **APPENDIX N. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19**

This appendix is to address the modification set-up in study conduct during the outbreak of the Coronavirus disease 2019 (COVID-19) pandemic.

The changes will be effective for the period of the COVID-19 pandemic and when the situation at specific sites/countries allows the return to regular study activities, this appendix will be void for those sites/countries.

The following sections of the protocol are affected:

### **Section 3.1. General Study Design and Study Schematic Diagram; Section 3.5. Schedule of Study Procedures and Assessments**

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 and safety scales via teleconference (TC) and/or videoconference (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; otherwise, subject status should be NOT COMPLETED DUE TO: 'Other' 'COVID-19 logistical reasons prevented patient's continuation in the study'. If the patient does not continue in the study due to site closure, the subject status should be NOT COMPLETED DUE TO: 'Other' 'COVID-19 logistical reasons prevented patient's continuation in the study'.

In the event that a patient completes the oral stabilization stage (Stage 1) but cannot come to the site for the baseline visit for randomization (eg, due to quarantine, isolation, patient's concern or closure of the site clinic), it may be possible to extend the duration of Stage 1 on a case-by-case basis, following discussion between the investigator and the sponsor study physician.

In addition, the test and placebo IMP (as applicable) may be administered according to the schedule outlined in the protocol by unblinded study personnel, or home care service providers trained according to study specifications, via visits to the patient's place of residence. The patient's consent to the home visit will be collected in advance, where possible, by phone and documented in the patient's chart. The IMP will be transported, prepared, and administered in a blinded fashion per the conditions specified in the pharmacy manual and the injection instructions, provided that proper barrier precautions can be effectively implemented to minimize any risk of exposure, and that site staff follow CDC guidelines and local health authority procedures.

Modifications to other procedures and assessments (ECG, lab sample collection, pharmacokinetic sampling, etc) will be performed per implemented contingency measures according to sponsor instructions and the corresponding manual. For example, if central lab samples cannot be collected for safety assessments, sites may have patients visit a local reference lab to perform the assessments. At-home nursing visits may be used to perform safety assessments such as ECG, laboratory sample collection, vital signs, and nursing assessments to determine any new adverse events.

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.

**Section 5.1.1. Test Investigational Medicinal Product; Section 5.1.2. Placebo Investigational Medicinal Product; Table 4. Investigational Medicinal Products Used in the Study; Section 5.2.1. Storage and Security;**

For the IMPs (TV-46000 and TV-46000 placebo), limited excursions at room temperature are permitted to support easier home administration, if needed (details provided in the pharmacy manual).

**Section 5.2.3 Accountability**

Any syringes of IMP transported for home administration will be returned to the clinic to maintain accountability. Used needles will be disposed of immediately after administration in accordance with site (or the group home's) SOP.

**Section 5.9. Randomization and Blinding**

In the event of an emergency situation (eg, COVID-19 pandemic), in case off-site IMP administration is warranted, the IMP will be transported, prepared, and administered in a blinded fashion per the conditions specified in the pharmacy manual and the injection instructions, provided that proper barrier precautions can be effectively implemented to minimize any risk of exposure, and that site staff follow CDC guidelines and local health authority procedures.

**Section 6. Assessment of Efficacy**

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.

**Section 7. Assessment of Safety**

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 safety scales (as well as inquiries regarding adverse events and use of concomitant medication) 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.

Modifications to other procedures and assessments (ECG, lab sample collection, pharmacokinetic sampling, etc) will be performed per implemented contingency measures according to sponsor instructions and the corresponding manual.

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.

**Section 7.4. Clinical Laboratory Tests**

If central lab samples cannot be collected for safety assessments, sites may have a home nursing visit to collect the required samples or have patients visit a local reference lab to perform the assessments.

**Section 7.6. Vital Signs; 7.7. Electrocardiography**

At-home nursing visits may be used to perform safety assessments such as ECG, vital signs, and nursing assessments to determine any new adverse events.

**Section 8.1. Pharmacokinetic Assessment**

If pharmacokinetic samples cannot be collected due to limitations in ability to carry out the procedure, an at-home nursing vendor or site personnel could perform the sample collection, processing and shipment to the CRO (ICON) central lab via appropriate courier. The samples should be collected and processed as described in supporting documentation provided to the vendor or site nurses as applicable.

**Section 9.5.3.3. Exploratory Efficacy Analysis****Section 10. Quality Control and Quality Assurance**

Deviations from the study conduct due to emergency situations (eg, the COVID-19 pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the CSR as applicable.

**Appendix C. Quality Control and Quality Assurance****Important Protocol Deviations**

Deviations from the study conduct due to emergency situations (eg, the COVID-19 pandemic), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data, etc), will be described in the appropriate sections of the CSR as applicable.

**Study Monitoring**

In case of an emergency situation (eg, the COVID-19 pandemic), monitors may not be able to access the investigational centers for on-site visits in a timely manner. A remote monitoring risk mitigation plan will be utilized for sites where on-site monitoring visits are not permitted due to an increased public health risk, in accordance with IRB approval. Details are provided in the monitoring plan.

**Appendix F. Lost to Follow-Up**

In case of an emergency situation (eg, COVID-19 pandemic), if a patient cannot return to the clinic for the scheduled visits, home visits may take place to mitigate the possibility of being lost to follow-up.

**NOTE:**

**Appendix G. List of Prohibited Medications/ Section 5.7. Prior and Concomitant Medication or Therapy**

Although not an operational modification per se, this is to notify that chloroquine, which is a QTc prolongator, was added to the text as an example of a prohibited medication that may pose a significant risk to patient participation in the study (see also separate entry in summary of changes).

“In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-OH risperidone, may be associated with a significant drug interaction with risperidone, or may pose a significant risk to patients’ participation in the study (eg, chloroquine, which is a QTc prolongator) are prohibited.”