Clinical Study Protocol

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability 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-30072

NCT03503318

Protocol with Amendment 03 Approval Date: 19 April 2020

Clinical Study Protocol with Amendment 03

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

A Randomized, Double-Blind, Placebo-Controlled Study on Efficacy, Safety, and Tolerability of TV-46000 in Adults and Adolescents with Schizophrenia

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

(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

Efficacy, Safety, and Tolerability Study (Phase 3)

IND number: 124384; NDA number: 213586; BLA number: Not applicable; EudraCT number: 2018-001619-65

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Amendment 03 Approval Date: 19 April 2020

Protocol Approval Date: 14 December 2017

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 (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:

Global Amendment 03	19 April 2020 (863 patients enrolled to date) The management of study activities during the COVID-19 pandemic are detailed in Appendix N. The following sections are affected: 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 9.5.4.2. Sensitivity Analysis; Section 10. Quality Control and Quality Assurance; Appendix C. Quality Control and Quality Assurance; Appendix F. Lost to Follow-Up;
Administrative Letter 03	09 February 2020

Global Amendment 02 with Revision 01	16 October 2019 (649 patients enrolled to date)
Global Amendment 02	02 September 2019 (584 patients enrolled to date)
Letter of Clarification 02	27 June 2019
Global Amendment 01	06 December 2018 (184 patients enrolled to date)
Letter of Clarification 01	26 June 2018
Local Amendment 01 for Bulgaria	28 May 2018 (6 patients enrolled to date)
Protocol with Revision 01	15 February 2018 (0 patients enrolled to date)

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 14 December 2017

Clinical Study Protocol with Amendment 03

IND number: 124384; NDA number: 213586; BLA number: Not applicable; EudraCT number: 2018-001619-65

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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

(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the Protocol Amendment 03 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 IMP and the conduct of the study. I agree to keep records on all patient information, investigational medicinal products (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.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted] Vice President Therapeutic Area Head Neurology and Psychiatry, Specialty Clinical Development	[redacted]	19-APR-2020

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 14 December 2017

Clinical Study Protocol with Amendment 03

IND number: 124384; NDA number: 213586; BLA number: Not applicable; EudraCT number: 2018-001619-65

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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

(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

I have read the Protocol Amendment 03 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 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 IMP and the conduct of the study. I agree to keep records on patient information, IMPs shipment and return forms, 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]

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-30072

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia (The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

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

Investigational New Drug (IND) Number: 124384

New Drug Application (NDA) Number: 213586

Biological License Application (BLA) Number: Not applicable

EudraCT Number: 2018-001619-65

EMA 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 (EV) code for the IMP, if applicable: SUB10335MIG

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

Indication: Maintenance treatment of schizophrenia in patients currently treated with oral antipsychotics

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

Number of Investigational Centers Planned: Approximately 80

Countries Planned: The study is planned to be conducted in North America and Bulgaria.

Planned Study Period: Q2 2018 to Q4 2020

Number of Patients Planned (total): The total number of patients planned to be enrolled into Stage 1 is approximately 860 adults (18 years of age and above), to achieve approximately 520 adults randomized to Stage 2. As an event-driven study, it may be possible to randomize more than 520 adult patients, as long as Stage 2 of the study ends when the number of events among adults reaches at least 90 (see **Sample Size Rationale**). 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 at screening, who have a confirmed diagnosis of schizophrenia, are clinically stable, and are eligible for risperidone treatment.

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in adult patients with schizophrenia.	The primary efficacy endpoint is time to impending relapse. Relapse is defined as 1 or more of the following items: • Clinical Global Impression–Improvement (CGI-I) of ≥5 (greater than or equal to minimally worse, ie, minimally worse, much worse or very much worse), **AND** – an increase of any of the following individual Positive and Negative Syndrome Scale (PANSS) items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥2 on that specific item since randomization, **OR** – an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization; • hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons • Clinical Global Impression-Severity of Suicidality (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2 • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage
A **key secondary objective** of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in the total population (adults and adolescents) and in adolescent patients with schizophrenia.	Key secondary endpoints are: • time to impending relapse (as defined under the primary objective) in the total population (adults and adolescents) • impending relapse rate at week 24 • percentage of patients who maintain stability at endpoint • percentage of patients achieving remission at endpoint • observed rate of impending relapse at endpoint • Drug Attitudes Inventory 10-item version **(adult patients only)** • Schizophrenia Quality of Life Scale (SQLS) **(adult patients only)** • time to impending relapse in adolescent patients with schizophrenia

Objectives	Endpoints
A **secondary objective** of this study is to evaluate the safety and tolerability of TV-46000 in the total population.	The safety variables include adverse events, extrapyramidal symptoms (EPS), risk of suicide events, depression symptoms, injection pain and other injection site reactions (local tolerability), vital signs, laboratory tests, physical examination, electrocardiogram (ECG) measurements, body weight, rescue medication use, time to all-cause discontinuation, all-cause discontinuation rates and discontinuation rates due to adverse events (tolerability), and the following rating scales: • Abnormal Involuntary Movement Scale (AIMS) • Simpson-Angus Scale (SAS) • Barnes Akathisia Rating Scale (BARS) • Columbia Suicide Severity Rating Scale (C-SSRS) • Calgary Depression Scale for Schizophrenia (CDSS) • CGI-SS
A **secondary objective** of this study is to evaluate the pharmacokinetics (PK) of oral risperidone and TV-46000 after administration of multiple doses in adults, adolescents, and the total population.	The pharmacokinetic endpoints are the plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OH-risperidone).

[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

General Study Design: This is a double-blind, randomized, relapse prevention study comparing a therapeutic dose of TV-46000 sc (every month [q1m] and every 2 months [q2m]) with placebo sc (q1m) in a 1:1:1 ratio.

Patients will undergo screening procedures/assessments within 30 days before the start of Stage 1. They should have had a diagnosis of schizophrenia for >1 year (diagnosis must be reconfirmed by Structured Clinical Interview for DSM-5 [SCID-5]) and have been generally responsive to antipsychotics in the past year based on investigator judgement (and discussions with family members, caregivers, or healthcare professionals as applicable). 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.

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. Patients can be accompanied by caregivers to visits.

Stage 1: Oral conversion and stabilization stage (12 weeks). Patients not already on oral risperidone or injectable risperidone (RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI) and on any antipsychotic (other than clozapine), and who can benefit from conversion to oral risperidone based on the investigator's judgement, will be converted to oral risperidone (2 to 5 mg/day) to ensure that they 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 who are already on risperidone but can still benefit from the study based on the investigator's judgement will also undergo the oral stabilization stage. Open-label oral risperidone (2 to 5 mg/day) will be used to stabilize patients to the treatments (the dose will be based on clinical judgement). Patients will come to the clinic for 4 visits (weeks -12, -10, -8, and -4) for dose adjustments; however, additional visits may be required for dose adjustments. Patients will be assessed by [redacted]. Additionally, telephone contacts will take place at weeks -6 and -2, or more frequently if required in the judgement of the investigator.

Stability on risperidone, while also adequately controlling for symptoms of schizophrenia, will be assessed at baseline and 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]

Blood samples for plasma drug concentration will be collected during the in-clinic visits (besides screening) and adverse event inquiry will be performed at all visits and telephone calls/teleconferences (TCs).

If a patient withdraws from the study prior to the randomization 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.

Stage 2: Double-blind maintenance stage (variable in duration). Stabilized patients (see definition above) will be randomized to receive TV-46000 q1m sc injections, TV-46000 q2m sc injections, or placebo q1m sc injections in a 1:1:1 ratio. Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized. Patients in the TV-46000 groups will receive a dose of TV-46000 (q1m or q2m) that is equivalent to the oral dose on which they were stabilized in Stage 1. The maximal dose administered to adult patients will be equivalent to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents will be equivalent to 4 mg/day. Patients randomized to TV-46000 q1m or placebo sc will receive an sc injection of TV-46000 or placebo, respectively, at baseline and every 4 weeks (q4w) thereafter. Patients randomized to TV-46000 q2m will receive a TV-46000 injection at baseline and every 8 weeks (q8w) thereafter and a placebo sc injection 4 weeks after baseline and q8w thereafter to ensure blinding of the doses and durations of the TV-46000 injections and the placebo injections.

The study will continue on an outpatient basis, and telephone contacts will take place weekly between clinic visits. If, in the judgment of the investigator, the patient is likely to relapse or pose a danger to himself/herself or others, that patient may be invited for an unscheduled visit and/or hospitalized if needed, and treatment with the study drug may be discontinued.

Per definition, an exacerbation in symptoms during Stage 1 cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. Randomized patients, who relapse or meet 1 or more of the withdrawal criteria should be invited to perform the Early Termination (ET) visit as soon as possible, within 4 weeks of the last injection. Patients who remain relapse-free when the study is terminated should be invited to perform the End-of-Treatment (EoT) visit within 4 weeks of the last injection. Therefore, a patient is considered a study completer if he or she experienced impending relapse or remained relapse-free at the time of study termination.

During the conduct of this study, an Independent Data Monitoring Committee (IDMC) will review accumulating unblinded safety and pharmacokinetic data on a regular basis, as detailed in the IDMC charter, to ensure the continuing safety of the study patients and study conduct issues. The specific details regarding the IDMC sessions will be outlined in the IDMC charter.

Brief Summary of Study Design for the Trial Registry(s): The purpose of the study is to evaluate the efficacy, safety, and tolerability of different dose regimens of TV-46000 administered sc as compared to placebo during maintenance treatment in adult and adolescent patients with schizophrenia. The study will include male and female patients, 13 to 65 years of age at screening, who have a confirmed diagnosis of schizophrenia, are clinically stable, and are eligible for risperidone treatment. Patients will be randomized to receive doses of TV-46000 q1m, TV-46000 q2m, or placebo q1m sc injections in a 1:1:1 ratio. Patients randomized to TV-46000 q1m or placebo will receive an sc injection of TV-46000 or placebo, respectively, at baseline and q4w thereafter. Patients randomized to TV-46000 q2m will receive a TV-46000 sc injection at baseline and q8w thereafter and a placebo sc injection 4 weeks after baseline and q8w thereafter to ensure blinding of the doses and durations of the TV-46000 injections and the

placebo injections. The doses of TV-46000 will be equivalent to 2 to 5 mg/day of oral risperidone. The primary efficacy endpoint is time to impending relapse, which will be measured by CGI-I, PANSS, and CGI-SS scores, hospitalization due to worsening of psychotic symptoms, or violent behavior. The duration of patient participation in the study will include up to 4 weeks of screening, 12 weeks of the oral conversion/stabilization stage, and a double-blind maintenance stage. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free at the time of study termination. Patients will subsequently complete all end-of-study assessments. When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. If they choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. For all other patients, there will be 2 follow-up/exit visits that will take place at 4 weeks and 8 weeks after the last dosing visit. During the follow-up/exit period, patients will be treated according to the investigator's judgement.

Method of Randomization and Blinding: Patients will be randomized to receive doses of TV-46000 q1m sc injection, TV-46000 q2m sc injection, or placebo q1m sc injection in a 1:1:1 ratio. Randomization will be stratified by gender (male or female) and the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg). The doses of TV-46000 will be equivalent to 2 to 5 mg/day of oral risperidone (equivalent to the oral dose on which the patient was stabilized in Stage 1). As a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized. Patients randomized to TV-46000 q1m or placebo sc will receive an sc injection of TV-46000 or placebo, respectively, at baseline and q4w thereafter. Patients randomized to TV-46000 q2m will receive a TV-46000 sc injection at baseline and q8w thereafter and a placebo sc injection 4 weeks after baseline and q8w thereafter to ensure blinding of the doses and durations of the TV-46000 injections and the placebo injections.

Patients and investigators will remain blinded to the identity of the treatment administered to each patient. Due to the differences between the TV-46000 product and placebo, an unblinded nurse, not associated with rating the patient (including assessment of the injection site if needed) and 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 unblinded nurse will [redacted] in a room separated 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.

The sponsor's clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for final analysis and the IMP assignment is known.

In the event of an emergency (ie, where knowledge of the study drug assignment is needed to make treatment decisions for the patient), the treatment group and dose to which the patient has been allocated can be determined by accessing the Interactive Response Technology (IRT) system.

Pharmacokinetic sample analysis and drug concentration calculations will be performed during the course of the study. [redacted].

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

Test IMP: [redacted]

In general, 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 oral risperidone 2 to 5 mg/day per the conversion table below. Patients that will require a stabilization dose below 2 mg/day will not be randomized in the study. The maximal dose administered to adult patients will be equivalent to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents will be equivalent to 4 mg/day. As a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.

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

Conversion Table Between Oral Risperidone and TV-46000 Doses

Frequency of TV-46000 Administration	Oral Risperidone Doses and Corresponding TV-46000 Doses			
	2 mg/day	3 mg/day	4 mg/day	5 mg/day (Adults Only)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 arm and the left. 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 dosing manual.

[redacted]

Reference IMP: None

Placebo IMP: [redacted]

Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	TV-46000; risperidone extended-release injectable suspension for sc administration	TV-46000 placebo
Formulation	sterile extended-release injectable product	sterile extended release injectable product
Storage conditions	[redacted]	[redacted]
Unit dose strength(s)/dosage level(s)	**Treatment** / **Dosing volume (mL)** [redacted] Further dosing instructions are detailed in the pharmacy manual.	

IMP name	Test IMP	Placebo IMP
Route of administration	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.
Dosing instructions	q1m or q2m injections per the patient's assigned treatment group. The injection will be administered by an unblinded independent nurse	q1m injections per the patient's assigned treatment group. The injection will be administered by an unblinded independent nurse
Packaging	[redacted]	[redacted]
Manufacturer	[redacted]	[redacted]

[redacted].

Duration of Patient Participation and Maximal Exposure to IMP: The duration of patient participation in the study will include up to 4 weeks of screening, 12 weeks of the oral conversion/stabilization stage, and a double-blind maintenance stage.

Patients are expected to participate in the study for its entire duration, and undergo the scheduled visits and assessments as detailed in the protocol.

The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free at the time of study termination.

When the study ends, eligible patients may be offered the opportunity to enter the long-term TV46000-CNS-30078 extension study to assess the safety and tolerability of extended-release risperidone.

If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. For all other patients (ie, patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study), there will be 2 follow-up/exit visits that will take place at 4 weeks and 8 weeks after the last dosing visit. During the follow-up/exit period, patients will be treated according to the investigator's judgement.

Study Duration: Approximately 30 months, from Q2 2018 (first patient in) to Q4 2020 (last patient out).

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.

Plans for Treatment or Care after the Patient has Ended Participation in the Study:

In case the patient is withdrawn from this study, no further treatment is planned by the sponsor after the patient completes their participation in this study. Patients will be advised to return to their primary physician for additional treatment. Patients may be treated in the meantime per investigator judgment and instruction as applicable.

When the study ends, eligible patients may be offered the opportunity to enter the long-term TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol, and a separate protocol was issued for it.

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

a. The patient has a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for >1 year (diagnosis must be reconfirmed by SCID-5) and has had ≥1 episode of relapse in the last 24 months.

b. The patient has been responsive to an antipsychotic treatment (other than clozapine) in the past year based on investigator judgement (and discussions with family members, caregivers, or healthcare professionals as applicable).

c. [Revision 1] The patient has provided written informed consent and is competent to do so. For adolescent patients, written informed consent has been provided by each patient's parent or legal guardian, and written assent has been provided by 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, tablet ingestion, sc depot injection, and discontinuation 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 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. [Revision 1]The patient is a male or female of any ethnic origin, 13 through 65 years of age at screening.

k. [Revision 2] The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive, at screening.

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 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 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:

   – 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 and intrauterine hormone-releasing system; these need to be 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 follow-up procedures and assessments as specified in this protocol.

Randomization Criteria:

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

p. The patient has not experienced mental or physical deterioration, which prevents participation in the study per investigator judgement.

q. The patient has demonstrated good compliance in following protocol requirements during Stage 1.

   – 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).

r. 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 ≤80
   - minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
   - CGI-S score ≤4 (moderately ill)
   - CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2

Exclusion Criteria: Patients will not be enrolled/randomized in this study if they meet any of the following criteria:

a. The patient has a current clinically significant DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic 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, clinically significant tardive dyskinesia, or other medical condition that would expose the patient to undue risk.

d. [Revision 1] 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 RNA 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 currently has or has 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 investigator's judgement.

h. The patient has a significant risk of committing suicide based on the patient's medical history or 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 previously participated in a Teva-sponsored clinical study with TV-46000.

j. The patient has a clinically significant deviation from normal in the physical examination.

k. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results.

   – 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.

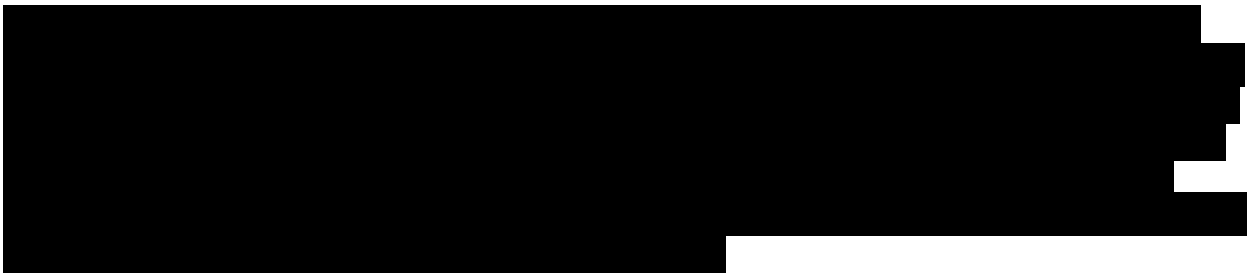
p. The patient has used an investigational drug within 3 months prior to screening or has participated in a non-drug clinical trial within 30 days prior to screening.

q. The patient is using or consuming the medications prohibited in this protocol.

Statistical Considerations

Sample Size Rationale: Median time to impending relapse was observed to be 7 months in the placebo group in a similarly designed study (Kane et al 2012). Assuming a similar placebo effect in this study, as well as a hazard ratio of 2.50 (placebo vs each TV-46000 arm) and a randomization ratio of 1:1:1 (q1m:q2m:placebo) with 2 primary hypotheses to be tested (q1m vs placebo and q2m vs placebo) at a 2-sided alpha of 0.050, the total number of events across treatment groups that will attain a statistical power of at least 90% to meet success criteria in both comparisons (East 6 [Version 6.3] manual, 2014) is 90 relapse events. This number of events will need to be observed during Stage 2 of the study in the ITT analysis set (adult patients). The sample size rationale is based on the adult patients. There is no estimation of the sample size in the adolescent population, and their number is not known at this time.

[redacted]



Primary Efficacy Analysis: Time to impending relapse will be calculated as the earliest date the patient meets ≥1 of the impending relapse criteria minus the randomization date plus 1. Data from patients who did not relapse will be censored at the last valid assessment. Time to impending relapse for TV-46000 and placebo will be compared using the stratified log-rank test at the significance levels described (see **Multiple Comparisons and Multiplicity)**. Hazard ratios and their 2-sided 95% confidence intervals (CIs) for TV-46000 q1m and q2m versus placebo will be analyzed using a Cox proportional hazard model, with treatment and the aforementioned stratification variables as the factors (see **Method of Randomization and Blinding)**. Kaplan-Meier curves will be provided to present impending relapse rate data over time. The primary analysis will be conducted on the population of adult patients.

Sensitivity Analysis: A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment at the time the first relapse was observed via the interval censoring method. Sensitivity analysis will also be conducted by tipping point analysis, that imputes time to relapse for dropouts (for reasons suspected to be related to relapse) with increasing risk to relapse, compared to similar patients in the same treatment group that continue treatment. The per-protocol analysis set will also be used to as a suplemental analysis to evaluate the primary efficacy variable. Details will be provided in the statistical analysis plan.

Key Secondary Efficacy Analysis 1: Time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis. The Cox proportional hazard model will include patient age group (if applicable) along with treatment, and the aforementioned stratification variables as the factors. The details about the Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 2: Impending relapse rate at week 24 will be estimated using the Kaplan-Meier method and calculated as 1 minus the proportion of adult and adolescent patients free of impending relapse events at week 24. The Greenwood formula will be used to calculate standard errors for impending relapse rates at week 24, and the pooled standard errors will be used for hypothesis testing using z statistics, assuming that the differences between TV-46000 and placebo follow a normal distribution of large samples.Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 3: The analyses of the proportion of patients who maintain stability at endpoint in Stage 2 will be described in the statistical analysis plan. Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 4: The analyses of the proportion of patients achieving remission at endpoint in Stage 2 will be described in the statistical analysis plan. Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 5: The observed impending relapse rates at endpoint will be compared between groups using the Cochran–Mantel–Haenszel (CMH) test adjusting for stratification variables. Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 6: Change from baseline of DAI-10 at endpoint will be compared between groups using repeated measures ANCOVA . Type-I statistical control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 7: Change from baseline of SQLS at endpoint will be compared between groups using repeated measures ANCOVA. Type-I statistical control will be discussed in **Multiple Comparisons and Multiplicity.**

Key Secondary Efficacy Analysis 8: Time to impending relapse in adolescent patients will be assessed if the number of randomized adolescents will be at least 10, with clinically sufficient exposure. The method will be similar to the Primary Efficacy Analysis. The details about the Type-I statistical error control will be discussed in **Multiple Comparisons and Multiplicity.**

[redacted]

In the event that prefilled syringes become available during the study, data relating to the ease of dosing administration will be listed.

Multiple Comparisons and Multiplicity:

At the final analysis after at least 90 relapse events, a fixed sequential (hierarchical) testing approach will be implemented. The first primary efficacy hypothesis comparing q1m to placebo will be tested with a 2-sided alpha of 0.05; if significant, the second primary efficacy hypothesis comparing q2m to placebo will be tested with a 2-sided alpha of 0.05. If the first primary hypothesis test fails to reach statistical significance, no further formal hypothesis testing will be performed.

Type-I error will be further controlled for the key secondary endpoints by employing the fixed sequential (hierarchical) approach to the secondary endpoints. Accordingly, secondary endpoints will be analyzed only if primary efficacy endpoints have a p-value less than or equal to alpha of 0.05.

For the key secondary endpoints, if the resulting 2-sided p-value from the first comparison is significant, then the next comparison of interest will be interpreted inferentially at the same alpha level. This process will continue either until all comparisons of interest are interpreted inferentially or until the point at which the resulting 2-sided hypothesis is insignificant at the same alpha level. At the point where a comparison is found to be insignificant, no further comparisons will be interpreted inferentially. Further details about the Type-I statistical error control for the key secondary endpoints will be discussed in the statistical analysis plan.

There will be no multiplicity control for all other exploratory efficacy endpoints, which will be tested at a nominal 5% level.

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

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 test IMP (ie, reasonable possibility defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group. 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 EPS scale scores (BARS, AIMS, and SAS) and CDSS during Stage 2, will be presented using descriptive statistics by treatment group. Adjustment to stratification factors may be conducted as appropriate.

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.

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.

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.

Safety data collected in Stage 1 will also be summarized using descriptive statistics in the enrolled patients set.

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

Separate summaries for adolescent patients may be presented separately for some analyses, as applicable, and will be described in the Statistical Analysis Plan.

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

All-cause discontinuation rates and discontinuation rates due to adverse events (dropout rates) will be calculated as the number of patients who withdrew early, and the number of patients who withdrew early due to adverse events, respectively, divided by the number of patients in each treatment group and will be presented using descriptive statistics.

Time to all-cause discontinuation will be calculated as the discontinuation date minus the randomization date plus 1. Kaplan-Meier curves for the time to discontinuation as a result of all causes will be plotted.

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

Pharmacokinetic Analysis: Blood samples will be collected from all patients for quantitation of the plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety, at weeks -12, -10, -8, and -4 in Stage 1, at baseline, every 4 weeks in Stage 2, and at the follow-up/exit visits. During Stage 2 of the study, blood samples for PK assessment will be taken within an hour prior to sc dose administration.

[redacted]

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 the 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. Drug concentrations over time [C(t)] reported by time (visit) and treatment (q1m, q2m, and oral) will be presented using descriptive statistics (n, mean, standard deviation, median, minimum, geometric mean, and coefficient of variation).

Additional pharmacokinetic parameters may be determined if data permits.

In addition, the pharmacokinetics of TV-46000 (and if data permits, also of oral risperidone) will be evaluated by using a population pharmacokinetics approach and reported separately from the main study report.

Pharmacokinetic/Pharmacodynamic Analysis: [redacted]

Biomarker and Pharmacogenetics Analysis: Biomarker and pharmacogenetic analysis plans and results will be outlined in a separate document.

Planned Interim Analyses: There will be no interim analysis in this study.

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Abbreviation	Term
β-HCG	Beta human chorionic gonadotropin
ADR	averse drug reaction
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BARS	Barnes Akathisia Rating Scale
CA	competent authority
[redacted]	[redacted]
[redacted]	[redacted]
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
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CMH	Cochran–Mantel–Haenszel
[redacted]	[redacted]
[redacted]	[redacted]
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
C(t)	concentrations of drug over time [C(t)] reported by time (visit) and treatment

Abbreviation	Term
CYP	cytochrome P450
DAI-10	Drug Attitudes Inventory 10-item version
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram/electrocardiography
EOS	end of study
EOT	end of treatment
EPS	extrapyramidal symptoms
EQ-5D-5L	5-Level EuroQol Five Dimensions Questionnaire
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
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
im	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
LAI	long-acting injectable
LOCF	last observation carried forward
LSO	local safety officer
NDA	New Drug Application
NOAEL	no observed adverse effect level
NPRS	Numeric Pain Rating Scale
OTC	over-the-counter

Abbreviation	Term
PANSS	Positive and Negative Syndrome Scale
PI	prescribing information
PK	pharmacokinetic(s)
PP	per-protocol
PSP	Personal and Social Performance Scale
q1m	every month
q2m	every 2 months
q3m	every 3 months
q4w	every 4 weeks
q8w	every 8 weeks
RNA	ribonucleic acid
RO	receptor occupancy
RSI	reference safety information
SAS	Simpson-Angus Scale
sc	subcutaneous
SCID-5	Structured Clinical Interview for DSM-5
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SQLS	Schizophrenia Quality of Life Scale
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
[redacted]	[redacted]
TC	telephone call/teleconference
ULN	upper limit of normal
US	United States (of America)
US FDA	United States Food and Drug Administration
VC	videoconference
vs	versus

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 and Travis 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 and Curson 1994, Hughes 2007, Keith and Kane 2003, Walburn et al 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 et al 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 is 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, thought disorder), neurocognitive impairments, psychophysiological abnormalities, and the presence of structural brain abnormalities (Asarnow et al 1995, Bo and Haahr 2016, Rapoport et al 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 and Haahr 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 and Harrison 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. [redacted]
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 [redacted] the dose [redacted] 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 and Sharif 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 purpose of the study is to compare the safety and efficacy of different durations of TV-46000 administered sc versus placebo. 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 et al 2017). Enrollment of adolescents in this study will provide data for evaluating the efficacy, safety and tolerability of TV-46000 in this patient population.

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

1.2. Findings from Nonclinical and Clinical Studies

1.2.1. Nonclinical Studies

The nonclinical pharmacology and toxicology of risperidone have been well established for oral and intramuscular (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] 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] but their size showed a trend toward reduction. In 3 single-dose pharmacokinetic and local tolerance non-Good Laboratory Practice (GLP) studies in minipigs, 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]. 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 systematically in rats, dogs, and minipigs 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-month 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

[redacted] The study found that TV-46000, administered at sub-therapeutic [redacted], was safe and well tolerated when administered as an sc injection to either the posterior upper arm or the abdomen. [redacted]

[redacted] to evaluate the safety, tolerability, and pharmacokinetics of TV-46000 in patients with schizophrenia or schizoaffective disorder was also completed. A total of 96 patients with schizophrenia or schizoaffective disorder were allocated into 8 sequential cohorts of 12 patients each. Study participants were clinically stable patients who are currently on antipsychotic treatment of oral risperidone. The study included 5 single-dose cohorts [redacted] and 2 multiple-dose cohorts [redacted]. In addition, interchangeability of injection site was assessed via administration of a similar dose [redacted] to the abdomen and to the upper arm.

[redacted]

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 ≥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).

The safety and efficacy of risperidone LAI (RISPERDAL® CONSTA®, Janssen Pharmaceuticals) 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 [redacted] risperidone LAI while participating in a 12-week, double-blind, placebo-controlled study. The most common adverse drug reactions (ADRs) in patients with schizophrenia (≥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).

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 [redacted] 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.

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 there are only limited data on ADRs associated with this formulation. However, the safety profile of the active ingredient, risperidone, given in a different long-acting parenteral formulation has been well characterized. The licensed risperidone long-acting injection, RIPERDAL CONSTA, 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 of TV-46000 is favorable following review of the available data. Additional safety information on TV-46000, including RSI, is presented in the TV-46000 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 (im) risperidone was generally well tolerated over the dose range of [redacted]. The most common adverse events in clinical studies (≥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 (≥5% of risperidone treated patients) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth.

Based on the extensive safety and efficacy database for oral and im risperidone, and preliminary findings from the TV-46000 clinical development program thus far, the sponsor anticipates a favorable risk-benefit profile for administration of an extended-release suspension of risperidone for sc injection in adult patients with schizophrenia. To date, the only new safety signals that were identified in the TV-46000 Phase 1 program were some types of injection site reactions (see Section 1.2.2.2). They have not significantly impacted TV-46000's benefit-risk profile nor have they presented a significant burden to the patients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in adult patients with schizophrenia.	The primary efficacy endpoint is time to impending relapse. Relapse is defined as 1 or more of the following items: • Clinical Global Impression–Improvement (CGI-I) of ≥5 (greater than or equal to minimally worse, ie, minimally worse, much worse or very much worse), **AND** – an increase of any of the following individual Positive and Negative Syndrome Scale (PANSS) items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥2 on that specific item since randomization, **OR** – an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization • hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons • Clinical Global Impression-Severity of Suicidality (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2 • violent behavior resulting in clinically significant self-injury, injury to another person, or property damage
A **key secondary objective** of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in a total population (adults and adolescents) and in adolescent patients with schizophrenia.	Key secondary endpoints are: • time to impending relapse (as defined under the primary objective) in the total population (adults and adolescents) • impending relapse rate at week 24 • percentage of patients who maintain stability at endpoint • percentage of patients achieving remission at endpoint • observed rate of impending relapse at endpoint • Drug Attitudes Inventory 10-item version (**adult patients only**) • Schizophrenia Quality of Life Scale (SQLS) (**adult patients**

Objectives	Endpoints
	only) • time to impending relapse in adolescent patients with schizophrenia
A **secondary objective** of this study is to evaluate the safety and tolerability of TV-46000 in the total population.	The safety variables include adverse events, extrapyramidal symptoms (EPS), risk of suicide events, depression symptoms, injection pain and other injection site reactions (local tolerability), vital signs, laboratory tests, physical examination, electrocardiogram (ECG) measurements, body weight, rescue medication use, time to all-cause discontinuation, all-cause discontinuation rates and discontinuation rates due to adverse events (tolerability), and the following rating scales: • Abnormal Involuntary Movement Scale (AIMS) • Simpson-Angus Scale • Barnes Akathisia Rating Scale • Columbia Suicide Severity Rating Scale (C-SSRS) • Calgary Depression Scale for Schizophrenia (CDSS) • CGI-SS
A **secondary objective** of this study is to evaluate the pharmacokinetics of oral risperidone and TV-46000 after administration of multiple doses in adults, adolecsents, and the total population.	• The pharmacokinetic endpoints are the plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OH-risperidone).

Justification of Primary Endpoint

The primary endpoint of the study is time to impending relapse compared with placebo. Time to impending relapse is a well-accepted endpoint for the evaluation of efficacy during maintenance therapy with antipsychotics.

2.2. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a double-blind, randomized, relapse prevention study comparing a therapeutic dose of TV-46000 sc q1m and q2m with placebo sc (q1m) in a 1:1:1 ratio.

Patients will undergo screening procedures/assessments within 30 days before the start of Stage 1. They should have had a diagnosis of schizophrenia for >1 year (diagnosis must be reconfirmed by Structured Clinical Interview for DSM-5 [SCID-5]) and have been generally responsive to antipsychotics in the past year based on investigator judgment (and discussions with family members, caregivers, or healthcare professionals as applicable). 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.

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. Patients can be accompanied by caregivers to visits.

Stage 1: Oral conversion and stabilization stage (12 weeks). Patients not already on oral risperidone or injectable risperidone (RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI) and on any antipsychotic (other than clozapine), and who can benefit from conversion to oral risperidone based on the investigator's judgement, will be converted to oral risperidone (2 to 5 mg/day) to ensure that they tolerate risperidone and that the doses are adequate to treat their positive symptoms. Patients who are already on risperidone but can still benefit from the study based on the investigator's judgement will also undergo the oral stabilization stage. Open-label oral risperidone (2 to 5 mg/day) will be used to stabilize patients to the treatments (the dose will be based on clinical judgement). 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 dose adjustments (Table 1); however, additional visits may be required for dose adjustments. Patients will be assessed by 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), and Clinical Global Impression-Severity of Suicidality (CGI-SS). Additionally, telephone contacts will take place at weeks -6 and -2, or more frequently if required in the judgement of the investigator (see Table 1 for more details).

[redacted]

- [redacted]

Blood samples for plasma drug concentration will be collected during the in-clinic visits (besides screening) and adverse event inquiry will be performed at all visits and telephone calls/teleconferences (TCs).

If a patient withdraws from the study prior to the randomization 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.

Stage 2: Double-blind maintenance stage (variable in duration). Stabilized patients (see definition above) will be randomized to receive TV-46000 q1m sc injections, TV-46000 q2m sc injections, or placebo q1m sc injections in a 1:1:1 ratio. Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.

Patients in the TV-46000 groups will receive a dose of TV-46000 (q1m or q2m) that is equivalent to the oral dose on which they were stabilized in Stage 1. The maximal dose administered to adult patients will be equivalent to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents will be equivalent to 4 mg/day. Patients randomized to TV-46000 q1m or placebo sc will receive an sc injection of TV-46000 or placebo, respectively, at baseline and every 4 weeks (q4w) thereafter. Patients randomized to TV-46000 q2m will receive a TV-46000 injection at baseline and every 8 weeks (q8w) thereafter, and a placebo sc injection 4 weeks after baseline and q8w thereafter, to ensure blinding of the doses and durations of the TV-46000 injections and the placebo injections.

The study will continue on an outpatient basis (Table 2), and telephone contacts will take place weekly between clinic visits. If, in the judgment of the investigator, the patient is likely to relapse or pose a danger to himself/herself or others, that patient may be invited for an unscheduled visit and/or hospitalized if needed, and treatment with the study drug may be discontinued.

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 the 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.

The duration of patient participation in the study will include up to 4 weeks of screening, 12 weeks of the oral conversion/stabilization stage, and a double-blind maintenance stage. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or

remain relapse-free during the double-blind phase until the study is terminated because at least 90 relapse events are recorded in the study adult population.

Per definition, an exacerbation in symptoms during Stage 1 cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. Randomized patients who relapse or meet 1 or more of the withdrawal criteria should be invited to perform the Early Termination (ET) visit as soon as possible, within 4 weeks of the last injection. Patients who remain relapse-free when the study is terminated should be invited to perform the End-of-Treatment visit within 4 weeks of the last injection. Therefore, a patient is considered a study completer if he or she experienced impending relapse or remained relapse-free at the time of study termination.

Patients will subsequently complete all end-of-study assessments. When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol, and a separate protocol was issued for it. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. For all other patients (ie, patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study), there will be 2 follow-up/exit visits that will take place at 4 weeks and 8 weeks after the last dosing visit. During the follow-up/exit period, patients will be treated according to the investigator's judgement.

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.

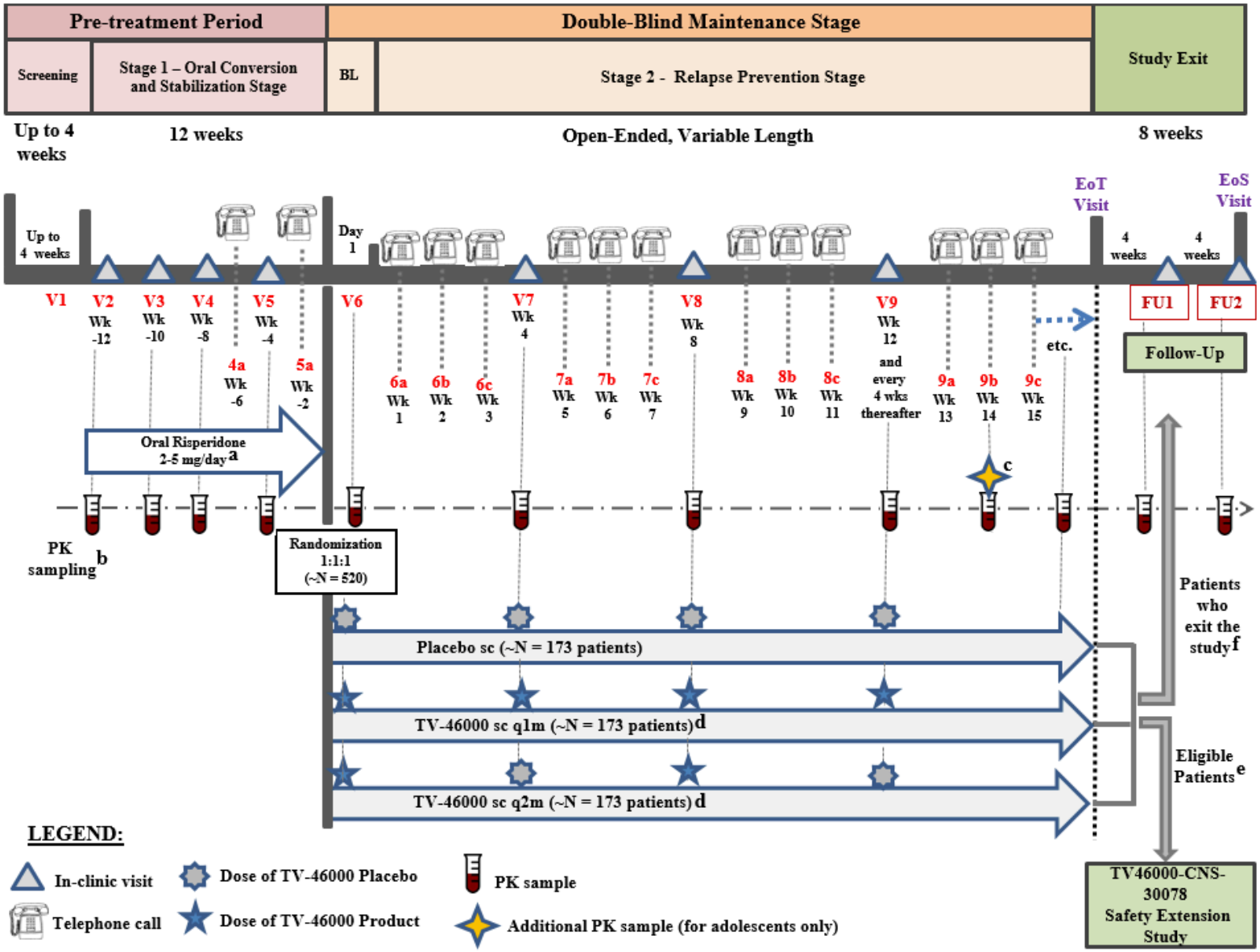
The study duration will be approximately 30 months, from Q2 2018 (first patient in) to Q4 2020 (last patient out).

During the conduct of this study, an Independent Data Monitoring Committee (IDMC) will review accumulating unblinded safety and PK data on a regular basis to ensure the continuing safety of the study patients and study conduct issues (see Section 5.10.3).

For COVID-19 updates, refer to Appendix N.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



[a] Adolescent patients will receive doses equivalent to 2-4 mg/day oral risperidone. Patients that will require a stabilization dose below 2 mg/day will not be randomized in the study.

[b] With the exception of the screening visit, pharmacokinetic samples will be collected at each in-clinic visit.

[c] [redacted]

[d] Patients randomized to the TV-46000 q1m or q2m sc groups in Stage 2 will receive TV-46000 sc at doses equivalent to the 2 to 5 mg/day dose of oral risperidone on which they were stabilized during Stage 1. Adolescent patients will receive a maximal TV-46000 dose equinvalent to 4 mg/day oral risperidone.

[e] When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol and is detailed in a separate protocol. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study.

[f] For patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study, there will be 2 follow-up/exit visits that will take place 4 weeks and 8 weeks after the last dosing visit.

BL = baseline; EoS=end of study; EoT = end of treatment; FU = Follow Up; PK = pharmacokinetics; q1m=every month; q2m=every 2 months; sc=subcutaneous; TC – telephone call/teleconference; Wk = week.

3.2. Planned Number of Patients and Countries

Approximately 1260 patients will be screened to achieve enrollment of approximately 860 adult patients in Stage 1, including approximately 70 adult patients in Bulgaria.

The number of randomized adult patients in Stage 2 is planned to be approximately 520, including approximately 55 adult patients in Bulgaria. Details on the definition of evaluable patients and determination of the sample size are given in Section 9.1. Adolescent patients will only be enrolled in the US; any enrolled adolescents will be in addition to the aforementioned total.

The study is planned to be conducted in approximately 80 investigational centers in North America and Bulgaria.

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.

[redacted]

Moreover, the drug class of LAI atypical antipsychotics has not been studied extensively in children or adolescents (Lytle et al 2017). Although compliance in children and adolescents treated with antipsychotics is substantially higher than in adults, ranging from approximately 74% to 88% (Pogge et al 2005, Yazdi et al 2008), LAIs may be considered for patients with confirmed schizophrenia and with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medication, and poor insight (Ferrin et al 2016). In the Pediatric Study

[redacted]

Antipsychotic LAIs are viewed as maintenance therapy in stable patients with schizophrenia, but they are not currently approved for treatment of acute symptoms. Thus, the population for this study consists of adult and adolescent patients with chronic schizophrenia and excludes patients with acute disease. Only patients who have been stabilized on oral therapy with risperidone will be randomized into the double-blind maintenance stage of the study.

3.4. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5.3.1) 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:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the investigational medicinal product (IMP)

3.5. [redacted]

[redacted]

For COVID-19 updates, refer to Appendix N.

Table 1: TV46000-CNS-30072 (RISE) Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – Pre-Treatment Period (Screening and Stage 1)

Study Period	**Pre-treatment Period**							**N/A**
	Screening	**Stage 1: Oral Conversion and Stabilization Stage**[a]						**Unscheduled Visit**
Visit number	**V1**	**V2**	**V3**[b]	**V4**	**V4a**	**V5**	**V5a**	
Time point **Procedures and assessments**	**Wk -16**	**Wk -12**	**Wk -10**	**Wk -8**	**Wk -6**	**Wk -4**[c]	**Wk -2**	**As deemed necessary by the investigator**[d]
Allowed time window	**+4 weeks**	**±3 days**						**N/A**
In-Clinic Visit	X	X	X	X		X		X
Telephone Call [e, f]					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[g, h]	X			X				
Virology and thyroid screening tests[i]	X							
Urine drug screen	X							
Concomitant medication inquiry	X	X	X	X		X		X
Full physical examination, including weight	X[j]	X						
Vital signs measurement[k]	X	X	X	X		X		X
12-lead ECG[l]	X							
FSH Test[m]	X							
Serum β-HCG test for women of childbearing potential	X							

Study Period	**Pre-treatment Period**							**N/A**
	Screening	**Stage 1: Oral Conversion and Stabilization Stage**[a]						**Unscheduled Visit**
Visit number	**V1**	**V2**	**V3**[b]	**V4**	**V4a**	**V5**	**V5a**	
Time point **Procedures and assessments**	**Wk -16**	**Wk -12**	**Wk -10**	**Wk -8**	**Wk -6**	**Wk -4**[c]	**Wk -2**	**As deemed necessary by the investigator**[d]
Allowed time window	**+4 weeks**	**±3 days**						**N/A**
In-Clinic Visit	X	X	X	X		X		X
Telephone Call [e, f]					X		X	
Urine β-HCG test for women of childbearing potential		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	X	X	X	X		X		
CGI-I[n]		X	X	X		X		
AIMS	X	X	X	X		X		
BARS	X	X	X	X		X		
SAS	X	X	X	X		X		
C-SSRS	X	X	X	X	X	X	X	X
PSP **(in adult patients only)**	X							
SQLS **(in adult patients only)**	X							
EQ-5D-5L **(in adult patients only)**	X							
CDSS	X	X	X	X		X		
Healthcare resource utilization	X							
DAI-10 **(in adult patients only)**	X							

Study Period	**Pre-treatment Period**							**N/A**
	Screening	**Stage 1: Oral Conversion and Stabilization Stage**[a]						**Unscheduled Visit**
Visit number	**V1**	**V2**	**V3**[b]	**V4**	**V4a**	**V5**	**V5a**	
Time point **Procedures and assessments**	**Wk -16**	**Wk -12**	**Wk -10**	**Wk -8**	**Wk -6**	**Wk -4**[c]	**Wk -2**	**As deemed necessary by the investigator**[d]
Allowed time window	**+4 weeks**	**±3 days**						**N/A**
In-Clinic Visit	X	X	X	X		X		X
Telephone Call [e, f]					X		X	
Blood samples for plasma drug concentration[o]		X	X	X		X		
Oral risperidone dispensing (For qd intake)[p]		X	X	X		X		
Dosage review and adjustment		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[q]					X		X	

[a] If a patient withdraws from the study prior to the randomization 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.

[b] 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.

[c] 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.

[d] 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 procedures which are currently marked 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.

[e] 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 contacts that take place 2 weeks after visit 4 will be referred to as “visit 4a”).

[f] Each contact will include inquiries about injection site pain, suicidal ideation and behavior, 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).

[g] Clinical laboratory tests (serum chemistry, hematology, and urinalysis) may also be performed at any time if clinically indicated.

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

[i] Includes HIV, HBsAg, hepatitis C antibody, TSH, T3, and T4.

[j] Height will be measured at the screening visit only.

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

[l] At screening, ECG measurements will be done in triplicate. The mean of the 3 measurements will be used to determine study eligibility.

[m] The FSH test will only be performed for women with no menses for 12 months in order to confirm postmenopausal status.

[n] CGI-I during Stage 1 will be relative to screening.

[o] During the in-clinic visits in Stage 1, if possible, the blood samples for PK assessment should be taken within an hour prior to dosing. In any case, the hour of the last dose taken prior to collection of the pharmacokinetic sample will be recorded on the CRF.

[p] 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.

[q] 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 a psychiatric deterioration as a result of 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.

β-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; EQ-5D-5L=5-Level EuroQol Five Dimensions Questionnaire; ET=early termination; FSH=follicle stimulating hormone; FU=follow-up; HbsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; NPRS=Numeric Pain Rating Scale; PANSS=Positive and Negative Syndrome Scale; PK = pharmacokinetics; 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; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; V = Visit; Wk=week.

Table 2: TV46000-CNS-30072 (RISE) Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – Baseline, Double-Blind Maintenance Stage (Stage 2), End of Treatment/Early Termination and Follow-Up

Study Period	**Double-Blind Maintenance Stage[a]**															**Follow-Up**		**N/A**
	BL	**Stage 2: Relapse Prevention**																
	BL		**The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.**												**End of Treatment (EoT)/Early Termination (ET) Visit**	**Exit[b]**		**Unscheduled Visit[c]**
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**		**FU1**	**FU2**	**As deemed necessary by the investigator**
Time point **Procedures and assessments**	**Day1**	**Wk 1-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**		**4 Wks after last dosing visit**	**8 Wks after last dosing visit (EoS)**	
Allowed time window	**±3 days**															**±3 days**		**N/A**
In-Clinic Visit	X		X		X		X		X		X		X		X	X	X	X
Telephone Call[d, e]		X		X		X		X		X		X		X				
Inclusion and exclusion criteria	X[f]																	
Clinical laboratory tests[g, h]	X				X				X				X		X	X	X	
Urine drug screen	X														X			
Concomitant medication inquiry	X		X		X		X		X		X		X		X	X	X	X
Fully physical examination, including weight	X														X	X	X	
Vital signs measurement[i]	X		X		X		X		X		X		X		X	X	X	X
12-lead ECG[j]	X				X				X				X		X[k]	X	X	
Serum β-HCG test for women of childbearing potential	X															X	X	

Study Period	**Double-Blind Maintenance Stage[a]**														**Follow-Up**		**N/A**
	BL	**Stage 2: Relapse Prevention**															
	BL		**The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.**											**End of Treatment (EoT)/Early Termination (ET) Visit**	**Exit[b]**		**Unscheduled Visit[c]**
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**	**FU1**	**FU2**	**As deemed necessary by the investigator**
Time point **Procedures and assessments**	**Day1**	**Wk 1-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**4 Wks after last dosing visit**	**8 Wks after last dosing visit (EoS)**	
Allowed time window	**±3 days**														**±3 days**		**N/A**
In-Clinic Visit	X		X		X		X		X		X		X		X	X	X
Telephone Call[d, e]		X		X		X		X		X		X		X			
Urine β-HCG test for women of childbearing potential[l]	X		X		X		X		X		X		X		X		
Inquiry about pregnancy status (for women of childbearing potential)		X		X		X		X		X		X		X			
PANSS	X		X		X		X		X		X		X		X	X	X
CGI-S	X		X		X		X		X		X		X		X	X	
CGI-SS	X		X		X		X		X		X		X		X	X	
CGI-I[m]			X		X		X		X		X		X		X	X	
AIMS	X		X		X		X		X		X		X		X	X	
BARS	X		X		X		X		X		X		X		X	X	
SAS	X		X		X		X		X		X		X		X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP **(in adult patients only)**	X				X		X[n]						X		X	X	

Study Period	**Double-Blind Maintenance Stage[a]**														**Follow-Up**		**N/A**
	BL	**Stage 2: Relapse Prevention**															
	BL		**The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.**											**End of Treatment (EoT)/Early Termination (ET) Visit**	**Exit[b]**		**Unscheduled Visit[c]**
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**	**FU1**	**FU2**	**As deemed necessary by the investigator**
Time point **Procedures and assessments**	**Day1**	**Wk 1-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**4 Wks after last dosing visit**	**8 Wks after last dosing visit (EoS)**	
Allowed time window	**±3 days**														**±3 days**		**N/A**
In-Clinic Visit	X		X		X		X		X		X		X		X	X	X
Telephone Call[d, e]		X		X		X		X		X		X		X			
SQLS **(in adult patients only)**	X				X		X[n]						X		X	X	
EQ-5D-5L **(in adult patients only)**	X				X		X[n]						X		X	X	
CDSS	X		X		X		X		X		X		X		X	X	
Healthcare resource utilization	X						X[n]						X		X	X	
DAI-10 **(in adult patients only)**	X														X	X	
Blood sample for pharmacogenetic analysis	X[o]																
Blood sample for biomarker analysis[p]	X														X	X	
Blood samples for plasma drug concentration[q]	X		X		X		X		X		X		X		X	X	X[r]

Study Period	**Double-Blind Maintenance Stage[a]**														**Follow-Up**		**N/A**
	BL	**Stage 2: Relapse Prevention**															
	BL		**The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.**											**End of Treatment (EoT)/Early Termination (ET) Visit**	**Exit[b]**		**Unscheduled Visit[c]**
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**	**FU1**	**FU2**	**As deemed necessary by the investigator**
Time point **Procedures and assessments**	**Day1**	**Wk 1-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**4 Wks after last dosing visit**	**8 Wks after last dosing visit (EoS)**	
Allowed time window	**±3 days**														**±3 days**		**N/A**
In-Clinic Visit	X		X		X		X		X		X		X		X	X	X
Telephone Call[d, e]		X		X		X		X		X		X		X			
Blood samples for plasma drug concentration **(Adolescents only)**							X[s]										
Assessment of stability	X[t]																
Randomization	X																
Placebo sc administration[u]	X		X		X		X		X		X		X		X[v]		
TV-46000 q1m sc administration[u]	X		X		X		X		X		X		X		X[v]		
TV-46000 q2m sc administration[u, w]	X				X				X				X		X[v]		
Questions to assess ease of study drug administration[x]	X		X		X												
Adverse event inquiry (including SAE reporting, injection site-related events including pain)[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Double-Blind Maintenance Stage[a]**														**Follow-Up**		**N/A**
	BL	**Stage 2: Relapse Prevention**															
	BL		**The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.**											**End of Treatment (EoT)/Early Termination (ET) Visit**	**Exit[b]**		**Unscheduled Visit[c]**
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**	**FU1**	**FU2**	**As deemed necessary by the investigator**
Time point **Procedures and assessments**	**Day1**	**Wk 1-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**4 Wks after last dosing visit**	**8 Wks after last dosing visit (EoS)**	
Allowed time window	**±3 days**														**±3 days**		**N/A**
In-Clinic Visit	X		X		X		X		X		X		X		X	X	X
Telephone Call[d, e]		X		X		X		X		X		X		X			
Inquiry regarding alcohol consumption/illicit drug use	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[z]		X		X		X		X		X		X		X			

[a] The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated because at least 90 relapse events are recorded in the study in the ITT analysis set. Patients will continue study visits and assessments as shown in the table (ie, the same assessments performed at visits Visits 7 and 8 will be repeated at visits Visits 9 and 10, respectively). However, note that functional measures (PSP, SQLS, and EQ-5D-5L) and the healthcare resource utilization will be performed every 12 weeks.

[b] When the study ends, eligible patients may be offered the opportunity to enter TV46000-CNS-30078, the long-term safety and tolerability extension study. This extension study is beyond the scope of this protocol and is detailed in a separate protocol. If the patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. All other patients (ie, patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study), will undergo these 2 follow-up/exit visits. During the follow-up/exit period patients will be treated according to the investigator's judgement.

[c] 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 procedures which are currently marked 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.

[d] Telephone contacts 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).

[e] Each contact will include inquiries about injection site pain, suicidal ideation and behavior, 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).

[f] Patient must meet randomization criteria in addition to other relevant inclusion criteria before randomization.

[g] Clinical laboratory tests (serum chemistry, hematology, and urinalysis) may also be performed at any time if clinically indicated.

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

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

[j] 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.

[k] During the EoT visit, if in the judgment of the investigator the patient will not roll over into the extension study or will not come to one or both of the follow-up visits – an ECG should be performed.

[l] Urine β 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 study drug is administered.

[m] CGI-I during Stage 2 will be relative to the baseline visit.

[n] As of Visit 9, inclusive, this assessment will be conducted every 12 weeks thereafter (Visits 12, 15, 18, and so on).

[o] 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.

[p] Blood 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.

[q] Blood samples for PK assessment will be taken within an hour prior to dosing.

[r] 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 the 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.

[s] Another pharmacokinetic sample will be collected from adolescent patients at a supplementary in-clinic visit at Week 14 (2 Weeks after Visit 9). If it is not possible to take the sample at this visit, it may be taken 2 weeks after another in-clinic visit. Two additional samples, 3 weeks and 1 week post-injection, respectively, may be taken at the sponsor's discretion.

[t] Stability is defined as meeting all of the following criteria for at least for 4 consecutive weeks prior to the baseline visit: outpatient status; PANSS total score ≤80; minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; Clinical Global Impression of Severity (CGI-S) score ≤4 (moderately ill); and CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2.

[u] Study drug will be administered per the patient's assigned treatment group.

[v] Applicable only for EoT visit (ie, not ET). If in the judgment of the investigator, the patient will not roll over into the extension study or will not come to one or both of the follow-up visits – a dose of study drug should not be given in this EoT/ET EoT visit.

[w] Patients randomized to the TV-46000 q2m group will receive a TV-46000 injection at the baseline visit and q8w thereafter and a placebo sc injection 4 weeks after baseline and q8w thereafter to ensure blinding.

[x] In the event that prefilled syringes become available during the study, this will be completed by the unblinded nurse who administers the study drug to the patients following the first 3 injections to each patient.

[y] 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.

[z] 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 a psychiatric deterioration as a result of 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.

β-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; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitudes Inventory 10-item version; ECG = electrocardiography; EQ-5D-5L=5-Level EuroQol Five Dimensions Questionnaire; EoS=end of study ;EoT=end of treatment; ET=early termination;FU=follow-up; NPRS=Numeric Pain Rating Scale; PANSS=Positive and Negative Syndrome Scale; PSP=Personal and Social Performance Scale; q1m = once monthly; 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; 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 be enrolledin this study only if they meet all of the following criteria:

a. The patient has a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for >1 year (diagnosis must be reconfirmed by SCID-5) and has had ≥1 episode of relapse in the last 24 months.

b. The patient has been responsive to an antipsychotic treatment (other than clozapine) in the past year based on investigator judgement (and discussions with family members, caregivers or healthcare professionals as applicable).

c. [Revision 1] The patient has provided written informed consent and is competent to do so. For adolescent patients, written informed consent has been provided by each patient's parent or legal guardian, and written assent has been provided by 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, tablet ingestion, sc depot injection, and discontinuation 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 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. [Revision 1] The patient is a male or female of any ethnic origin, 13 through 65 years of age at screening.

k. [Revision 2] The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive at screening.

l. The patient is in adequate health as determined by medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, urinalysis, and serology.

m. [Revision 1] Women of childbearing potential (see Appendix E) 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 drugs and for the duration of the study and for 120 days after the last injection of study drug. Highly effective methods of contraception include:

- 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 and intrauterine hormone-releasing system; these need to be 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. [Revision 1] 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 follow-up procedures and assessments as specified in this protocol.

Randomization Criteria:

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

p. The patient has not experienced mental or physical deterioration, which prevents participation in the study per investigator judgement.

q. The patient has demonstrated good compliance in following protocol requirements during Stage 1.

   – 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).

r. 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 ≤80
   - minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
   - CGI-S score ≤4 (moderately ill)
   - CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2

4.2. Patient Exclusion Criteria

Patients will not be enrolled/randomized in this study if they meet any of the following criteria:

a. The patient has a current clinically significant DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic 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, clinically significant tardive dyskinesia, or other medical condition that would expose the patient to undue risk.

d. [Revision 1] 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 RNA 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 currently has or has 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 investigator's judgement.

h. The patient has a significant risk of committing suicide based on the patient's medical history or 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 previously participated in a Teva-sponsored clinical study with TV-46000.

j. The patient has a clinically significant deviation from normal in the physical examination.

k. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results.

   – 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 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 the medications prohibited in this protocol.

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 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 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 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. 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. Alternatively, if the opportunity is available and the patient is eligible, the patient may be offered the option to participate in TV46000-CNS-30078, the long-term safety and tolerability extension study.

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 case report form (CRF); both the adverse events page and the relevant page of the CRF will be completed at that time.

The patient will be monitored 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 test IMP or study procedure is made). 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

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. A serious or intolerable adverse event develops that necessitates discontinuation at the discretion of the investigator.
3. The investigator believes 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. A patient requires concomitant medication that may interfere with the pharmacokinetics of the study drug.
6. A patient relapses, as defined by the study's relapse criteria (Section 9.5.1).
7. A 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 ≥30 ms 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. A patient exhibits an event of possible drug-induced liver injury that requires immediate study treatment cessation and is defined as follows:
   - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 times the upper limit of normal (ULN)
   - ALT or AST >5×ULN for more than 2 weeks
   - ALT or AST >3×ULN and total bilirubin level >2×ULN or international normalized ratio >1.5
   - ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

4.3.3. Pharmacokinetic Sampling in Case of Patient Withdrawal

Note: Withdrawal under the above criteria (see Section 4.3.2) 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 an 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 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

A patient who is randomized but does not complete all treatment periods will not be replaced with another eligible patient.

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) will need to be resigned.

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. 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

Investigational medicinal product is defined as the test IMP (Table 4).

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 [redacted].

For COVID-19 updates, refer to Appendix N.

[redacted]

5.1.1.1. Starting Dose and Dose Levels

In general, TV-46000 will be administered to patients in the abdomen (except as indicated below) by sc injection, at intervals of q1m or q2m, at a dose equivalent to oral risperidone 2 to 5 mg/day on which they were stabilized in Stage 1, per the conversion table below (Table 3). The maximal dose administered will be equivalent to an oral risperidone dose of 5 mg/day. Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.

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

Table 3: Conversion Table Between Oral Risperidone and TV-46000 Doses

Frequency of TV-46000 Administration	Oral Risperidone Doses and Corresponding TV-46000 Doses			
	2 mg/day	3 mg/day	4 mg/day	5 mg/day (Adults Only)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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 arm and the left. If the chosen site is the abdomen, the injection will be administerd in an alternating manner to the right and to the left of the umbilicus. Further details will be provided in the dosing manual.

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]

Additional details about sc injection administration can be found in the study manual.

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 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.

For COVID-19 updates, refer to Appendix N.

5.3. [redacted]

[redacted]

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

The US FDA requires a placebo-controlled study to demonstrate the efficacy and safety of TV-46000 for the maintenance treatment of patients with chronic schizophrenia. While it has been demonstrated that regular use of antipsychotics reduces the rate of relapses, treatment compliance is poor, which is often related to side effects. It is considered justified to treat patients with placebo after they have been stabilized on oral active treatment. Patients who experience a relapse will discontinue study drug and may be treated using standard of care.

5.4. Other Medicinal Products/Non-Investigational Medicinal Products

In the US, oral risperidone for stabilization (Table 5) will be a commercial product supplied by the study center. In Bulgaria, oral risperidone for stabilization (Table 5) will be a commercial product supplied centrally by the sponsor. The brand name of the oral risperidone supplied will be recorded on the source documentation.

Oral risperidone is to be stored according to the manufacturer's Summary of Product Characteristics (SmPC).

Note that oral risperidone is mandated for use in this study; 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[a]
Unit dose strength(s)/dosage level(s)	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)

[a] 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 case the patient is withdrawn from this study, no further treatment is planned by the sponsor after the patient completes their participation in this study. Patients will be advised to return to their primary physician for additional treatment. Patients may be treated in the meantime per investigator judgment and instruction as applicable.

When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol, and a separate protocol was issued for it.

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/exit period. Patient 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. [redacted]

[redacted]

5.8. [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

Patients will be randomized to receive doses of TV-46000 q1m sc injection, TV-46000 q2m sc injection, or placebo q1m sc injection in a 1:1:1 ratio. Randomization will be stratified by gender (male or female) and the dose of oral risperidone on which the patient was stabilized during Stage 1 (2/3, 4, or 5 mg). The doses of TV-46000 will be equivalent to 2 to 5 mg/day of oral risperidone (equivalent to the oral dose on which the patient was stabilized in Stage 1). Patients randomized to TV-46000 q1m or placebo sc will receive an sc injection of TV-46000 or placebo, respectively, at baseline and q4w thereafter. Patients randomized to TV-46000 q2m will receive a TV-46000 injection at baseline and q8w thereafter and a placebo sc injection 4 weeks after baseline and q8w thereafter to ensure blinding of the doses and durations of the TV-46000 injections and the placebo injections.

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

[redacted]

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The randomization list will be assigned to the relevant treatment groups through a qualified service provider (eg, via the Interactive Response Technology [IRT] system). The generation of the randomization list and management of the IRT system will be done by a qualified service provider under the oversight of the responsible function at Teva. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

The sponsor's clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for final analysis, and the IMP assignment is known. However, if a prioritized sample analysis is needed, bioanalytical and IDMC clinical pharmacology representatives are unblinded.

In the event of an emergency (ie, where knowledge of the study drug assignment is needed to make treatment decisions for the patient), the treatment group and dose to which the patient has been allocated can be determined by accessing the IRT system. All investigational centers will

be provided with details on 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 pharmacist at each investigational center who will dispense the IMPs will know the IMP assignments for each patient. In addition, up to 2 other individuals from each investigational center will know the IMP assignments to provide quality assurance and oversight in their preparation and administration, as necessary. These individuals will not be involved in conduct of any study procedures and assessment of any adverse events and should not discuss the medication assignment or appearance with others (except for the unblinded nurse administering the medication).

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. At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP.

5.10.2. Blinding and Unblinding

Pharmacokinetic data will be assessed during the study. Personnel responsible for bioanalysis will be provided with the randomization code in order to facilitate the analysis. However, the personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide unblinded pharmacokinetic concentration data to the unblinded statistician for provision to the IDMC members for review, and to a pharmacometrics modeler, independent of the study team, for update of the population pharmacokinetic model. In addition, the modeler may receive other relevant patient information to update the model (such as demography, certain clinical laboratory results, etc). The detailed process of data delivery to the IDMC will be described in the IDMC charter. The detailed process of pharmacokinetic analysis during the course of the study will be described in the pharmacokinetic analysis plan. The pharmacokinetic concentrations and modeling results will not be available to the sponsor's study team until unblinding of study.

For information about personnel who may be aware of IMP assignments (including an unblinded nurse and an unblinded pharmacist), see Section 5.9. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

In case of a serious adverse event, 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 each investigational center via the IRT, 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. The patient's IMP assignment should not be revealed to the sponsor.

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.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), the Global Patient Safety and Pharmacovigilance (GPSP) team may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

5.10.3. Data Monitoring Committee

During the conduct of this study there will be an IDMC that will review accumulating unblinded safety and pharmacokinetic data on a regular basis (as detailed in the IDMC charter) to ensure the continuing safety of the study patients and any study conduct issues.

The IDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician and a pharmacokinetic specialist.

The IDMC chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

The IDMC will provide recommendations about modifying, stopping, or continuing the study. The conduct and specific details regarding the IDMC sessions will be outlined in the IDMC charter.

5.11. [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 Clinical Global Impression–Improvement (CGI-I) scale permits a global evaluation of the patient's improvement in symptoms overall. The CGI-I scale rates the patient's improvement relative to his or her symptoms on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) (Guy 1976a).

The CGI-I will be administered by the investigator/trained rater at all visits during the study (except for the screening and baseline visits).

6.1.2. Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al 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 by a clinician or trained mental health professional that 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 of 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 et al 2015).

6.2.2. Quality of Life Scales

6.2.2.1. Schizophrenia Quality of Life Scale (SQLS)

SQLS will be administered to adult patients only at the time points specified in Table 1 and Table 2, and is used to capture quality of life. The 33-item measure yields 3 subscale scores:

psychosocial, motivation/energy, and symptoms/side effects (Wilkinson et al 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 and de Charro 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 track very closely (r=0.93), and only the shorter DAI-10 will be used. 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 et al 1983, Nielsen et al 2012). A positive total score indicates a compliant response and a negative 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 et al 2000). The PSPis 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 indicating functioning so poor that intensive supervision is required.

6.2.5. Healthcare Resource Utilization

Healthcare resource utilization will be assessed for both adult and adolescent patients approximately every 3 months (at the time points specified in Table 1 and Table 2) for hospitalizations, emergency room (ER) visits, and outpatient visits (ie, not including protocol-mandated outpatient visits). Hospitalizations will be assessed as the percentage of patients with hospitalizations over the past 4 weeks, associated length of stay, and the number of hospitalizations among patients who were hospitalized. In addition, the percentage of patients with ER visits and number of ER visits over the past 4 weeks and the percentage of patients with outpatient visits and number of outpatient visits over the past 4 weeks will be evaluated.

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

6.2.6. Clinical Global Impression of Severity

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.

A relapse event, defined per one of the criteria listed (see primary endpoint definition in Section 2.1), will not be automatically classified as an adverse event unless specifically judged as such by the investigator.

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 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 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 case 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 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 Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 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 as follows:

Table 6: The Relationship of an Adverse Event to the IMP

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.	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: • It does not follow a reasonable temporal sequence from the administration of the IMP. • 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. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
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.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • 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. • 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. • It follows a known pattern of response to the IMP.

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 that time period from signature of the ICF 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.

A relapse event, defined per one of the criteria listed (see primary endpoint definition in Section 2.1), will not be automatically classified as a serious adverse event unless specifically judged as such by the investigator.

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 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 1 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 **al**l of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- ALT or AST increase of >3× the ULN
- total bilirubin increase of >2× 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 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 SUSAR reporting, the version of the RSI at the time of occurrence of the SUSAR applies.

A serious adverse event that is not included in the Listing of Adverse Reactions in the RSI by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The sponsor's 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 team.

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
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility and reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount 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 team 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.

For double-blind studies, blinding will be maintained for all study personnel except the unblinded nurse. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

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 end of study, 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 were 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 defect, 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 serious adverse event, as appropriate.

Since there is lack of data on human teratogenicity, genotoxicity, fetotoxicity, or spermatoxicity for this IMP, female partners of men participating in the study who become pregnant will be asked to sign an ICF and 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 defect, 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 serious adverse event, as appropriate.

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, 1 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 of the reference range will be judged by the investigator as belonging to 1 of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Table 7: [redacted]

For COVID-19 updates, refer to Appendix N.

7.4.1. [redacted]

Table 7.

[redacted]

7.5. Physical Examinations

Full physical examinations, including height (to be obtained at the screening visit only) 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) 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 of the reference ranges will be judged by the investigator as belonging to 1 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 at all other in-clinic visits. A qualified physician at a central diagnostic center will be interpreting the ECG.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to 1 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) 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 case an adverse event related to an injection site reaction is reported, an assessment of the sc injection site (ie, local tolerability [skin at injection site]) will be made. The presence and severity of erythema, swelling, induration, and pain at the injection site may be assessed using the scales 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/nodules 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 case an adverse event related to an injection site reaction is reported, intensity of injection pain will be assessed by patients using an 11-point NPRS (0 [no pain] to 10 mm [worst pain]) (Williamson and Hoggart 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 an increased risk of suicide attempt 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 or during this clinical study.

The study population being administered TV-46000 or placebo 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 scale.

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 et al 2011). The interview and rating for the C-SSRS will be conducted by a rater specifically trained to rate the scale (per the minimum requirements outlined by the scale author), regardless of education level, who has appropriate clinical trial experience with C-SSRS administration, after review and approval by the Teva clinical project physician or designee. 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 C-SSRS will be administered at screening (baseline/screening version) and all post-screening visits (“since last visit” version) during the study, as well as during phone contacts (“since last visit” version).

7.9.2. Clinical Global Impression-Severity of Suicidality

The CGI-SS scale provides an overall clinician-rated assessment of the risk of suicidality (Lindenmayer et al 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 and all visits during the study.

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 scored 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 and Angus 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 et al 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]

Table 8: [redacted]

[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/ BIOMARKERS/ PHARMACOGENOMICS

8.1. [redacted]

[redacted]

For COVID-19 updates, refer to Appendix N.

8.2. [redacted]

[redacted]

8.3. [redacted]

[redacted].

8.4. Pharmacogenetics

[redacted] The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research. The planned pharmacogenetic analysis and results of other potential genetic factors will be detailed in a separate document that will encompass the latest scientific advances related to this evaluation.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. 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).

9.1.

9.2. Analysis Sets

9.2.1. Enrolled Patients Set

The enrolled patients set will include all patients who have met study eligibility requirements for Stage 1 and received oral risperidone.

9.2.2. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include adult patients randomized to the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

The purpose of the primary analyses is to estimate the effect of randomized treatment only, omitting any effect of additional treatment that may be administered *after* discontinuation of the randomized treatment. Accordingly, the ITT analysis set complies with while-on-treatment strategy[1] that will be taken with regard to the intercurrent event of treatment discontinuation, with censoring at this intercurrent event. This study estimand will be the difference in time to relapse (survival) under the treatment to which the patient was initially randomized until last treatment or early termination of all adult patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg.

9.2.3. Extended Intent-to-Treat Analysis Set

The extended intent-to-treat (eITT) analysis set will include all patients (adults and adolescents) randomized to the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the eITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include all patients in the ITT analysis set who have no major protocol deviations. In this analysis set, treatment will be assigned based on the treatment patients actually received. The PP analysis set will be discussed before unblinding and findings will be documented in the study data review document.

9.2.5. Safety Analysis Set

The safety analysis set will include all randomized patients who receive ≥1 dose of study treatment or placebo in the double-blind maintenance stage (Stage 2). In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

9.2.6. Pharmacokinetics Analysis Set

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

9.3. Data Handling Conventions

For all variables, only those observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate missing data, unless otherwise specified. Data from

[1] ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guidance on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017. European Medicines Agency. 30 August 2017.

patients who did not relapse will be censored at the last valid relapse assessment date. Detailed data imputation rules will be described in the statistical analysis plan.

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

The eITT analysis set (Section 9.2.3) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. If the number of adolescents permits, summaries will also be presented by age subgroup.The primary analysis will be conducted on the ITT analysis set (Section 9.2.2), and the eITT analysis set (Section 9.2.3) will be used for analysis of the key secondary endpoints unless otherwise specified. The analysis set on which analysis for other endpoints will be conducted will be specified on a case-by-case basis. The enrolled patients set (Section 9.2.1) will be used for data summaries before the double-blind treatment stage.

9.4.1. Patient Disposition

Data from patients screened and enrolled in Stage 1; patients who were enrolled in Stage 1 but not randomized for the double-blind stage and reason for not randomized; patients who were randomized; patients who were randomized but not treated; patients in the ITT patients in the eITT, PP, safety, and pharmacokinetics analysis sets; patients who completed the study; and patients who withdrew from the study will be summarized using descriptive statistics. Data from patients who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics. Adolescent patient disposition may be summarized separately, if applicable.

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 the descriptive statistics. For continuous variables, descriptive statistics (number [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, the eITT analysis set, and the eITT subset of adolescents will be used for the summaries, as applicable.

9.5. Efficacy Analysis

9.5.1. Primary Endpoint

The primary efficacy endpoint is time to impending relapse. Patients meeting any 1 or more of the below impending relapse criteria are considered relapsed. Relapse is defined as 1 or more of the following items:

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

  - an increase of any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥2 on that specific item since randomization, **OR**
  - an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization
- hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons
- CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
- violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

Time to impending relapse will be calculated as the earliest date the patient meets ≥1 of the impending relapse criteria minus the randomization date plus 1.

The absolute increase of the combined score of the 4 PANSS items is the sum of the increases of those scores (ignoring the decreases).

9.5.2. Key Secondary Endpoints

The eITT analysis set (Section 9.2.3) will be used for all summaries in this section, unless otherwise specified.

For the endpoints that are evaluted only in the adult population, the analysis will be conducted on the ITT analysis set.

The key secondary endpoints are listed in Section 2.1 and described in detail below.

9.5.2.1. Time to Impending Relapse in the eITT Analysis Set

Time to impending relapse using the same definition and primary analysis that is described in Section 9.5.1 using the eITT analysis will be employed.

9.5.2.2. Impending Relapse Rate at Week 24

This rate will be estimated using the Kaplan-Meier method.

9.5.2.3. Percentage of Patients Who Maintain Stability at Endpoint

Stability is defined as meeting all of the following criteria for at least 4 consecutive weeks: outpatient status; PANSS total score ≤80; minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; CGI-S score ≤4 (moderately ill); and CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2.

The percentage will be calculated as the number of patients who maintained stability at endpoint divided by the number of eITT patients that adhere to treatment for at least 4 weeks or experienced relapse in the given treatment group.

This analysis estimates the treatment effect of randomized treatment on patient's stability once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with while on treatment estimand and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to maintain stability once they start the treatment if the patient adheres to the treatment long enough.

9.5.2.4. Percentage of Patients Achieving Remission at Endpoint

Positive symptom, negative symptom, and overall symptom remission will be examined and are defined by Andreasen et al (2005) including severity and duration criteria. All remission criteria can be derived from PANSS items.

For overall symptom remission, the patient must not relapse during the study and in addition, over a period of at least 6 months preceding the endpoint, maintain scores of ≤3 on each of the 8 specific PANSS items: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms/posturing), N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity).

The percentage will be calculated as the number of patients who achieved remission at endpoint divided by the number of eITT patients that adhere at least 6 months or experienced relapse in the given treatment group.

This analysis estimates the treatment effect of randomized treatment on patient's remission once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with the while on treatment estimand, and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to achieve remission once they start the treatment if the patient adheres to the treatment long enough.

9.5.2.5. Observed Rate of Impending Relapse at Endpoint

Observed rate of impending relapse will be calculated as the number of patients who relapsed by endpoint divided by the number of patients in each treatment group.

9.5.2.6. Drug Attitudes Inventory 10-item Version

The change from baseline to endpoint in total score will be calculated.

9.5.2.7. Schizophrenia Quality of Life Scale

The change from baseline to endpoint in total score will be calculated.

9.5.2.8. Time to Impending Relapse in Adolescent Patients with Schizophrenia

Time to impending relapse using the same definition and primary analysis that was described in Section 9.5.1 will be used on the eITT analysis set using adolescent patients alone.

This assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.

[redacted]

9.5.3.1. [redacted]

[redacted]

9.5.3.2. Healthcare Resource Utilization

The percentage of patients who were hospitalized, number of hospitalizations, and length of hospital stay (number of days); percentage of patients who had ER visits and number of ER visits; and percentage of patients who had outpatient visits and number of outpatient visits will be calculated.

9.5.3.3. Change in PANSS Total Score from Baseline to Endpoint

The change from baseline to endpoint in total score will be calculated.

9.5.3.4. CGI-I Score at Endpoint

CGI-I at endpoint will be analyzed.

9.5.3.5. Personal and Social Performance Scale

The change from baseline to endpoint in total score will be calculated.

9.5.4. Planned Method of Analysis

The ITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group. Analysis that will be conducted on the eITT analysis set or on the adolescent patient subset of the eITT will be described below, as applicable.

9.5.4.1. Primary Efficacy Analysis

Time to impending relapse will be calculated as the earliest date the patient meets ≥1 of the impending relapse criteria minus the randomization date plus 1. Data from patients who did not relapse will be censored at the last valid assessment. Time to impending relapse for TV-46000 and placebo will be compared using the stratified log-rank test at significance levels described in Section 9.6. Hazard ratios and their 2-sided 95% confidence intervals (CIs) for TV-46000 q1m

and q2m versus placebo will be analyzed using a Cox proportional hazard model, with treatment and stratification variables as the factors, as described in Section 5.9.

Kaplan-Meier curves will be provided to present impending relapse rate data over time.

9.5.4.2. Sensitivity Analysis

A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment at the time the first relapse was observed via the interval censoring method. Sensitivity analysis will also be conducted by tipping point analysis that imputes time to relapse for dropouts (for reasons suspected to be related to relapse) with increasing risk to relapse compared to similar patients in the same treatment group that continue treatment.

The PP analysis set will also be used as supplemental analysis to evaluate the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.

For COVID-19 updates, refer to Appendix N.

9.5.4.3. Subgroup Analysis

Additional subgroup analysis for the primary endpoint, including region, will be described in the statistical analysis plan.

9.5.4.4. Key Secondary Analyses

The fixed sequential (hierarchical) Strategy (FDA 2017) will be used to control the overall Type-I statistical error in the study for both primary and secondary efficacy endpoints. The key secondary endpoints will be analyzed in a pooled manner for q1m and q2m. The details about the Type-I statistical error control for the key secondary endpoints will be discussed in the statistical analysis plan.

9.5.4.4.1. Time to Event Key Secondary Analysis

For the key secondary endpoint discussed in Section 9.5.2.1, time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2). The Cox proportional hazard model will include patient age group (if applicable) along with treatment, and the aforementioned stratification variables as the factors.

For the key secondary endpoint discussed in Section 9.5.2.8, time to impending relapse in adolescent patients will be assessed if the number of randomized patients will be at least 10 with clinically sufficient exposure. The method will be similar to the Primary Efficacy Analysis, but will use the adolescent patients subset. Type-I statistical error control will be discussed in Multiple Comparisons and Multiplicity.

9.5.4.5. Key Secondary Efficacy Analysis 9.5.2.2-9.5.2.7

Impending relapse rate at week 24 will be estimated using the Kaplan-Meier method and calculated as 1 minus the proportion of patients free of impending relapse events at week 24. The Greenwood formula will be used to calculate standard errors for impending relapse rates at week

24, and the pooled standard errors will be used for hypothesis testing using z-statistics, assuming that the differences between TV-46000 and placebo follow a normal distribution of large samples.

Two-sided 95% CIs of the differences will also be calculated.

The observed impending relapse rates at endpoint will be compared between groups using the Cochran–Mantel–Haenszel (CMH) test adjusting for stratification variables.

The analyses of the proportion of patients who maintain stability at endpoint and the proportion of patients achieving remission at endpoint in Stage 2 will be described in the statistical analysis plan.

Change from baseline of DAI-10 and SQLS total score, will be analyzed using an analysis of covariance (ANCOVA) method, with treatment and stratification variables as factors and baseline (score at the end of Stage 1) as a covariate. Additional details regarding the anaysis will be documented in the statistical analysis plan.

The eITT analysis set (Section 9.2.3) will be used for all summaries in this section, unless otherwise specified.Type-I statistical error control will be discussed in Multiple Comparisons and Multiplicity.

[redacted]

9.6. Multiple Comparisons and Multiplicity

[redacted], a fixed sequential (hierarchical) testing approach will be implemented. If the resulting first p-value of the primary efficacy hypothesis test comparing q1m to placebo is found to be significant at 0.05 alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of

0.05. If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed.

Type-I error will be further controlled for the key secondary endpoints by employing fixed sequential (hierarchical) testing strategy within each endpoints family (primary endpoints and key secondary endpoints). Secondary endpoints will be analyzed in a pooled manner for the treatment groups if the two primary endpoints are found to be significant. Further details about the Type-I statistical error control will be discussed in the statistical analysis plan.

A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type-I error rate. The sequence of the secondary endpoints comparisons will be as follows:

1. Time to impending relapse in the eITT analysis set
2. Impending relapse rate at week 24
3. Percentage of patients who maintain stability at endpoint
4. Percentage of patients achieving remission at endpoint
5. Observed rate of impending relapse at endpoint
6. DAI-10 change from baseline to endpoint
7. SQLS change from baseline to endpoint
8. Time to impending relapse in adolescent patients with schizophrenia

If the first comparison is found to be significant, then the next comparison of interest will be interpreted inferentially at the same alpha level. This process will continue either until all comparisons were tested inferentially or until the point at which the resulting 2-sided test is insignificant at the same alpha level. [redacted]. Any p-value associated with these comparisons will be considered as nominal p-value and will not be used for inference.

[redacted]

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.5).

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 test IMP (ie, reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group. 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 (see 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. Adjustment to stratification factors may be conducted as appropriate.

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.

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.

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.

Safety data collected in Stage 1 will also be summarized using descriptive statistics in the enrolled patients set.

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

Separate summaries for adolescent patients may be presented separately for some analyses, as applicable, and will be described in the Statistical Analysis Plan.

9.8. Tolerability Analysis

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

All-cause discontinuation rates and discontinuation rates due to adverse events (dropout rates) will be calculated as the number of patients who withdrew early for all reasons, and the number of patients who withdrew early due to adverse events, respectively, divided by number of patients in each treatment group, and will be presented using descriptive statistics.

Time to all-cause discontinuation will be calculated as the discontinuation date minus the randomization date plus 1. Kaplan-Meier curves for the time to discontinuation as a result of all causes will be plotted.

Separate summaries for adolescent patients might be presented separately for some analyses, as applicable, and will be described in the Statistical Analysis Plan.

9.9.

9.11. Pharmacokinetic/Pharmacodynamic Analysis

9.13. Planned Interim Analysis

There will be no interim analysis in this study.

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 studies 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, 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 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.

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16. SUMMARY OF CHANGES

16.1. Global Amendment 03 (Dated 19 April 2020)

The primary reason for this amendment is to rescind the previous interim analyses strategy, and to perform the final statistical analysis of the study data when at least 90 relapse events are observed, without any interim analysis.

The original assumptions for sample size determination in the initial protocol were as follows:

- a placebo effect (namely, median time to impending relapse of 7 months in the placebo group) similar to that observed in a similarly-designed study (Kane et al 2012);
- a hazard ratio of 1.82 (placebo vs TV-46000 for both dosing regimens);
- a randomization ratio of 1:1:1 (q1m:q2m:placebo), with 2 primary hypotheses to be tested (q1m vs placebo and q2m vs placebo) at an overall 2-sided alpha of 0.050.

As the study progressed, the preliminary study design assumptions were found to no longer hold as the pooled cumulative number of relapse events (across all treatment groups, due to blinding) was lower than anticipated, based on the above mentioned median time to relapse and hazard ratio. A stronger treatment effect, a longer time to relapse for the placebo group, and an increased early termination (ET) rate - either as single factors or in combination - may cause this decrease in the rate of observed events. Since Teva personnel and delegates are blinded to the treatment assignments, the precise underlying reasons are not known at this time.

An earlier analysis will permit earlier completion of this double blind, placebo-controlled study (TV46000-CNS-30072) and earlier roll-over of patients into the ongoing TV46000-CNS-30078 safety extension study, in which all patients receive treatment with TV-46000.

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.

In addition to the reasons mentioned above, an earlier completion may be even more important now given the COVID-19 challenges.

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Table 2 (Study Procedures and Assessments) and Figure 1 (Overall Study Schematic Diagram) have also been revised to reflect the changes described below.

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE		
NDA number: ~~Not applicable~~ 213586	**NDA number: 213586**	New Drug Application number assigned. [Other section affected by this change: Investigator Agreement and Coordinating Investigator Agreement]
Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~ 145 Brandywine Parkway ~~Frazer, Pennsylvania~~ ~~19355~~ West Chester, Pennsylvania 19380 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 03, new address following relocation of sponsor offices.
CLINICAL STUDY PROTOCOL SYNOPSIS		
Sample Size Rationale: Median time to impending relapse was observed to be 7 months in the placebo group in a similarly designed study (~~RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI~~ Kane et al 2012).	Median time to impending relapse was observed to be 7 months in the placebo group in a similarly designed study (Kane et al 2012).	Correction. For consistency with Section 9.1.
LIST OF ABBREVIATIONS		
See New wording column	Added: COVID-19 = coronavirus disease 2019 TC = telephone call/teleconference; VC = videoconference	Newly-introduced abbreviations
1. INTRODUCTION AND BACKGROUND		
1.1. Introduction		
... [redacted]	[redacted]	Clarification and simplification.

Original text with changes shown	New wording	Reason/Justification for change
[redacted] ...	...	
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram		
The study will continue on an outpatient basis (~~Table 1~~Table 2), and telephone contacts will take place weekly between clinic visits.	The study will continue on an outpatient basis (Table 2), and telephone contacts will take place weekly between clinic visits.	Correction.
The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated ~~for efficacy due to a successful interim analysis or~~ because ~~207~~ at least 90 relapse events are recorded in the study adult population. ... Patients who remain relapse-free when the study is terminated ~~for efficacy due to a successful interim analysis or because 207 relapse events in adults are recorded in the study~~ should be invited to perform the End-of-Treatment visit within 4 weeks of the last injection.	The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated because at least 90 relapse events are recorded in the study adult population. ... Patients who remain relapse-free when the study is terminated should be invited to perform the End-of-Treatment visit within 4 weeks of the last injection.	There will be no interim analysis for efficacy in this study; the final analysis will be performed earlier due to the low event rate. Correction and simplification.
The study duration will be approximately 30 months, from Q2 2018 (first patient in) to Q4 2020 (last patient out). ~~In case of a successful interim analysis, the study will be terminated earlier (see Section 9.6)~~	The study duration will be approximately 30 months, from Q2 2018 (first patient in) to Q4 2020 (last patient out).	There will be no interim analysis for efficacy in this study.
See New wording column	Figure 1 (Overall Study Schematic Diagram) has been revised as described below: • Number of randomized patients was updated from ~417 to ~520; • Number of patients randomized to each treatment arm was updated from ~139 to ~173.	Updated enrollment projections.

Original text with changes shown	New wording	Reason/Justification for change
3.2. Planned Number of Patients and Countries		
Approximately ~~993~~ 1260 patients will be screened to achieve enrollment of approximately ~~695~~ 860 adult patients in Stage 1, including approximately ~~67~~ 70 adult patients in Bulgaria. The number of randomized adult patients in Stage 2 is planned to be approximately ~~417~~520, including approximately ~~40~~ 55 adult patients in Bulgaria.	Approximately 1260 patients will be screened to achieve enrollment of approximately 860 adult patients in Stage 1, including approximately 70 adult patients in Bulgaria. The number of randomized adult patients in Stage 2 is planned to be approximately 520, including approximately 55 adult patients in Bulgaria.	Updated enrollment projections.
3.4. Stopping Rules for the Study		
There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5.3.1) 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: • new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment • discontinuation of the development of the investigational medicinal product (IMP) ~~Two formal interim analyses are planned in this study, when the number of events observed in the intent-to-treat (ITT) analysis set reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events in adult patients, respectively). An Independent Data Monitoring Committee (IDMC) will conduct the interim analysis to assess efficacy for all randomized patients. Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m) at any of the interim analyses in order to stop the study early for success, as described in Section 9.6. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.~~	There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (Section 7.1.5.3.1) 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: • new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment • discontinuation of the development of the investigational medicinal product (IMP)	There will be no interim analysis for efficacy in this study.

Original text with changes shown	New wording	Reason/Justification for change
3.5. Schedule of Study Procedures and Assessments		
Study procedures and assessments with their time points are presented in Table 1 and Table 2.	Study procedures and assessments with their time points are presented in Table 1 and Table 2.	Correction.
Table 2: TV46000-CNS-30072 (RISE) Study Procedures and Assessments (In-Clinic Visits and Telephone Contacts) – Baseline, Double-Blind Maintenance Stage (Stage 2), End of Treatment/Early Termination and Follow-Up		
a. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated ~~for efficacy due to a successful interim analysis or~~ because ~~207~~ at least 90 relapse events are recorded in the study in the ITT analysis set ...	a. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated because at least 90 relapse events are recorded in the study in the ITT analysis set. ...	There will be no interim analysis for efficacy in this study; the final analysis will be performed earlier due to the low event rate.
5. TREATMENTS		
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. At the time of analysis (after the end of study ~~or at each interim analysis~~), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP. ~~The codes will be provided to an independent statistician who will perform the interim analyses.~~	Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP.	There will be no interim analysis for efficacy in this study.
5.10.3. Data Monitoring Committee		
During the conduct of this study there will be an IDMC that will review accumulating unblinded safety and pharmacokinetic data on a regular basis (as detailed in the IDMC charter) to ensure the continuing safety of the study patients and any study conduct issues. ~~The IDMC will perform up to 2 formal interim analyses for efficacy in this study (when the number of events observed reaches 43% and 60% of the planned 207 relapse events in the ITT analysis set [Section 3.4]). The second interim analysis will be performed if at least one of the p-values of the 2 primary comparisons is above 0.0101 at the first interim analysis.~~	During the conduct of this study there will be an IDMC that will review accumulating unblinded safety and pharmacokinetic data on a regular basis (as detailed in the IDMC charter) to ensure the continuing safety of the study patients and any study conduct issues. The IDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician and a pharmacokinetic specialist. ...	There will be no interim analysis for efficacy in this study.

Original text with changes shown	New wording	Reason/Justification for change
The IDMC will be composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician and a pharmacokinetic specialist. ...		
5.11. [redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
9.4. Study Population		
The eITT analysis set (Section 9.2.3) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. If the number of adolescents permits, summaries will also be presented by age subgroup.The primary analysis will be conducted on the ITT analysis set (Section 9.2.2), and the eITT analysis set (Section 9.2.3) will be used for analysis of the key secondary endpoints unless otherwise specified ~~the first key secondary endpoint will be conducted on the complete eITT analysis set (Section 9.2.3) and the second key secondary will be conducted on the adolescent subset of the eITT analysis set, if the number of adolescents permits~~. The analysis set on which analysis for other endpoints will be conducted will be specified on a case-by-case basis. The enrolled patients set (Section 9.2.1) will be used for data summaries before the double-blind treatment stage.	The eITT analysis set (Section 9.2.3) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. If the number of adolescents permits, summaries will also be presented by age subgroup.The primary analysis will be conducted on the ITT analysis set (Section 9.2.2), and the eITT analysis set (Section 9.2.3) will be used for analysis of the key secondary endpoints unless otherwise specified. The analysis set on which analysis for other endpoints will be conducted will be specified on a case-by-case basis. The enrolled patients set (Section 9.2.1) will be used for data summaries before the double-blind treatment stage.	Correction.

Original text with changes shown	New wording	Reason/Justification for change
9.4.2. Demographic and Baseline Characteristics		
The ITT analysis set, the eITT analysis set, and the eITT subset of adolescents will be used for the summaries, as applicable.	The ITT analysis set, the eITT analysis set, and the eITT subset of adolescents will be used for the summaries, as applicable.	Clarification.
9.5.2. Key Secondary Endpoints		
... The key secondary endpoints are ~~comprised of endpoints that correspond to the 2 key secondary objectives described~~ listed in Section 2.1 and described in detail below.	... The key secondary endpoints are listed in Section 2.1 and described in detail below.	Correction.
9.5.4. Planned Method of Analysis		
The ITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group. Analysis that will be conducted on the eITT analysis set or on the adolescent patient subset of the eITT will be described below, as applicable.	The ITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group. Analysis that will be conducted on the eITT analysis set or on the adolescent patient subset of the eITT will be described below, as applicable.	Clarification.
9.5.4.4.1. Time to Event Key Secondary Analysis		
For the key secondary endpoint~~s~~ discussed in Section 9.5.2.1,time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2).	For the key secondary endpoint discussed in Section 9.5.2.1,time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2).	Correction of typo.
9.6. Multiple Comparisons and Multiplicity		
~~There will be up to 2 formal interim analyses when the number of events observed reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events, respectively) in the ITT analysis set. At the first interim analysis, both primary efficacy tests will be tested at a 2-sided alpha of 0.0101. If both tests are significant at the first interim analysis, the study will be stopped early. If only 1 primary efficacy test (or none) is significant at the first interim analysis, the study will continue until the second interim analysis. If both tests are significant at the second interim analysis, the study will be stopped early. If only 1 primary efficacy test (or none) is significant at this interim analysis, the study will continue until 207 relapse events are observed.~~ At the final analysis after ~~207~~ at least 90 relapse events, a fixed sequential (hierarchical) testing approach will be implemented. If the resulting first p-value of the primary efficacy hypothesis test comparing q1m to placebo is found to be significant at 0.05 alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of 0.05. If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed. ...	At the final analysis after at least 90 relapse events, a fixed sequential (hierarchical) testing approach will be implemented. If the resulting first p-value of the primary efficacy hypothesis test comparing q1m to placebo is found to be significant at 0.05 alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of 0.05. If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed. ...	There will be no interim analysis for efficacy in this study; the final analysis will be performed earlier due to the low event rate.

Original text with changes shown	New wording	Reason/Justification for change
sequential (hierarchical) testing approach will be implemented. If the resulting first p-value of the primary efficacy hypothesis test comparing q1m to placebo is found to be significant at ~~0.0418~~ 0.05 alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of ~~0.0418~~ 0.05. If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed. ~~This procedure will adequately control overall type 1 error for a 2-sided alpha of 0.05 accounting for the interim analyses. The nominal alphas of 0.0101 at each interim analysis and 0.0418 at the final analysis were calculated using EAST 6 software, as described in the EAST 6 manual (East 6 [Version 6.3] manual, 2014).~~ …		
9.13. Planned Interim Analysis		
There will be no interim analysis in this study. ~~There will be up to 2 formal interim analyses when the number of events observed in the ITT analysis set reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events in adult patients, respectively). Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m) at any of the interim analyses in order to stop the study early for success as described in Section 9.6. If success criteria was not met [ie, if only 1 primary efficacy test (or none) is significant] at the first interim analysis (at 90 relapse events), the study will continue to the second interim analysis (at 125 relapse events). If only 1 primary efficacy test (or none) is significant at this interim analysis, (ie, if none of the interim analyses demonstrate success), the study will continue until 207 relapse events are reached.~~ ~~An IDMC will conduct the interim analyses to assess efficacy for all randomized patients. An IDMC charter will be developed for the interim analyses. Procedures will be taken to ensure the~~	There will be no interim analysis in this study.	Deleted since text is no longer relevant; no interim analysis for efficacy will be performed. The IDMC is described in Section 5.10.3. of the protocol.

Original text with changes shown	New wording	Reason/Justification for change
~~integrity of the study follows the IDMC charter. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.~~		
APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: +[redacted] Cell: +[redacted] Email: [redacted]	**Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study** [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] Email: [redacted]	Per Administrative Letter 03, updated to reflect change of responsibilities at Teva.
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
Note in Section g Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT): **Note:** The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free at the time of study termination ~~during the double-blind phase until the study is terminated for efficacy due to a successful interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set.~~	**Note in Section g Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT):** **Note:** The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free at the time of study termination.	There will be no interim analysis for efficacy in this study; the final analysis will be performed earlier due to the low event rate.
Note in Section c Stage 2: Relapse Prevention (Visit 6a, Week 1±3 days; Visit 6b, Week 2±3 days; and Visit 6c, Week 3±3 days [Telephone Contacts]) (Visit 7a, Week 5±3 days; Visit 7b, Week 6±3 days; and Visit 7c, Week 7±3 days [Telephone Contacts], 8a-8c, 9a-9c, etc.) **Note:** Telephone contacts will occur **weekly** between in-clinic visits during the double-blind maintenance stage (Stage 2) (see ~~Table 1~~ Table 2).	**Note in Section c Stage 2: Relapse Prevention (Visit 6a, Week 1±3 days; Visit 6b, Week 2±3 days; and Visit 6c, Week 3±3 days [Telephone Contacts]) (Visit 7a, Week 5±3 days; Visit 7b, Week 6±3 days; and Visit 7c, Week 7±3 days [Telephone Contacts], 8a-8c, 9a-9c, etc.)** **Note:** Telephone contacts will occur **weekly** between in-clinic visits during the double-blind maintenance stage (Stage 2) (see Table 2).	Correction.
APPENDIX G. LIST OF PROHIBITED MEDICATIONS (Other sections affected by this change: Section 5.7)		
... In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or	... In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or	Clarification due to COVID-19 pandemic.

Original text with changes shown	New wording	Reason/Justification for change
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.	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.	
[redacted]		
[redacted]	[redacted]	[redacted]
APPENDIX N. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19		
New appendix and text.	Additional text too numerous to include in this table; refer to Appendix N of this protocol.	Updated to manage study conduct during the COVID-19 pandemic.
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; 7.4. Clinical Laboratory Tests; 7.6. Vital Signs; 7.7. Electrocardiography; Section 8.1. Pharmacokinetic Assessment; Section 9.5.4.2. Sensitivity Analysis; Section 10. Quality Control and Quality Assurance; Appendix C. Quality Control and Quality Assurance; Appendix F. Lost to Follow Up		
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 03 (Dated 09 February 2020)

ADMINISTRATIVE LETTER 03

Study number: TV46000-CNS-30072

Clinical Study Protocol Amendment 02 with Revision 01

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

(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

Dated 16 October 2019

IND number: 124384; EudraCT number 2018-001619-65

09 February 2020

Dear Investigator:

The purpose of this letter is to notify you regarding 2 administrative issues pertaining to (i) a recent change in responsibilities at Teva, and (ii) an update regarding the new address of the sponsor offices in Pennsylvania, United States (US).

(i) Appointment of New Clinical Study Physician

Eran Harary, MD was the clinical study physician (CSP) and served as the Sponsor's Medical Expert for the study since its initiation in 2018. After his appointment as Vice President, Therapeutic Area Head of Neurology and Psychiatry, earlier this year (see Section 16.2 and Appendix A in the protocol), he concomitantly continued to serve 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 Eran as the CSP. My contact details are provided below:

[redacted]
Senior Director, Specialty Clinical Development
Teva Branded Pharmaceutical Products R&D, Inc.
Tel: [redacted]
Cell: [redacted]
Email: [redacted]

(ii) Relocation of Teva Offices in Pennsylvania

The Teva offices in Pennsylvania, 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.

Please feel free to contact me at + [redacted] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Senior Director, Specialty Clinical Development
Teva Branded Pharmaceutical Products R&D, Inc.

Cc: [redacted], Study File.

16.3. Global Amendment 02 with Revision 01 (Dated 16 October 2019)

The primary reason for this revision of Global Amendment 02 is to reorganize the statistical analyses with the introduction of the fixed sequential (hierarchy) method to control the Type-I error for the primary analyses in the final analysis and a reconsideration and hierarchy of the key secondary endpoints.

A comparison table showing the changes from Global Amendment 02 to Global Amendment 02 with Revision 01 with is provided below. Previous text is presented in the column titled "Original text with changes shown", and the revised or new text is presented in the column titled "new wording." Revised or new text is shown in bold italics and deleted text is shown in strike-through.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are considered significant by the Teva Authorized Representative.

These changes are unlikely to affect the safety or rights (physical or mental integrity) of the subjects in this clinical study or the scientific value of the clinical study.

Also, to adhere with current Teva standards, some formatting and editing changes have been made.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">TITLE PAGE (Other sections affected by this change: Header, Investigator Agreement; Coordinating Investigator Agreement)</td></tr>
<tr><td>Clinical Study Protocol <s>with</s> Amendment 02 with Revision 01</td><td>Clinical Study Protocol Amendment 02 with Revision 01</td><td>To denote the new global amendment with revision</td></tr>
<tr><td colspan="3">AMENDMENT HISTORY</td></tr>
<tr><td>The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:
<table>
<tr><td>Global Amendment 02 with Revision 01</td><td>16 October 2019 (649 patients enrolled to date)</td></tr>
<tr><td>Global Amendment 02</td><td>02 September 2019 (584 patients enrolled to date)</td></tr>
<tr><td>Letter of Clarification 02</td><td>27 June 2019</td></tr>
<tr><td>Global Amendment 01</td><td>06 December 2018 (184 patients enrolled to date)</td></tr>
<tr><td>…</td><td>…</td></tr>
</table>
The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.</td><td>The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:
<table>
<tr><td>Global Amendment 02 with Revision 01</td><td>16 October 2019 (649 patients enrolled to date)</td></tr>
<tr><td>Global Amendment 02</td><td>02 September 2019 (584 patients enrolled to date)</td></tr>
<tr><td>Letter of Clarification 02</td><td>27 June 2019</td></tr>
<tr><td>Global Amendment 01</td><td>06 December 2018 (184 patients enrolled to date)</td></tr>
<tr><td>…</td><td>…</td></tr>
</table>
The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.</td><td>This page was updated with the details of the documents issued since the last amendment</td></tr>
<tr><td colspan="3">2. STUDY OBJECTIVES AND ENDPOINTS</td></tr>
<tr><td colspan="3">2.1.Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Clinical Study Protocol Synopsis)</td></tr>
<tr><td><s>The</s> A key secondary objective of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in a total population (adults and adolescents) and in adolescent patients with schizophrenia.</td><td>A key secondary objective of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in a total population (adults and adolescents) and in adolescent patients with schizophrenia.</td><td>Correction</td></tr>
<tr><td><s>The k</s>Key secondary endpoints are:
<s>1.</s> time to impending relapse (as defined under the</td><td>Key secondary endpoints are:
• time to impending relapse (as defined under the</td><td>Revision and reorgarnization to the</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
primary objective) in the total population (adults and adolescents)~~, and~~ ***impending relapse rate at week 24*** ***percentage of patients who maintain stability at endpoint*** ***percentage of patients achieving remission at endpoint*** ***observed rate of impending relapse at endpoint*** ***Drug Attitudes Inventory 10-item version (adult patients only)*** ***Schizophrenia Quality of Life Scale (SQLS) (adult patients only)*** ~~2.~~ time to impending relapse in adolescent patients with schizophrenia. ~~**NOTE:** The assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.~~	primary objective) in the total population (adults and adolescents) • impending relapse rate at week 24 • percentage of patients who maintain stability at endpoint • percentage of patients achieving remission at endpoint • observed rate of impending relapse at endpoint • Drug Attitudes Inventory 10-item version (**adult patients only**) • Schizophrenia Quality of Life Scale (SQLS) (**adult patients only**) • time to impending relapse in adolescent patients with schizophrenia	secondary endpoints
~~A **secondary objective** of this study is to evaluate the specific efficacy parameters of TV-46000 in the total population beyond the measures of the primary objective.~~	Not applicable	Correction due to moving the endpoints up to key secondary endpoints
~~Secondary efficacy endpoints are as follows:~~ ~~• impending relapse rate at week 24~~ ~~• observed rate of impending relapse at endpoint~~ ~~• percentage of patients who maintain stability at endpoint (Section 9.5.3.3)~~ ~~percentage of patients achieving remission at endpoint (Section 9.5.3.4)~~	Not applicable	Correction (now included under the key secondary endpoints)
The following quality of life and healthcare resource utilization measures will be assessed: ~~• Schizophrenia Quality of Life scale **(adult patients only)**~~ • 5-Level EuroQol Five Dimensions Questionnaire **(adult patients only)** ~~• Drug Attitudes Inventory 10-item version **(adult patients only)**~~ **...**	The following quality of life and healthcare resource utilization measures will be assessed: • 5-Level EuroQol Five Dimensions Questionnaire **(adult patients only)** **...**	Correction (now included under the key secondary endpoints)

Original text with changes shown	New wording	Reason/Justification for change
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
9.5. EFFICACY ANALYSIS		
9.5.2. Key Secondary Endpoints		
~~The key secondary endpoints are:~~ ~~1 time to impending relapse (as defined under the primary objective) in the eITT analysis set, and~~ ~~2 time to impending relapse in adolescent patients with schizophrenia.~~ **~~NOTE:~~** ~~The assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.~~ The eITT analysis set (Section 9.2.***3***) will be used for all summaries in this section, unless otherwise specified. For the endpoints that are evaluted only in the adult population, the analysis will be conducted on the ITT analysis set. ***The key secondary endpoints are comprised of endpoints that correspond to the 2 key secondary objectives described in***	The eITT analysis set (Section 9.2.3) will be used for all summaries in this section, unless otherwise specified. For the endpoints that are evaluted only in the adult population, the analysis will be conducted on the ITT analysis set. The key secondary endpoints are comprised of endpoints that correspond to the 2 key secondary objectives described in Section 2.1.	Revision and reorganization to the section 9.5.2. The section numbers will be updated accordingly.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1.		
9.5.2.1. Time to Impending Relapse in the eITT Analyses Set		
Not applicable	Time to impending relapse using the same definition and primary analysis that is described in section 9.5.1 using the eITT analysis will be employed.	New section added, included in the key secondary endpoints
9.5.2.2 Impending Relapse Rate at Week 24		
This rate will be estimated using the Kaplan-Meier method	This rate will be estimated using the Kaplan-Meier method	Reorganization of the section (now included under the key secondary endpoints)
9.5.2.3. Percentage of Patients Who Maintain Stability at Endpoint		
The percentage will be calculated as the number of patients who maintained stability at endpoint divided by the number of ***eITT*** patients ***that adhere to treatment for at least 4 weeks or experienced relapse*** in the given treatment group. ***This analysis estimates the treatment effect of randomized treatment on patient's stability once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with while on treatment estimand and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to maintain stability once they start the treatment if the patient adheres to the treatment long enough.***	The percentage will be calculated as the number of patients who maintained stability at endpoint divided by the number of eITT patients that adhere to treatment for at least 4 weeks or experienced relapse in the given treatment group. This analysis estimates the treatment effect of randomized treatment on patient's stability once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with while on treatment estimand and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to maintain stability once they start the treatment if the patient adheres to the treatment long enough.	Revision and reorganization to the section
9.5.2.4. Percentage of Patients Achieving Remission at Endpoint		
For overall symptom remission, the patient must not relapse during the study and in addition, over a period of at least 6 months preceding the endpoint, maintain scores of ≤3 on each of the 8 specific PANSS items: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms/posturing), N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity).	For overall symptom remission, the patient must not relapse during the study and in addition, over a period of at least 6 months preceding the endpoint, maintain scores of ≤3 on each of the 8 specific PANSS items: P1 (delusions), G9 (unusual thought content), P3 (hallucinatory behavior), P2 (conceptual disorganization), G5 (mannerisms/posturing), N1 (blunted affect), N4 (social withdrawal), and N6 (lack of spontaneity).	Revision and reorganization of the section

Original text with changes shown	New wording	Reason/Justification for change
The percentage will be calculated as the number of patients who achieved remission at endpoint divided by the number of eITT patients that adhere at least 6 months or experienced relapse in the given treatment group. ***This analysis estimates the treatment effect of randomized treatment on patient's remission once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with the while on treatment estimand, and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to achieve remission once they start the treatment if the patient adheres to the treatment long enough.*** ~~The analysis will be detailed in the statistical analysis plan.~~	The percentage will be calculated as the number of patients who achieved remission at endpoint divided by the number of eITT patients that adhere at least 6 months or experienced relapse in the given treatment group. This analysis estimates the treatment effect of randomized treatment on patient's remission once the patient adheres to treatment long enough until the last treatment. The use of eITT analysis complies with the while on treatment estimand, and will be comprised of the difference in proportions under the treatment to which the patient was initially randomized of all patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. Accordingly, this estimand addresses the clinical question to what extent patients improve their chances to achieve remission once they start the treatment if the patient adheres to the treatment long enough.	
9.5.2.5. Observed Rate of Impending Relapse at Endpoint		
Observed rate of impending relapse will be calculated as the number of patients who relapsed by endpoint divided by the number of patients in each treatment group.	Observed rate of impending relapse will be calculated as the number of patients who relapsed by endpoint divided by the number of patients in each treatment group.	Reorganization of the section (now included under the key secondary endpoints)
9.5.2.6. Drug Attitudes Inventory 10-item Version		
The change from baseline to endpoint in total score will be calculated	The change from baseline to endpoint in total score will be calculated	Reorganization of the section (now included under the key secondary endpoints)
9.5.2.7.Schizophrenia Quality of Life Scale		
The change from baseline to endpoint in total score will be calculated	The change from baseline to endpoint in total score will be calculated	Reorganization of the section (now included under the key secondary endpoints)

Original text with changes shown	New wording	Reason/Justification for change
9.5.2.8. Time to Impending Relapse in aAdolescent Patients with Schizophrenia		
Not applicable	Time to impending relapse using the same definition and primary analysis that was described in section 9.5.1 will be used on the eITT analysis set using adolescent patients alone. This assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.	New section added, included in the key secondary endpoints
9.5.4.2. Sensitivity Analyses		
The PP analysis set will also be used ***as supplemental analysis*** to evaluate the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.	The PP analysis set will also be used as supplemental analysis to evaluate the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.	Clarification to the sensitivity analyses
9.5.4.4. Key Secondary Analyses		
The fixed sequential (hierarchical) Strategy (FDA 2017) will be used to control the overall Type-I statstical error in the study for both primary and secondary efficacy endpoints. The key secondary endpoints will be analyzed in a pooled manner for q1m and q2m.The details about the Type-I statistical error control for the key secondary endpoints will be discussed in the statistical analysis plan.	The fixed sequential (hierarchical) Strategy (FDA 2017) will be used to control the overall Type-I statstical error in the study for both primary and secondary efficacy endpoints. The key secondary endpoints will be analyzed in a pooled manner for q1m and q2m.The details about the Type-I statistical error control for the key secondary endpoints will be discussed in the statistical analysis plan.	New text added
9.5.4.4.1. Time to Event Key Secondary Analyses		
Time to Event Key Secondary Analyses ~~1~~	Time to Event Key Secondary Analyses	Correction to the title
For the key secondary endpoints discussed in Section 9.5.2.1, ~~T~~*t*ime to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2). The Cox proportional hazard model will include patient age group (if applicable) along with treatment, and the aforementioned stratification variables as the factors. ~~The details about the Type I statistical error control will be discussed in Section 9.6~~. ***For the key secondary endpoint discussed in Section 9.5.2.8,*** ~~T~~*t*ime to impending relapse in adolescent patients will be assessed if the number of randomized patients will be at least 10 with clinically sufficient exposure. The method will be similar to the Primary Efficacy Analysis, but will use the	For the key secondary endpoints discussed in Section 9.5.2.1, time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2). The Cox proportional hazard model will include patient age group (if applicable) along with treatment, and the aforementioned stratification variables as the factors. For the key secondary endpoint discussed in Section 9.5.2.8, time to impending relapse in adolescent patients will be assessed if the number of randomized patients will be at least 10 with clinically sufficient exposure. The method will be similar to the Primary Efficacy Analysis, but will use the adolescent patients subset. Type-I statistical error control will be discussed	Clarification to the key secondary analysis

Original text with changes shown	New wording	Reason/Justification for change
adolescent patients subset. ~~The details about the~~ Type I statistical error control will be discussed in~~-~~ ~~Section 9.6.~~ ***Multiple Comparisons and Multiplicity.***	in Multiple Comparisons and Multiplicity.	
9.5.4.5. Key Secondary Efficacy Analysis 9.5.2.2-9.5.2.7		
Key Secondary Efficacy Analysis ***9.5.2.2-9.5.2.7***	Key Secondary Efficacy Analysis 9.5.2.2-9.5.2.7	Correction to the title
Impending relapse rate at week 24 will be estimated using the Kaplan-Meier method and calculated as 1 minus the proportion of patients free of impending relapse events at week 24. The Greenwood formula will be used to calculate standard errors for impending relapse rates at week 24, and the pooled standard errors will be used for hypothesis testing using z-statistics, assuming that the differences between TV-46000 and placebo follow a normal distribution of large samples. ~~The tests will be conducted at a nominal 2-sided alpha of 0.05.~~	Impending relapse rate at week 24 will be estimated using the Kaplan-Meier method and calculated as 1 minus the proportion of patients free of impending relapse events at week 24. The Greenwood formula will be used to calculate standard errors for impending relapse rates at week 24, and the pooled standard errors will be used for hypothesis testing using z-statistics, assuming that the differences between TV-46000 and placebo follow a normal distribution of large samples.	Change due to the implementation of the hierarchy
Change from baseline of DAI-10 and SQLS total score, will be analyzed using an analysis of covariance (ANCOVA) method, with treatment and stratification variables as factors and baseline (score at the end of Stage 1) as a covariate. Additional details regarding the analysis will be documented in the statistical analysis plan.	Change from baseline of DAI-10 and SQLS total score, will be analyzed using an analysis of covariance (ANCOVA) method, with treatment and stratification variables as factors and baseline (score at the end of Stage 1) as a covariate. Additional details regarding the analysis will be documented in the statistical analysis plan.	New text added
The eITT analysis set (Section 9.2***.3***) will be used for all summaries in this section, unless otherwise specified. ***Type-I statistical error control will be discussed in Multiple Comparisons and Multiplicity.***	The eITT analysis set (Section 9.2.3) will be used for all summaries in this section, unless otherwise specified. Type- I statistical error control will be discussed in Multiple Comparisons and Multiplicity.	Change added
[redacted]		
[redacted]	[redacted]	[redacted]
9.6 Multiple Comparisons and Multiplicity		
If both tests are significant at the first interim analysis, the study will be stopped ***early***. If only 1 primary efficacy test (or none) is significant at the first interim analysis, the study will continue until the second interim analysis. If both tests are significant at the second interim analysis, the study will be stopped ***early*** …	If both tests are significant at the first interim analysis, the study will be stopped early. If only 1 primary efficacy test (or none) is significant at the first interim analysis, the study will continue until the second interim analysis. If both tests are significant at the second interim analysis, the study will be stopped early …	Clarifiication and correction to the multiple Comparisons and Multiplicity methodology for the primary analyses

Original text with changes shown	New wording	Reason/Justification for change
At the final analysis ***after 207 events, a fixed sequential (hierarchical) testing approach will be implemented . If the resulting first p-value of the*** ~~both~~ primary efficacy ~~tests~~ ***hypothesis test comparing q1m to placebo*** ~~will be conducted with 2-sided~~ ***is found to be significant at*** ~~alphas of~~ 0.0418 ***alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of 0.0418*** ~~if 1 primary efficacy test is not significant at a 2-sided alpha of 0.0418, the other will be tested at a 2-sided alpha of 0.0418 divided by 2.~~ ***If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed.*** This procedure will adequately control overall Type-I error for a 2-sided alpha of 0.05 ***accounting for the interim analyses***. The nominal alphas of 0.0101 at each interim analysis and 0.0418 at the final analysis were calculated using EAST 6 software, as described in the EAST 6 manual (East 6 [Version 6.3] manual, 2014). Type-I error will be further controlled for the ~~2~~ key secondary endpoints by employing ~~the~~ ***fixed sequential (***hierarchical***) testing strategy within each endpoints family (primary endpoints and key secondary endpoints)***~~approach~~, Secondary endpoint***s*** ~~#1~~ will be analyzed ***in a pooled manner*** ~~only in case the 2~~ ***for the treatment groups if the two primary endpoints are found to be*** ~~primary efficacy endpoints have~~ ***significant.*** ~~p-values less than or equal to alpha of 0.0418. In that case, key secondary endpoint #1 will be tested for the 2 dosing regimens using the same approach. Namely, tests for the 2 dosing regimens will be conducted with 2-sided alphas of 0.0418; if one of the comparisons for the key secondary endpoint #1 is not significant at a 2-sided alpha of 0.0418, the other will be tested at a 2-sided alpha of 0.0418 divided by 2.~~ ***Further details about the Type-I statistical error control will be discussed in the statistical analysis plan.*** ***A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type-I error rate. The sequence of the secondary endpoints comparisons will be as follows*** ~~If secondary endpoint #1 is successful on both dosing regimens~~	At the final analysis after 207 events, a fixed sequential (hierarchical) testing approach will be implemented. If the resulting first p-value of the primary efficacy hypothesis test comparing q1m to placebo is found to be significant at 0.0418 alpha, then the second primary efficacy hypothesis (q2m vs. placebo) will be interpreted inferentially at the same alpha level of 0.0418. If the first primary hypothesis fails to reach significance no further formal hypothesis testing will be performed. This procedure will adequately control overall Type-I error for a 2-sided alpha of 0.05 accounting for the interim analyses. The nominal alphas of 0.0101 at each interim analysis and 0.0418 at the final analysis were calculated using EAST 6 software, as described in the EAST 6 manual (East 6 [Version 6.3] manual, 2014). Type-I error will be further controlled for the key secondary endpoints by employing fixed sequential (hierarchical) testing strategy within each endpoints family (primary endpoints and key secondary endpoints). Secondary endpoints will be analyzed in a pooled manner for the treatment groups if the two primary endpoints found to be significant. Further details about the Type-I statistical error control will be discussed in the statistical analysis plan. A fixed-sequence (hierarchical) testing procedure will be implemented to control the Type-I error rate. The sequence of the secondary endpoints comparisons will be as follows: 1. Time to impending relapse in the eITT analysis set 2. Impending relapse rate at week 24 3. Percentage of patients who maintain stability at endpoint 4. Percentage of patients achieving remission at endpoint 5. Observed rate of impending relapse at endpoint 6. DAI-10 change from baseline to endpoint 7. SQLS change from baseline to endpoint 8. Time to impending relapse in adolescent patients with schizophrenia If the first comparison is found to be significant, then the next comparison of interest will be interpreted inferentially at the	

Original text with changes shown	New wording	Reason/Justification for change
~~against placebo, and there are at least 10 adolescent patients in the study with clinically sufficient exposure, then the 2 dosing regimens in the adolescent study population will be tested against placebo in the same way as described for the primary efficacy endpoint and key secondary endpoint #1.~~ 1. ***Time to impending relapse in the eITT analysis set*** 2. ***Impending relapse rate at week 24*** 3. ***Percentage of patients who maintain stability at endpoint*** 4. ***Percentage of patients achieving remission at endpoint*** 5. ***Observed rate of impending relapse at endpoint*** 6. ***DAI-10 change from baseline to endpoint*** 7. ***SQLS change from baseline to endpoint*** 8. ***Time to impending relapse in adolescent patients with schizophrenia*** ***If the first comparison is found to be significant, then the next comparison of interest will be interpreted inferentially at the same alpha level. This process will continue either until all comparisons were tested inferentially or until the point at which the resulting 2-sided is insignificant at the same alpha level.*** [redacted] ***ny p-value associated with these comparisons will be considered as nominal p-value and will not be used for inference.*** There will be no multiplicity control for all other ***exploratory*** efficacy endpoints ~~(secondary or exploratory)~~, which will be tested at a nominal 5% level.	same alpha level. This process will continue either until all comparisons were tested inferentially or until the point at which the resulting 2-sided is insignificant at the same alpha level [redacted] ny p-value associated with these comparisons will be considered as nominal p-value and will not be used for inference. There will be no multiplicity control for all other exploratory efficacy endpoints , which will be tested at a nominal 5% level.	
REFERENCES		
Not applicable	FDA, Multiple Endpoints in Clinical Trials. Guidance for Industry. DRAFT GUIDANCE. January 2017	Reference added

16.4. Global Protocol Amendment 02 (Dated 02 September 2019)

The primary reason for this global amendment is to revise the number of relapse events at which the formal, pre-specified interim analysis will be conducted. In addition to the originally-planned, single interim analysis that was to be conducted when 125 relapse events were observed, the Sponsor now plans to also conduct an earlier interim analysis when 90 relapse events are reached. Since the study's initiation, the rate of observed relapse events (pooled across all treatment groups due to blinding) is lower than expected. This may be due to a longer median time to relapse than assumed for the placebo group, or a higher hazard ratio than assumed during the study planning. An earlier analysis, if successful, will allow the Sponsor to stop this double-blind, placebo-controlled study and roll the patients over earlier into the long term TV46000-CNS-30078 extension study (in which all patients receive treatment with TV-46000) without affecting the statistical power of the study, while maintaining control of the type-I error. Patients randomized to the q1m or q2m treatment arms in the RISE study will continue on their assigned treatment regimen in the extension study, and patients randomized to the placebo arm in the RISE study will be re-randomized in a 1:1 manner to the q1m or q2m treatment arms in the extension study.

These changes to the statistical methodology are unlikely to affect the safety (physical or mental integrity) or rights of the patients in this clinical Phase 3 study, the secondary endpoints of the study or the study's scientific value, since the focus on the impending time to relapse as the primary endpoint is maintained, as well as the originally-planned time points for the interim and final analysis, and the overall control of type-I error using the same principles and methodology originally used for the study. Moreover, from an ethical perspective, adding an earlier interim analysis will enable patients on placebo to receive effective treatment earlier, if the treatment is found to be effective.The technical details of the planned statistical analysis of the study data will be provided in the Statistical Analysis Plan.

Further clarifications and changes related to study conduct were also implemented in this amendment. These include (but are not limited to) prolongation of study duration (although in case of a successful interim analysis, the study will be terminated earlier), change of inclusion criterion k to omit the BMI percentile limitation, updates to the planned number of enrolled patients per updated projections, clarification of procedures to be performed during unscheduled visits (per Clarification Letter 02 dated 27 June 2019) and clarification regarding highly effective birth control methods (see Appendix E) and some administrative details (see Appendix A).

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are not considered significant by the Teva Authorized Representative. The study schema (Figure 1), Table 1 (Screening and Stage 1), Table 2 (Stage 2 and Follow-Up) and the corresponding footnotes, have been revised to reflect the changes described below.

A comparison table showing the changes from Global Amendment 01 to Global Amendment 02 is provided below. Previous text is presented in the column titled "Original text with changes shown", and the revised or new text is presented in the column titled "new wording." Revised or new text is shown in bold italics and deleted text is shown in strike-through.

Also, to adhere with current Teva standards, some formatting and editing changes have been made.

Changes to the Protocol

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">TITLE PAGE (Other sections affected by this change: Investigator Agreement; Coordinating Investigator Agreement)</td></tr>
<tr><td>Clinical Study Protocol with Amendment <s>01</s> 02</td><td>Clinical Study Protocol with Amendment 02</td><td>To denote the new global amendment.</td></tr>
<tr><td colspan="3">AMENDMENT HISTORY</td></tr>
<tr><td>AMENDMENT HISTORY
The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:<table><tr><td>Global Amendment 02</td><td>02 September 2019 (584 patients enrolled to date)</td></tr><tr><td>Letter of Clarification 02</td><td>27 June 2019</td></tr><tr><td>Global Amendment 01</td><td>06 December 2018 (184 patients enrolled to date)</td></tr><tr><td>…</td><td>…</td></tr></table>The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.</td><td>AMENDMENT HISTORY
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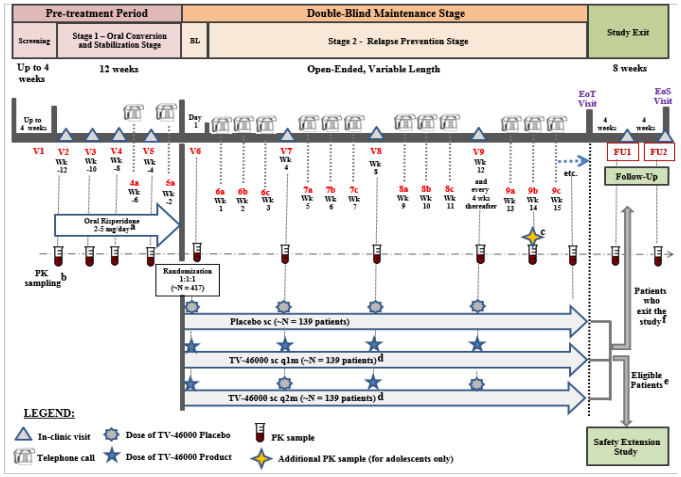
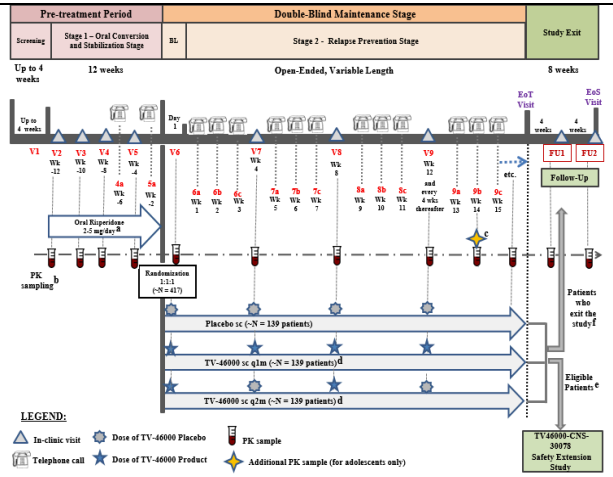
<tr><td colspan="3">SPONSOR PROTOCOL APPROVAL</td></tr>
<tr><td>Sponsor’s Authorized Representative
[redacted]
Vice President
Therapeutic Area Head, Neurology and Psychiatry,
Specialty Clinical Development</td><td>Sponsor’s Authorized Representative
[redacted]
Vice President
Therapeutic Area Head, Neurology and Psychiatry,
Specialty Clinical Development</td><td>This reflects a change in responsibilities at Teva.</td></tr>
<tr><td colspan="3">1. INTRODUCTION AND BACKGROUND INFORMATION</td></tr>
<tr><td colspan="3">1.2.2.1 Clinical Pharmacology Studies</td></tr>
<tr><td>A Phase 1 single and multiple ascending dose study (TV46000-SAD-10055) to evaluate the safety, tolerability, and</td><td>A Phase 1 single and multiple ascending dose study (TV46000-SAD-10055) to evaluate the safety,</td><td>Text updated to reflect completion of the 10055 study and final results</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
pharmacokinetics of TV-46000 in patients with schizophrenia or schizoaffective disorder ~~is ongoing~~ ***was also completed***. … ~~A preliminary~~ ***The*** comparison of different sites of injection of a single [redacted] sc dose administered in the abdomen versus the upper arm, ~~suggests~~ ***indicated that*** there are no ~~clinically~~ ***therapeutically*** relevant differences in exposure ***and that either the abdomen or upper arm could be used for sc injection without significantly altering the controlled-release drug delivery of risperidone***.	tolerability, and pharmacokinetics of TV-46000 in patients with schizophrenia or schizoaffective disorder was also completed. … The comparison of different sites of injection of a single [redacted] sc dose administered in the abdomen versus the upper arm indicated that there are no therapeutically relevant differences in exposure and that either the abdomen or upper arm could be used for sc injection without significantly altering the controlled-release drug delivery of risperidone.	(CSR issued 21 December 2018).
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram		
… The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy ~~at the~~ ***due to a successful*** interim analysis or because 207 relapse events are recorded in the study adult population. … Patients who remain relapse-free when the study is terminated for efficacy ~~at the~~ ***due to a successful*** interim analysis or because 207 relapse events in adults are recorded in the study should be invited to perform the End-of-Treatment visit within 4 weeks of the last injection. … Patients will subsequently complete all end-of-study assessments. When the study ends, eligible patients may be offered the opportunity to enter ~~an~~ ***the TV46000-CNS-30078*** extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol~~.~~***,*** ~~A~~ ***and a*** separate protocol ~~will~~ ***was*** issued for ~~the extension study as applicable~~ ***it***. … The study duration will be approximately ~~18~~***30*** months, from	… The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy due to a successful interim analysis or because 207 relapse events are recorded in the study adult population. … Patients who remain relapse-free when the study is terminated for efficacydue to a successful interim analysis or because 207 relapse events in adults are recorded in the study should be invited to perform the End-of-Treatment visit within 4 weeks of the last injection. … Patients will subsequently complete all end-of-study assessments. When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol, and a separate protocol was issued for it.	Clarification following the addition of an earlier interim analysis. Updated to the expected duration of the full study (207 relapse events) per the current projections. The number of the safety extension study was added.

Original text with changes shown	New wording	Reason/Justification for change
Q2 2018 (first patient in) to Q4 ~~2019~~***2020*** (last patient out). ***In case of a successful interim analysis, the study will be terminated earlier (see Section 9.6)***. …	… The study duration will be approximately 30 months, from Q2 2018 (first patient in) to Q4 2020 (last patient out). In case of a successful interim analysis, the study will be terminated earlier (see Section 9.6) …	
		The number of the safety extension study was added to the study schema.
[e] When the study ends, eligible patients may be offered the opportunity to enter ~~an~~ ***the TV46000-CNS-30078*** extension study to assess the long-term safety and tolerability ***of extended-release risperidone***. This extension study is beyond the scope of this protocol and ~~will be~~ ***is*** detailed in a separate protocol ~~as applicable~~. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study.	[e] When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol and is detailed in a separate protocol. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study.	The protocol for the 30078 extension study was issued, and its number was therefore implemented.
3.2. Planned Number of Patients and Countries		
Approximately ~~795~~***993*** patients will be screened to achieve enrollment of approximately ~~596~~***695*** adult patients in Stage 1, including approximately ~~57~~***67***adult patients in Bulgaria.	Approximately 993 patients will be screened to achieve enrollment of approximately 695 adult patients in Stage 1, including approximately 67 adult patients in Bulgaria.	Corrected per updated enrollment projections and screen failure rate.

Original text with changes shown	New wording	Reason/Justification for change
3.4. Stopping Rules for the Study		
~~One~~ ***Two*** formal interim ~~analysis~~ ***analyses*** ~~will be conducted~~ ***are planned in this study***, when the number of events observed in the intent-to-treat (ITT) analysis set ~~(~~reaches ***43.5% and*** 60% of the planned 207 relapse events (***90 and*** 125 events in adult patients, ***respectively***). An Independent Data Monitoring Committee (IDMC) will conduct the interim analysis to assess efficacy for all randomized patients. Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m), ***at any of the interim analyses in order to stop the study early for success,*** as described in Section 9.6. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.	Two formal interim analyses are planned in this study, when the number of events observed in the intent-to-treat (ITT) analysis set reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events in adult patients, respectively). An Independent Data Monitoring Committee (IDMC) will conduct the interim analysis to assess efficacy for all randomized patients. Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m) at any of the interim analyses in order to stop the study early for success, as described in Section 9.6. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.	Revised due to the addition of another, earlier interim analysis.
3.5. Schedule of Study Procedures and Assessments		
Table 1:		
d. 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 procedures which are currently marked 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 <u>not</u> due to a potential relapse or a change in the patient's medical status per clinical judgement.***	d. 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 procedures which are currently marked 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 **<u>not</u>** due to a potential relapse or a change in the patient's medical status per clinical judgement.	Clarification regarding procedures to be performed during unscheduled visits, per Letter of Clarification 02.
q. The specific questions asked will be at the discretion of the investigator. ~~This~~ ***A*** list of suggested questions ~~are detailed in the study manual~~ ***will be provided to the investigator***.	q. 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	Corrected since there is no study manual; the list was provided to the investigators and is also available

Original text with changes shown	New wording	Reason/Justification for change
Psychiatric adverse events or suspicion of a psychiatric deterioration as a result of 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.	or suspicion of a psychiatric deterioration as a result of 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.	vis the study portal.
Table 2:		
a. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy ~~at the~~ ***due to a successful*** interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set. …	a. The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy due to a successful interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set. ...	Revised due to the addition of another, earlier interim analysis.
b. When the study ends, eligible patients may be offered the opportunity to enter ~~a~~***TV46000-CNS-30078, the*** long-term safety and tolerability extension study. This extension study is beyond the scope of this protocol ***and is detailed in a separate protocol***. If the patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. All other patients (ie, patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study), will undergo these 2 follow-up/exit visits. During the follow-up/exit period patients will be treated according to the investigator's judgement.	b. When the study ends, eligible patients may be offered the opportunity to enter TV46000-CNS-30078, the long-term safety and tolerability extension study. This extension study is beyond the scope of this protocol and is detailed in a separate protocol. If the patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. All other patients (ie, patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study), will undergo these 2 follow-up/exit visits. During the follow-up/exit period patients will be treated according to the investigator's judgement.	Name of the extension study added.
c. 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 procedures which are currently marked 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***	c. 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 procedures which are currently marked 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	Clarification regarding procedures to be performed during unscheduled visits, per Letter of Clarification 02.

Original text with changes shown	New wording	Reason/Justification for change
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 <u>not</u> due to a potential relapse or a change in the patient's medical status per clinical judgement.	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 **<u>not</u>** due to a potential relapse or a change in the patient's medical status per clinical judgement.	
p. Blood 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***.	p. Blood 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.	Clarification.
z. The specific questions asked will be at the discretion of the investigator. ~~This~~ ***A*** list of suggested questions ~~are detailed in the study manual.~~ ***will be provided to the investigator*** Psychiatric adverse events or suspicion of a psychiatric deterioration as a result of 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.	z. 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 a psychiatric deterioration as a result of 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.	Corrected since there is no study manual; the list was provided to the investigators and is also available vis the study portal.
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		
k. [Revision ~~1~~***2***] The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive at screening. ~~For adolescent patients, the BMI should be at least in the 50th percentile for age and gender and must not exceed 38.0 kg/m^2.~~	k. [Revision 2] The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive at screening.	This limitation was removed to encourage enrollment of otherwise eligible adolescents.
4.3.1.General Withdrawal Criteria		
… Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate. Alternatively, if the opportunity is available and the patient is eligible, the patient may be offered the option to participate in ~~a~~ ***TV46000-CNS-30078, the*** long-term safety and tolerability extension study. …	… Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate. Alternatively, if the opportunity is available and the patient is eligible, the patient may be offered the option to participate in TV46000-CNS-30078, the long-term safety and tolerability extension study. …	Name of the extension study added.

Original text with changes shown	New wording	Reason/Justification for change
5. TREATMENTS		
5.1.2. Placebo Investigational Medicinal Product		
TV-46000 placebo is available as an extended-release [redacted]	[redacted]	Correction; wording on PFS added for consistency with the packaging description in the Table of Investigational Medicinal Products Used in the Study.
Table 4: Investigational Medicinal Products Used in the Study		
[redacted]		Clarification; [redacted] dose should also be marked as Adults Only, since this dose is comparable to 5 mg oral risperidone for the TV-46000 q1m product. Correction; [redacted] dose has been marked as Adults Only for consistency with the protocol synopsis.
5.5. Treatment After the End of the Study		
… When the study ends, eligible patients may be offered the opportunity to enter ~~an~~ ***the TV46000-CNS-30078*** extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol~~. A~~, ***and a*** separate protocol ~~will~~ ***was*** issued for ~~the extension study as applicable~~ ***it***.	… When the study ends, eligible patients may be offered the opportunity to enter the TV46000-CNS-30078 extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol, and a separate protocol was issued for it.	Name of the extension study added.
5.7. Prior and Concomitant Medication or Therapy		

Original text with changes shown	New wording	Reason/Justification for change
… ***In general, a*** ~~A~~ntidepressants, antipsychotics (other than study drug), and mood stabilizers will not be permitted as concomitant medications. However, ***some*** antidepressants and mood 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. No dose changes or new administrations of these drugs will be permitted during the study. If these are required as rescue medications, this should lead to a consideration of discontinuation from the study due to exacerbation or relapse.	… In general, antidepressants, antipsychotics (other than study drug), and mood stabilizers will not be permitted as concomitant medications. However, some antidepressants and mood 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. No dose changes or new administrations of these drugs will be permitted during the study. If these are required as rescue medications, this should lead to a consideration of discontinuation from the study due to exacerbation or relapse.	Clarification that exceptions are allowed for some antidepressants under the conditions listed.
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. At the time of analysis (after the end of study or at ***each*** interim analysis), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP. The codes will be provided to an independent statistician who will perform ~~an~~ ***the*** interim ~~analysis~~ ***analyses***.	Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (after the end of study or at each interim analysis), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant SOP. The codes will be provided to an independent statistician who will perform the interim analyses.	Clarification.
5.10.3. Data Monitoring Committee		
… The IDMC will perform ~~1~~ ***up to 2*** formal interim ~~analysis~~ ***analyses*** ~~of~~ ***for*** efficacy in this study (when the number of events observed reaches 43.5% and 60% of the planned 207 relapse events in the ITT analysis set [Section 3.4]). ***The second interim analysis will be performed if at least one of the p-values of the 2 primary comparisons is above 0.0101 at the first interim analysis.*** …	… The IDMC will perform up to 2 formal interim analyses for efficacy in this study (when the number of events observed reaches 43.5% and 60% of the planned 207 relapse events in the ITT analysis set [Section 3.4]). The second interim analysis will be performed if at least one of the p-values of the 2 primary comparisons is above 0.0101 at the first interim analysis. …	Revised due to the addition of another, earlier interim analysis.
8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS/BIOMARKERS/PHARMACOGENOMICS		
8.3. [redacted]		
[redacted]	[redacted]	

Original text with changes shown	New wording	Reason/Justification for change
with a known or hypothesized role in schizophrenia or response to antipsychotic medications***, unless the patient declines testing or local regulations prohibit testing***.	biomarkers with a known or hypothesized role in schizophrenia or response to antipsychotic medications, unless the patient declines testing or local regulations prohibit testing.	
9. [redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
used, the p-value for the other comparison (the significant comparison), should be significant at a 2-sided alpha/2 level. Assuming the above, a total of 207 relapse events will need to be observed during Stage 2 of the study ~~for~~in the ITT analysis set (adult patients) in the 3 treatment groups (combined) ***in order*** to ~~have a statistical power or approximately~~ ***attain*** 90% ***power*** (East 6 [Version 6.3] manual, 2014). The sample size rationale is based on the adult patients. There is no estimation of the sample size in the adolescent population, and their number is not known at this time. Assuming an accrual time of 6 months and a maximal treatment duration during the double-blind stage of approximately 13 months, approximately 139 adult patients will need to be randomized to each treatment group for a total of 417 adult patients randomized. Assuming that ~~30%~~ ***40%*** of the patients enrolled in Stage 1 will not be randomized to the double-blind phase (Stage 2), a total of ~~596~~ ***approximately 695*** adult patients will need to be enrolled into Stage 1. As an event-driven study, depending on the actual recruitment rate and percentage of patients who are enrolled in Stage 1 and are randomized to Stage 2, it may be possible to randomize more than 417 adult patients, as long as Stage 2 of the study ends ***due to a successful interim analysis or*** when the number of relapse events in the ITT analysis set reaches 207.	Assuming an accrual time of 6 months and a maximal treatment duration during the double-blind stage of approximately 13 months, approximately 139 adult patients will need to be randomized to each treatment group for a total of 417 adult patients randomized. Assuming that 40% of the patients enrolled in Stage 1 will not be randomized to the double-blind phase (Stage 2), a total of approximately 695 adult patients will need to be enrolled into Stage 1. As an event-driven study, depending on the actual recruitment rate and percentage of patients who are enrolled in Stage 1 and are randomized to Stage 2, it may be possible to randomize more than 417 adult patients, as long as Stage 2 of the study ends due to a successful interim analysis or when the number of relapse events in the ITT analysis set reaches 207.	
9.2.2. Intent-to-Treat Analysis Set		
The intent-to-treat (ITT) analysis set will include adult patients randomized to the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. ***The purpose of the primary analyses is to estimate the effect of randomized treatment only, omitting any effect of additional treatment that may be administered after discontinuation of the randomized treatment. Accordingly, the ITT analysis set complies with while-on-treatment strategy[1] that will be taken with regard to the intercurrent***	The intent-to-treat (ITT) analysis set will include adult patients randomized to the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The purpose of the primary analyses is to estimate the effect of randomized treatment only, omitting any effect of additional treatment that may be administered *after* discontinuation of the randomized treatment. Accordingly, the ITT analysis set complies with while-	Per ICH guidance the description of the estimand was included for clarification and elaboration of the previous ITT definition. The citation of the guidance was added as a footnote.

Original text with changes shown	New wording	Reason/Justification for change
event of treatment discontinuation, with censoring at this intercurrent event. This study estimand will be the difference in time to relapse (survival) under the treatment to which the patient was initially randomized until last treatment or early termination of all adult patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. ***[1] ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guidance on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017. European Medicines Agency. 30 August 2017***	on-treatment strategy[1] that will be taken with regard to the intercurrent event of treatment discontinuation, with censoring at this intercurrent event. This study estimand will be the difference in time to relapse (survival) under the treatment to which the patient was initially randomized until last treatment or early termination of all adult patients who were successfully stabilized on oral risperidone at a daily dose range of 2 mg to 5 mg. [1] ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guidance on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017. European Medicines Agency. 30 August 2017	
9.4. Study Population		
The eITT analysis set ~~(Section 9.3)~~ ***(Section 9.2.3)*** will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. ***If the number of adolescents permits, summaries will also be presented by age subgroup.*** The primary analysis will be conducted on the ITT analysis set ***(Section 9.2.2)***, the first key secondary endpoint will be conducted on the complete eITT analysis set ***(Section 9.2.3)*** and the second key secondary will be conducted on the adolescent subset of the eITT analysis set***, if the number of adolescents permits***. The analysis set on which analysis for other ~~end points~~ ***endpoints*** will be conducted will be specified on a case**-**by-case basis. The enrolled patients set ***(Section 9.2.1)*** will be used for data summaries before the double-blind treatment stage.	The eITT analysis set (Section 9.2.3) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. If the number of adolescents permits, summaries will also be presented by age subgroup. The primary analysis will be conducted on the ITT analysis set (Section 9.2.2), the first key secondary endpoint will be conducted on the complete eITT analysis set (Section 9.2.3) and the second key secondary will be conducted on the adolescent subset of the eITT analysis set, if the number of adolescents permits. The analysis set on which analysis for other endpoints will be conducted will be specified on a case-by-case basis. The enrolled patients set (Section 9.2.1) will be used for data summaries before the double-blind treatment stage.	Correction of cross-link to correct sub-section. Clarification regarding data analysis and presentation.
9.5.1. Primary Endpoint		
… Time to impending relapse will be calculated as the earliest date the patient meets ≥1 of the impending relapse criteria minus the randomization date plus 1.	… Time to impending relapse will be calculated as the earliest date the patient meets ≥1 of the impending relapse criteria minus the randomization date plus 1.	Clarification regarding the absolute increase of the combined score defined in the primary endpoint.

Original text with changes shown	New wording	Reason/Justification for change
The absolute increase of the combined score of the 4 PANSS items is the sum of the increases of those scores (ignoring the decreases).	The absolute increase of the combined score of the 4 PANSS items is the sum of the increases of those scores (ignoring the decreases).	
9.5.5.2. Sensitivity Analysis		
A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment ~~when~~ ***at the time*** the first relapse was observed via the interval censoring method. Sensitivity analysis will also be conducted by ~~classifying dropouts~~ ***tipping point analysis that imputes time to relapse for dropouts*** (for reasons ~~other than~~ ***suspected to be related to*** relapse) ~~as relapse events instead of censoring~~ ***with increasing risk to relapse, compared to similar patients in the same treatment group that continue treatment***. The PP analysis set will also be used to ~~assess~~***evaluate*** the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.	A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment at the time the first relapse was observed via the interval censoring method. Sensitivity analysis will also be conducted by tipping point analysis that imputes time to relapse for dropouts (for reasons suspected to be related to relapse) with increasing risk to relapse, compared to similar patients in the same treatment group that continue treatment. The PP analysis set will also be used to evaluate the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.	Correction of the former methodology; the current methodology is tipping point analysis. Correction in terminology.
9.6. Multiple Comparisons and Multiplicity		
There will be ~~1~~ ***up to 2 forma***l interim ~~analysis~~ ***analyses*** when the number of events observed reaches ***43.5% and*** 60% of the planned 207 relapse events (***90 and*** 125 events***, respectively***) in the ITT analysis set. At ~~this~~ ***the first*** interim analysis, both primary efficacy tests will be tested at a 2-sided alpha of 0.0101. If both tests are significant at the ***first*** interim analysis, the study ~~may~~will be stopped. If only 1 primary efficacy test (or none) is significant at the ***first*** interim analysis, the study will continue until the ***second interim analysis. If both tests are significant at the second interim analysis, the study will be stopped. If only 1 primary efficacy test (or none) is significant at this interim analysis, the study will continue until 207*** ~~required number of~~ relapse events are observed At the final analysis, both primary efficacy tests will be conducted with 2-sided alphas of ~~0.0464~~ ***0.0418***; if 1 primary efficacy test is not significant at a 2-sided alpha of ~~0.0464~~ ***0.0418***, the other will be tested at a 2-sided alpha of ~~0.0464~~ ***0.0418*** divided by 2. This procedure will adequately control overall type 1 error for a 2-sided alpha of 0.05. The nominal alphas of 0.0101 at ~~the~~	There will be up to 2 formal interim analyses when the number of events observed reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events, respectively) in the ITT analysis set. At the first interim analysis, both primary efficacy tests will be tested at a 2-sided alpha of 0.0101. If both tests are significant at the first interim analysis, the study will be stopped. If only 1 primary efficacy test (or none) is significant at the first interim analysis, the study will continue until the second interim analysis. If both tests are significant at the second interim analysis, the study will be stopped. If only 1 primary efficacy test (or none) is significant at this interim analysis, the study will continue until 207 relapse events are observed At the final analysis, both primary efficacy tests will be conducted with 2-sided alphas of 0.0418; if 1 primary efficacy test is not significant at a 2-sided alpha of 0.0418, the other will be tested at a 2-sided alpha of 0.0418 divided by 2. This procedure will adequately control overall type 1	Clarification following addition of a 2nd interim analysis.

Original text with changes shown	New wording	Reason/Justification for change
each interim ***analysis*** and ~~0.0464~~ ***0.0418*** at the final analysis were calculated using EAST 6 software as described in the EAST 6 manual (East 6 [Version 6.3] manual, 2014). Type-I error will be further controlled for the 2 key secondary endpoints by employing the hierarchical approach. Secondary endpoint #1 will be analyzed only in case the 2 primary efficacy endpoints have p-values less than or equal to alpha of ~~0.0464~~ ***0.0418***. In that case, key secondary endpoint #1 will be tested for the 2 dosing regimens using the same approach. Namely, tests for the 2 dosing regimens will be conducted with 2-sided alphas of ~~0.0464~~ ***0.0418***; if one of the comparisons for the key secondary endpoint #1 is not significant at a 2-sided alpha of ~~0.0464~~ ***0.0418***, the other will be tested at a 2-sided alpha of ~~0.0464~~ ***0.0418*** divided by 2. …	error for a 2-sided alpha of 0.05. The nominal alphas of 0.0101 at each interim analysis and 0.0418 at the final analysis were calculated using EAST 6 software as described in the EAST 6 manual (East 6 [Version 6.3] manual, 2014). Type-I error will be further controlled for the 2 key secondary endpoints by employing the hierarchical approach. Secondary endpoint #1 will be analyzed only in case the 2 primary efficacy endpoints have p-values less than or equal to alpha of 0.0418. In that case, key secondary endpoint #1 will be tested for the 2 dosing regimens using the same approach. Namely, tests for the 2 dosing regimens will be conducted with 2-sided alphas of 0.0418; if one of the comparisons for the key secondary endpoint #1 is not significant at a 2-sided alpha of 0.0418, the other will be tested at a 2-sided alpha of 0.0418 divided by 2. …	
9.7. Safety Analysis		
Safety assessments and time points are provided in Table 1 ***and Table 2***.	Safety assessments and time points are provided in Table 1 and Table 2.	Correction; addition of cross-link to other Table of Assessments.
9.13. Planned Interim Analysis		
There will be ~~1~~ ***up to 2*** formal interim ~~analysis~~ ***analyses*** when the number of events observed in the ITT analysis set reaches ***43.5% and*** 60% of the planned 207 relapse events (***90 and*** 125 events in adult patients***, respectively***). ***Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m) at any of the interim analyses in order to stop the study early for success as described in*** Section ~~*9.5.5.2*~~ ***9.6. If success criteria was not met [ie, if only 1 primary efficacy test (or none) is significant] at the first interim analysis (at 90 relapse events), the study will continue to the second interim analysis (at 125 relapse events). If only 1 primary efficacy test (or none) is significant at this interim analysis, (ie, if none of the interim analyses demonstrate***	There will be up to 2 formal interim analyses when the number of events observed in the ITT analysis set reaches 43.5% and 60% of the planned 207 relapse events (90 and 125 events in adult patients, respectively). Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101) for both risperidone treatment groups (q1m and q2m) at any of the interim analyses in order to stop the study early for success as described in Section 9.6. If success criteria was not met [ie, if only 1 primary efficacy test (or none) is significant] at the first interim analysis (at 90 relapse events), the study will continue to the second interim analysis (at 125 relapse events). If only 1 primary	Revised due to the addition of another, earlier interim analysis. Re-organization of section text for clarification. Correction of cross-link to correct section of protocol.

Original text with changes shown	New wording	Reason/Justification for change
success), the study will continue until 207 relapse events are reached. An IDMC will conduct the interim ~~analysis~~ analyses to assess efficacy for all randomized patients. An IDMC charter will be developed for the interim analyses. Procedures will be taken to ensure the integrity of the study ~~that~~ follow***s*** the IDMC charter. ~~Results will need to demonstrate statistically significant effects in the primary analysis of the primary endpoint (at a significance level of 0.0101for both risperidone treatment groups (q1m and q2m)) as described in Section 9.5.5.2~~. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.	efficacy test (or none) is significant at this interim analysis, (ie, if none of the interim analyses demonstrate success), the study will continue until 207 relapse events are reached. An IDMC will conduct the interim analyses to assess efficacy for all randomized patients. An IDMC charter will be developed for the interim analyses. Procedures will be taken to ensure the integrity of the study follows the IDMC charter. The IDMC could recommend to discontinue the study for ethical reasons, most notably continued exposure to placebo, if efficacy is established.	
APPENDIX A . CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Sponsor's Authorized Representative [redacted] Vice President, Therapeutic Area Head, Neurology and Psychiatry Specialty Clinical Development Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Email: [redacted]	**Sponsor's Authorized Representative** [redacted] Vice President, Therapeutic Area Head, Neurology and Psychiatry Specialty Clinical Development Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Email: [redacted]	This reflects a change in responsibilities at Teva.
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study [redacted] ~~Senior Director, Global Clinical Development, Neuropsychiatry~~ Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: + [redacted] Email: [redacted]	**Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study** [redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] Email: [redacted]	Eran Harary was appointed as the Therapeutic Area Head, thus the title change as above. He remains the Sponsor's medical expert for the study.
Medical Monitor*s* ***For US:*** [redacted] Medical Director ICON PLC	**<u>For US:</u>** [redacted] Medical Director ICON PLC	Addition of the contact details for the medical monitor for Bulgaria.

Original text with changes shown	New wording	Reason/Justification for change
Mobile: [redacted] Email: [redacted] ***For Bulgaria:*** [redacted] ***Medical Director*** ***ICON PLC*** ***Mobile:*** +[redacted] ***Email:*** [redacted]	Mobile: [redacted] Email: [redacted] **For Bulgaria:** [redacted] Medical Director ICON PLC Mobile: [redacted] Email: [redacted]	
Rater Training for Clinical Scales and Utilization Measures ~~Bracket~~ ***Signant Health (formerly Bracket)*** 575 E. Swedesford Road, Ste 200 Wayne, PA 19087 United States	**Rater Training for Clinical Scales and Utilization Measures** 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.
Bioassay and Pharmacokinetic Sample Analysis ~~Please refer to the study Trial Master File.~~ ***Teva Pharmaceutical Works P. Ltd. Co. (TPW)*** ***Bioanalytical Laboratory*** ***Pallagi St. 13*** ***Debrecen 4042*** ***Hungary***	**Bioassay and Pharmacokinetic Sample Analysis** 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.
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
b. Stage 1: Oral Conversion and Stabilization (Telephone Contacts [Visit 4a, Week -6±3 days and Visit 5a, Week -2±3 days]) (Other sections affected by this change: c. Stage 2: Relapse Prevention [Telephone Contacts]).		
... • brief set of clinical questions to detect psychotic symptoms – the specific questions asked will be at the discretion of the investigator. ***A list of suggested questions will be provided to the investigator.***	... • brief set of clinical questions to detect psychotic symptoms – the specific questions asked will be at the discretion of the investigator. A list of suggested questions will be provided to the investigator.	Added for clarity and consistency with corresponding footnote inTable 1 and Table 2.
Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Baseline [Visit 6, Day 1 ±3 days]) (Other sections affected by this change: g. Early Termination (ET) Visit/End-of-Treatment Visit (EoT); Follow-up/ Exit Period		
... • blood sample for pharmacogenetic analysis***, unless the patient declines testing or local regulations prohibit testing.***	... • blood sample for pharmacogenetic analysis, unless the patient declines testing or local regulations prohibit testing.	Added for clarity and consistency with corresponding footnotes in Table 2 and other protocol sections.

Original text with changes shown	New wording	Reason/Justification for change
• blood sample for biomarker analysis***, unless the patient declines testing or local regulations prohibit testing.*** ---	• blood sample for biomarker analysis, unless the patient declines testing or local regulations prohibit testing. ...	
g. Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT)		
Note: The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy ~~at the~~ due to a successful interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set.	**Note:** The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy due to a successful interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set.	Revised due to the addition of another, earlier interim analysis.
Follow-up/Exit Period (Follow-up Visit 1 [4 weeks after last dosing visit] and Follow-up Visit 2 [8 weeks after the last dosing visit, End-of-Study (EoS) Visit])		
Note: Eligible patients who choose to enter the ***long term TV46000-CNS-30078*** extension study will not need to complete the follow-up/exit visits in this study.	**Note:** Eligible patients who choose to enter the long term TV46000-CNS-30078 extension study will not need to complete the follow-up/exit visits in this study.	Name of the extension study added.
Unscheduled Visits		
… Procedures performed during unscheduled visits will include the following: • concomitant medication review; • inquiry about changes in use of alcohol and illicit drugs • vital sign measurements • adverse event inquiry (including serious adverse event reporting, injection site-related events including pain) • C-SSRS ("Since Last Visit" version) (if visit scheduled to assess psychiatric adverse events) • PANSS and review of relapse criteria Other procedures may be performed at the discretion of the investigator. ***In addition, to reduce patient burden and to avoid***	… Procedures performed during unscheduled visits will include the following: • concomitant medication review; • inquiry about changes in use of alcohol and illicit drugs • vital sign measurements • adverse event inquiry (including serious adverse event reporting, injection site-related events including pain) • C-SSRS ("Since Last Visit" version) (if visit scheduled to assess psychiatric adverse events) • PANSS and review of relapse criteria Other procedures may be performed at the discretion of the investigator. In addition, to reduce patient burden and to avoid	Clarification regarding procedures to be performed during unscheduled visits, per Letter of Clarification 02.

Original text with changes shown	New wording	Reason/Justification for change
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 <u>not</u> 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.*** …	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 **<u>not</u>** 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. …	
APPENDIX E. BIRTH CONTROL METHODS AND PREGNANCY TESTING		
… **Postmenopausal women *are defined as*:** • 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy … **~~Description of different birth control methods~~** ***Description of ~~H~~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, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month	… **Postmenopausal women are defined as:** • 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy … **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. Such methods include the following: • Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these	Only highly effective birth control methods should be used in this study. Therefore, unnecessary information was deleted. The information provided in this appendix was aligned with that in the 30078 protocol for consistency and in line with the Clinical Trials Facilitation Group (CTFG) document "Recommendation related to contraception and pregnancy testing in clinical trials" (Final Version, 2014-09-15). The paragraphs on pregnancy tests in women of childbearing potential were deleted since the time points for pregnancy testing are defined in the protocol.

Original text with changes shown	New wording	Reason/Justification for change
(for IMPs potentially teratogenic/genotoxic) before the first dose of IMP. • Progestogen-only hormonal contraception (oral, injectable, 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 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. • Periodic abstinence (eg, calendar, ovulation, symptothermal, 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, MHRA). ~~**Acceptable birth control methods:**~~ ~~Acceptable birth control methods that result in a failure rate of more than 1% per year include: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but not highly effective methods of birth control.~~ ~~**Unacceptable birth control methods:**~~	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, 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 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. • Periodic abstinence (eg, calendar, ovulation, symptothermal, 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, MHRA). **Male contraception** Male patients must always use a condom. … **Pregnant female partners of male study**	

Original text with changes shown	New wording	Reason/Justification for change
~~Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.~~ **Male contraception** Male patients must always use a condom~~, except in cases of no genotoxicity; or no demonstrated or suspected human teratogenicity/fetotoxicity~~. … ~~**Contraception for female partners of male study participants:**~~ ~~Female partners (who are not pregnant) of male study participants must use contraception for non-pregnant women of childbearing potential until the end of relevant systemic exposure in case of IMPs with genotoxicity or IMPs with no genotoxicity but demonstrated or suspected human teratogenicity/fetotoxicity.~~ ~~**Pregnancy tests in women of childbearing potential:**~~ ~~**1.**Conduct monthly pregnancy testing from first dose of IMP until last dose of IMP and additional 30 days in case the IMP does not have a marketing authorization and has suspected human teratogenicity/genotoxicity/fetotoxicity. Conduct monthly pregnancy testing and in case the IMP has a marketing authorization, if the IMP has a demonstrated or suspected human teratogenicity/genotoxicity/fetotoxicity according to Risk Safety Information. Shorter testing intervals are to be considered depending on drug dosing schedule.~~ ~~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.~~ ~~For IMPs with unlikely risk of human teratogenicity/fetotoxicity, additional pregnancy testing is~~	**participants:** Male study participants must use condoms during intercourse if their female partners are pregnant.	

Original text with changes shown	New wording	Reason/Justification for change
~~generally not necessary. This refers to IMPs for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.~~ **Pregnant female partners of male study participants:** Male study participants must use condoms during intercourse if their female partners are pregnant.		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
All blood tubes will be labeled with the patient code number. ~~If required by local regulations, following DNA extraction from the pharmacogenetic blood sample, the DNA sample will be labeled with a new code (ie, double coding).~~	All blood tubes will be labeled with the patient code number.	Correction; text relevant to PGx samples deleted from here and moved to Appendix J.
APPENDIX J. PHARMACOGENETIC ASSESSMENTS		
A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent for pharmacogenetic assessments at the time point detailed in Table 2, ***unless the patient declines testing or local regulations prohibit testing***. ***All blood tubes will be labeled with the patient code number. If required by local regulations, following DNA extraction from the pharmacogenetic blood sample, the DNA sample will be***	A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent for pharmacogenetic assessments at the time point detailed in Table 2, unless the patient declines testing or local regulations prohibit testing. All blood tubes will be labeled with the patient code number. If required by local regulations, following DNA extraction from the pharmacogenetic	Added for clarity and consistency with corresponding footnote in Table 2 and Section 8.4. Correction; relevant text moved here from Appendix I.

Original text with changes shown	New wording	Reason/Justification for change
labeled with a new code (ie, double coding). Genetic variability in the metabolizer gene, cytochrome P450 2D6 (CYP2D6), will be evaluated for an association with drug concentrations of TV-46000 and oral risperidone.	blood sample, the DNA sample will be labeled with a new code (ie, double coding). Genetic variability in the metabolizer gene, cytochrome P450 2D6 (CYP2D6), will be evaluated for an association with drug concentrations of TV-46000 and oral risperidone.	

16.5. Letter of Clarification 02 (27 June 2019)

TEVA Pharmaceuticals

LETTER OF CLARIFICATION 02

Study number: TV46000-CNS-30072

Clinical Study Protocol with Amendment 01

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

(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)

Dated 06 December 2018

IND number: 124384; EudraCT number: 2018-001619-65

27 June 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:

- concomitant medication review;
- inquiry about changes in use of alcohol and illicit drugs
- vital sign measurements
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- C-SSRS ("Since Last Visit" version) (if visit scheduled to assess psychiatric adverse events)
- PANSS and review of relapse criteria

These assessments are marked with an "X" in Table 1 and Table 2 of the protocol. 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:

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(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] (at +1[redacted] or [redacted]) or the Teva Clinical Program Manager, [redacted] (at +[redacted]) if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Senior Director, Global Clinical Development, Neuropsychiatry

Teva Branded Pharmaceutical Products R&D Inc.

Cc: [redacted] Study File.

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16.6. Global Protocol Amendment 01 (Dated 06 December 2018)

The primary reason for this global amendment is to allow adolescent patients (aged 13-17 years) to enroll in this clinical study and receive treatment with TV-46000, following regulatory interactions with FDA. To this end, assent to study procedures was introduced, some inclusion criteria were modified and 2 new key secondary endpoints for data analysis were added. Clarifications regarding risperidone dosing and assessment of certain scales relevant to adolescent patients were also added.

Further clarifications and changes related to study conduct were also implemented in this amendment. These include (but are not limited to) splitting the Table of Assessments into 2 separate tables (1 for each stage of the study) for clarity. The end-of-study (EoS)/Early Termination (ET) visit is now depicted as a separate visit, and the repeating 24-week visit window (ie, Visit 7-12c, 13-18c, etc) is depicted to better detail the assessments performed at the various visits. Other examples include: a urine pregnancy test was added to the baseline visit, specifying which scales will only be performed in adult patients, and up to 3 additional pharmacokinetic samples will be collected from adolescents.

In addition, the country-specific items introduced in the Local Amendment 01 for Bulgaria (dated 28 May 2018) and in the Clarification Letter (dated 26 June 2018) were implemented as applicable.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are considered significant by the Teva Authorized Representative.

Table 1 (Screening and Stage 1), Table 2 (Stage 2 and Follow-Up), the Overall Study Schematic Diagram, and the corresponding footnotes, have been revised to reflect changes described below.

A comparison table showing the changes from the Protocol with Revision 01 to Amendment 01 is provided below. Previous text is presented in the column titled "Original text with changes shown", and the revised or new text is presented in the column titled "new wording." Revised or new text is shown in bold italics and deletions are shown in strike-through.

Throughout the protocol, cross-references to both Table 1 and Table 2 were created for certain procedures and assessments as applicable. If this was the only change made to the section text, it is not depicted in the comparison table.

Also, in order to adhere with current Teva standards, some formatting and editing changes have been made.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">TITLE PAGE (Other sections affected by this change: Investigator Agreement; Coordinating Investigator Agreement)</td></tr>
<tr><td>Clinical Study Protocol with Amendment 01</td><td>Clinical Study Protocol with Amendment 01</td><td>To denote the global amendment.</td></tr>
<tr><td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia</td><td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia</td><td>To reflect the introduction of the possibility to enroll adolescent patients in the study.</td></tr>
<tr><td>A Randomized, Double-Blind, Placebo-Controlled Study on Efficacy, Safety, and Tolerability of TV-46000 in Adults and Adolescents with Schizophrenia</td><td>A Randomized, Double-Blind, Placebo-Controlled Study on Efficacy, Safety, and Tolerability of TV-46000 in Adults and Adolescents with Schizophrenia</td><td>To reflect the introduction of the possibility to enroll adolescent patients in the study.</td></tr>
<tr><td>[Not applicable]</td><td>(The RISE Study – The RIsperidone Subcutaneous Extended-release Study)</td><td>Addition of study name to protocol.</td></tr>
<tr><td>EudraCT number: <s>Not applicable</s> 2018-001619-65</td><td>EudraCT number: 2018-001619-65</td><td>Number added for study conduct in EU.</td></tr>
<tr><td>PREFACE</td><td></td><td></td></tr>
<tr><td>This Clinical Study Protocol with Revision 01 includes updates to the original protocol dated 14
December 2017.</td><td>[Deleted]</td><td>Preface deleted and moved to Section 16.4 as part of Summary Changes to protocol.</td></tr>
<tr><td colspan="3">AMENDMENT HISTORY</td></tr>
<tr><td>[Not applicable]</td><td>AMENDMENT HISTORY
The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:
<table>
<tr><td>Global Amendment 01</td><td>06 December 2018
(184 patients enrolled to date)</td></tr>
<tr><td>Letter of Clarification 01</td><td>26 June 2018</td></tr>
</table></td><td>This page was added in the amendment for tracking history.</td></tr>
</table>

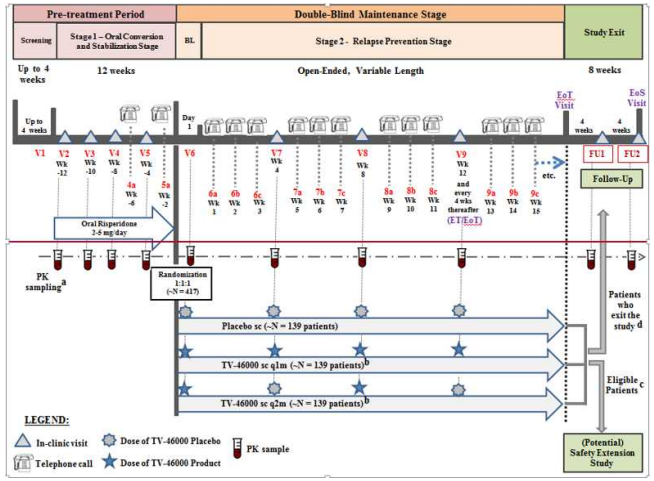
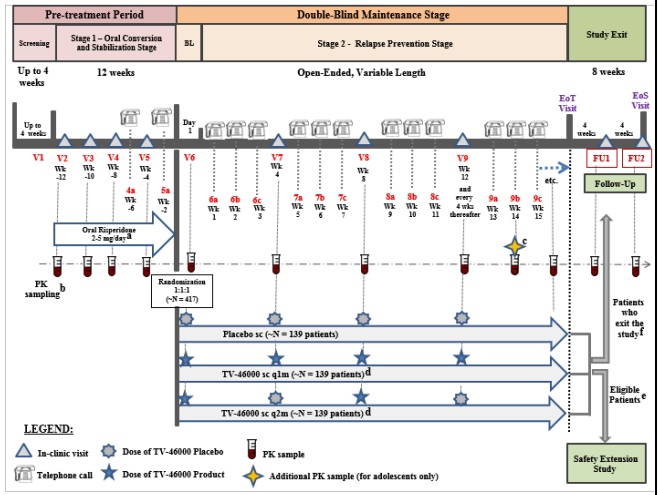
Original text with changes shown	New wording	Reason/Justification for change
	<table><tr><td>Local Amendment 01 for Bulgaria</td><td>28 May 2018 (6 patients enrolled to date)</td></tr><tr><td>Protocol with Revision 01</td><td>15 February 2018 (0 patients enrolled to date)</td></tr></table> The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.	
LIST OF ABBREVIATIONS		
[Not applicable]	FSH = Follicle stimulating hormone	Newly-added abbreviation.
[Not applicable]	SmPC = Summary of Product Characteristics	Newly-added abbreviation.
1. INTRODUCTION AND BACKGROUND INFORMATION		
1.1 Introduction		
[Not applicable]	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 is 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, thought disorder), neurocognitive impairments, psychophysiological abnormalities, and the presence of structural brain abnormalities (Asarnow et al 1995, Bo and Haahr 2016, Rapoport et al 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 and Haahr 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	New text regarding schizophrenia in the pediatric population. Literature references added to reference list.

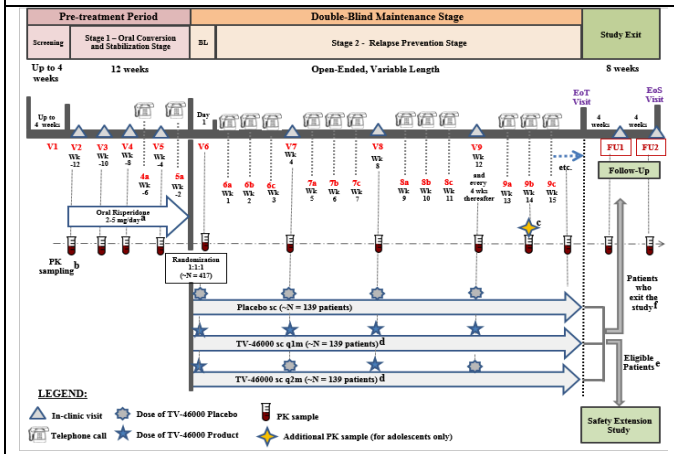
Original text with changes shown	New wording	Reason/Justification for change
	functions and brain structure in patients with schizophrenia have shown the same degenerative patterns, regardless of the patient's age at the onset of the disorder (Weinberger and Harrison 2011).	
The purpose of the study is to compare the safety and efficacy of different durations of TV-46000 administered sc versus placebo. ***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 et al 2017). Enrollment of adolescents in this study will provide data for evaluating the efficacy, safety and tolerability of TV-46000 in this patient population.***	The purpose of the study is to compare the safety and efficacy of different durations of TV-46000 administered sc versus placebo. 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 et al 2017). Enrollment of adolescents in this study will provide data for evaluating the efficacy, safety and tolerability of TV-46000 in this patient population.	Added justification for inclusion of adolescents in the study.
2. STUDY OBJECTIVES AND ENDPOINTS		
2.1. Primary and Secondary Study Objectives and Endpoints		
[Not applicable]	The **key secondary objective** of this study is to evaluate the efficacy of TV-46000 during maintenance treatment in a total population (adults and adolescents) and in adolescent patients with schizophrenia. The key secondary endpoints are: 1. time to impending relapse (as defined under the primary objective) in the total population (adults and adolescents), and 2. time to impending relapse in adolescent patients with schizophrenia. **NOTE:** The assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.	Pursuant to inclusion of adolescent patients in the study, a secondary objective and two key secondary endpoints were added for analysis of study data.
A **secondary objective** of this study is to evaluate the specific efficacy parameters of TV-46000 ***in the total population*** beyond the measures of the primary objective.	A **secondary objective** of this study is to evaluate the specific efficacy parameters of TV-46000 in the total population beyond the measures of the primary objective.	Clarification.
A **secondary objective** of this study is to evaluate the safety and tolerability of TV-46000 ***in the total population***.	A **secondary objective** of this study is to evaluate the safety and tolerability of TV-46000 in the total population.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
A **secondary objective** of this study is to evaluate the pharmacokinetics of oral risperidone and TV-46000 after administration of multiple doses ***in adults, adolescents, and the total population***.	A secondary objective of this study is to evaluate the pharmacokinetics of oral risperidone and TV-46000 after administration of multiple doses in adults, adolescents, and the total population.	Clarification.
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
3. STUDY DESIGN		
3.1. General Study Design and Study Schematic Diagram		
Patients will provide informed ***consent or assent, as applicable,*** at the screening visit. ***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. Patients can be accompanied by caregivers to visits. Open-label oral risperidone (2 to 5 mg/day) will be used to stabilize patients to the treatments (the dose will be based on clinical judgement). ***Adolescent patients will receive a maximal dose of 4 mg/day.*** ***If a patient withdraws from the study prior to the randomization 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.***	Patients will provide informed consent or assent, as applicable, at the screening visit. 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. Patients can be accompanied by caregivers to visits. Open-label oral risperidone (2 to 5 mg/day) will be used to stabilize patients to the treatments (the dose will be based on clinical judgement). Adolescent patients will receive a maximal dose of 4 mg/day**.** If a patient withdraws from the study prior to the randomization 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.	Newly-added text pertaining to study conduct for adolescents: provision of assent, mandatory caregiver presence, maximal dose received. Clarification regarding other aspects of study conduct. Definition of study completers added. Sentence on unscheduled PK samples revised throughout the document to clarify that unscheduled PK samples do not need to be collected during Stage 1, and this is relevant only for Stage 2. The word "potential" was removed from the safety extension study,

Original text with changes shown	New wording	Reason/Justification for change
Stage 2: Double-blind maintenance stage (variable in duration). Stabilized patients (see definition above) will be randomized to receive TV-46000 q1m sc injections, TV-46000 q2m sc injections, or placebo q1m sc injections in a 1:1:1 ratio. ***Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.***	**Stage 2:** Double-blind maintenance stage (variable in duration). Stabilized patients (see definition above) will be randomized to receive TV-46000 q1m sc injections, TV-46000 q2m sc injections, or placebo q1m sc injections in a 1:1:1 ratio. Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.	since preparations for it have begun.
The maximal dose administered to adult patients will be equivalent to an oral risperidone dose of 5 mg/day***, and the maximal dose administered to adolescents will be equivalent to 4 mg/day.***	The maximal dose administered to adult patients will be equivalent to an oral risperidone dose of 5 mg/day, and the maximal dose administered to adolescents will be equivalent to 4 mg/day.	
During Stage 2, ~~U~~***u***nscheduled 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 the 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.	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 the 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	
The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy at the interim analysis or because 207 relapse events are recorded in the ***ITT analysis set***.	The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy at the interim analysis or because 207 relapse events are recorded in the ITT analysis set.	
Per definition, an exacerbation in symptoms during Stage 1 cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. Randomized patients who relapse or meet 1 or more of the withdrawal criteria should be invited to perform the Early	Per definition, an exacerbation in symptoms during Stage 1 cannot be defined as a relapse event, since relapse events can only occur following stabilization and randomization. Randomized patients who relapse or meet 1 or more of the	

Original text with changes shown	New wording	Reason/Justification for change
Termination (ET) visit as soon as possible, within 4 weeks of the last injection. Therefore, a patient is considered a study completer if he or she experienced impending relapse or remained relapse-free at the time of study termination. This ~~potential~~ extension study is beyond the scope of this protocol.	withdrawal criteria should be invited to perform the Early Termination (ET) visit as soon as possible, within 4 weeks of the last injection. Therefore, a patient is considered a study completer if he or she experienced impending relapse or remained relapse-free at the time of study termination. This extension study is beyond the scope of this protocol.	
Figure 1: Overall Study Schematic Diagram		
	 [a] Adolescent patients will receive doses equivalent to 2-4 mg/day oral risperidone. Patients that will require a stabilization dose below 2 mg/day will not be randomized in the study. [b] With the exception of the screening visit, pharmacokinetic samples will be collected at each in-clinic visit. [c] Another pharmacokinetic sample will be collected at Week 14 (2 weeks after Visit 9) from adolescent patients only. It is highly preferable to collect the sample at Week 14. However, if this is not possible, it may be collected 2	Schema and footnotes revised to reflect dosing and pharmacokinetic sampling in the adolescent patient population. The word "potential" was removed from the safety extension study, since preparations for it have begun.

Original text with changes shown	New wording	Reason/Justification for change
 [a] ***Adolescent patients will receive doses equivalent to 2-4 mg/day oral risperidone. Patients that will require a stabilization dose below 2 mg/day will not be randomized in the study.*** [b] With the exception of the screening visit, pharmacokinetic samples will be collected at each in-clinic visit. [c] ***Another pharmacokinetic sample will be collected at Week 14 (2 weeks after Visit 9) from adolescent patients only. 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 (3 weeks and 1 week post-injection, respectively) at the sponsor's discretion.*** [d] Patients randomized to the TV-46000 q1m or q2m sc groups in Stage 2 will receive TV-46000 sc at doses equivalent to the 2 to 5 mg/day dose of oral risperidone on which they were stabilized during Stage 1. ***Adolescent patients will receive a maximal TV-46000 dose equivalent to 4 mg/day oral risperidone.*** [e] When the study ends, eligible patients may be offered the opportunity to enter an extension study to assess the long-	weeks after another in-clinic visit. Up to 2 additional samples may also be collected from adolescent patients (3 weeks and 1 week post-injection, respectively) at the sponsor's discretion. [d] Patients randomized to the TV-46000 q1m or q2m sc groups in Stage 2 will receive TV-46000 sc at doses equivalent to the 2 to 5 mg/day dose of oral risperidone on which they were stabilized during Stage 1. Adolescent patients will receive a maximal TV-46000 dose equivalent to 4 mg/day oral risperidone. [e] When the study ends, eligible patients may be offered the opportunity to enter an extension study to assess the long-term safety and tolerability. This extension study is beyond the scope of this protocol and will be detailed in a separate protocol as applicable. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. [f] For patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study, there will be 2 follow-up/exit visits that will take place 4 weeks and 8 weeks after the last dosing visit.	

Original text with changes shown	New wording	Reason/Justification for change
term safety and tolerability. This extension study is beyond the scope of this protocol and will be detailed in a separate protocol as applicable. If patients choose to enter the extension study, they will not need to complete the follow-up/exit visits in this study. [f] For patients who experience a relapse event, meet 1 or more of the study discontinuation or withdrawal criteria, or do not consent to join the extension study, there will be 2 follow-up/exit visits that will take place 4 weeks and 8 weeks after the last dosing visit.		
3.2. Planned Number of Patients and Countries		
Approximately 795 patients will be screened to achieve enrollment of approximately 596 patients in Stage 1***, including approximately 57 patients in Bulgaria***. The number of randomized patients ***in Stage 2*** is planned to be approximately 417, ***including approximately 40 patients in Bulgaria.*** Details on the definition of evaluable patients and determination of the sample size are given in Section 9.1. The study is planned to be conducted in approximately 80 investigational centers in North America and ~~possibly other regions as well~~ ***Bulgaria***.	Approximately 795 patients will be screened to achieve enrollment of approximately 596 patients in Stage 1, including approximately 57 patients in Bulgaria. The number of randomized patients in Stage 2 is planned to be approximately 417, including approximately 40 patients in Bulgaria. Details on the definition of evaluable patients and determination of the sample size are given in Section 9.1. The study is planned to be conducted in approximately 80 investigational centers in North America and Bulgaria.	Information added regarding study projection in Bulgaria.
3.3. Justification for Study Design and Selection of Population		
[Not applicable]	Moreover, the drug class of LAI atypical antipsychotics has not been studied extensively in children or adolescents (Lytle et al 2017). Although compliance in children and adolescents treated with antipsychotics is substantially higher than in adults, ranging from approximately 74% to 88% (Pogge et al 2005, Yazdi et al 2008), LAIs may be considered for patients with confirmed schizophrenia and with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medication, and poor insight (Ferrin et al 2016). In the Pediatric Study Plan submitted to FDA, a partial waiver was proposed for patients 0 to 12 years of age, since	New text describing the justification of adolescent enrollment in the study.

Original text with changes shown	New wording	Reason/Justification for change
	necessary studies in this age group would be impossible or highly impracticable, and the inclusion of adolescent patients (13-17 years of age) in this Phase 3 program was proposed. The Agency concurred with these proposals. Non-clinical studies with TV-46000 in young and mature animals did not identify a particular concern for treatment of the targeted adolescent population aged 13 and above.	
Antipsychotic LAIs are viewed as maintenance therapy in stable patients with schizophrenia, but they are not currently approved for treatment of acute symptoms. Thus, the population for this study consists of adult ***and adolescent*** patients with chronic schizophrenia and excludes patients with acute disease. Only patients who have been stabilized on oral therapy with risperidone will be randomized into the double-blind maintenance stage of the study.	Antipsychotic LAIs are viewed as maintenance therapy in stable patients with schizophrenia, but they are not currently approved for treatment of acute symptoms. Thus, the population for this study consists of adult and adolescent patients with chronic schizophrenia and excludes patients with acute disease. Only patients who have been stabilized on oral therapy with risperidone will be randomized into the double-blind maintenance stage of the study.	Revision due to the option of adolescent enrollment in the study.
3.4. Stopping Rules for the Study		
One formal interim analysis will be conducted, when the number of events observed ***in the intent-to-treat (ITT) analysis set*** reaches 60% of the planned 207 relapse events (125 events in adult patients).	One formal interim analysis will be conducted, when the number of events observed in the intent-to-treat (ITT) analysis set reaches 60% of the planned 207 relapse events (125 events in adult patients).	Clarification.
3.5. Schedule of Study Procedures and Assessments		
TV46000-CNS-30072 Study Procedures and Assessments		
This was previously Table 1; both stages of the study were depicted.	The table was split into 2 separate tables: Table 1 (In-Clinic Visits and Telephone Contacts) for the pre-treatment period (Stage 1), and Table 2 for the double-blind, maintenance stage (Stage 2). The rows corresponding to each stage are included in the relevant table. Footnotes which are relevant to both are included under each table. Only newly-added or revised rows and footnotes are denoted in this summary of changes.	For further clarity, especially the assessments which are conducted at repeating time points.
General Revisions to Table 1 (Stage 1):	**Revisions to Table 1 (Stage 1):**	Assent must be obtained from adolescent patients.

Original text with changes shown	New wording	Reason/Justification for change
Informed consent ***(and assent, as applicable)*** [Not applicable] [Not applicable] Adverse event inquiry (including SAE reporting, ~~injection site-related events including pain~~)	Informed consent (and assent, as applicable) FSH test added aseparate procedure at screening for women without menses for the past 12 months. Addition of (adults patients only) to some assessments and procedures. Adverse event inquiry (including SAE reporting)	Clarification regarding FSH testing. Clarification in which patients these assessments should be performed. Revised since there are no injections during Stage 1.
[Not applicable]	a If a patient withdraws from the study prior to the randomization 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. b 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. m The FSH test will only be performed for women with no menses for 12 months in order to confirm postmenopausal status. o During the in-clinic visits in Stage 1, if possible, the blood samples for PK assessment should be taken within an hour prior to dosing. In any case, the hour of the last dose taken prior to collection of the pharmacokinetic sample will be recorded on the CRF.	Newly-added footnotes to Table 1.
[e] 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 contacts that take place ~~1,~~ 2~~, and 3~~ weeks after visit ~~6~~ ***4*** will be referred to as "visit ~~6a~~ ***4a***" ~~"visit 6b," and "visit 6c," respectively~~).	[e] 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 contacts that take place 2 weeks after visit 4 will be referred to as "visit 4a").	Footnote revised for applicability to Stage 1 of study.
At screening ~~and baseline~~, measurements will be done in	At screening, measurements will be done in triplicate. The	Footnote revised for applicability to

Original text with changes shown	New wording	Reason/Justification for change
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.~~	mean of the 3 measurements will be used to determine study eligibility.	Stage 1 of study.
General Revisions to Table 2 (Stage 2):		
During Stage 2, ~~U~~**u**nscheduled 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 the 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.	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 the 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.	Revised to clarify that unscheduled PK samples do not need to be collected during Stage 1, and this is relevant only for Stage 2.
[Not applicable]	In Table 2, an "X" was added to denote a urine β-HCG test will be performed at the baseline visit, in addition to the serum β-HCG.	For consistency with Section 7.4.2.2. which states that a urine test will be performed prior to every study drug administration, and since the serum result may not be available that day prior to dosing.
l. Urine ***β HCG*** (dipstick) will be ***performed at all visits where study drug is administered (prior to study drug administration). A negative result must be obtained before study study drug is administered*** ~~done prior to each study drug administration, except screening and baseline, where serum β-HCG tests are performed~~.	l. Urine β 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 study drug is administered.	Clarification regarding urine pregnancy testing during Stage 2.
n. ~~This assessment will be performed every 12 weeks.~~ ***As of Visit 9, inclusive, this assessment will be conducted every 12 weeks thereafter (Visits 12, 15, 18, and so on).***	n. As of Visit 9, inclusive, this assessment will be conducted every 12 weeks thereafter (Visits 12, 15, 18, and so on).	Footnote revised and elaborated for clarification regarding timing of certain assessments during Stage 2.
p. Blood for biomarker analyses will be collected as follows: 6 mL for serum, 6 mL for plasma, and ~~6.5~~ ***2.5*** mL for PAXgene RNA.	p. Blood for biomarker analyses will be collected as follows: 6 mL for serum, 6 mL for plasma, and 2.5 mL for PAXgene RNA.	Correction per laboratory manual.
[Not applicable]	s. Another pharmacokinetic sample will be collected from adolescent patients at a supplementary in-clinic visit at Week 14 (2 Weeks after Visit 9). If it is not possible to take the sample at this visit, it may be taken 2 weeks after another in-clinic visit. Two additional samples, 3 weeks	New footnote regarding pharmacokinetic sampling in adolescents.

Original text with changes shown	New wording	Reason/Justification for change
	and 1 week post-injection, respectively, may be taken at the sponsor's discretion.	
4. SELECTION AND WITHDRAWAL OF PATIENTS		
4.1. Patient Inclusion Criteria		
c. ***[Revision 1]*** The patient has provided written informed consent and is competent to do so. ***For adolescent patients, written informed consent has been provided by each patient's parent or legal guardian, and written assent has been provided by each patient.***	c. [Revision 1] The patient has provided written informed consent and is competent to do so. For adolescent patients, written informed consent has been provided by each patient's parent or legal guardian, and written assent has been provided by each patient.	Criterion revised to allow enrollment of adolescent patients in the study.
j. ***[Revision 1]*** The patient is a male or female of any ethnic origin, ~~***18***~~ ***13*** through 65 years of age at screening.	j. [Revision 1] The patient is a male or female of any ethnic origin, 13 through 65 years of age at screening.	Criterion revised to allow enrollment of adolescent patients in the study per regulatory input.
k. ***[Revision 1]*** The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive, at screening. ***For adolescent patients, the BMI should be at least in the 50th percentile for age and gender and must not exceed 38.0 kg/m^2.***	k. [Revision 1] The patient has a body mass index between 18.0 and 38.0 kg/m^2, inclusive, at screening. ***For adolescent patients, the BMI should be at least in the 50th percentile for age and gender and must not exceed 38.0 kg/m^2.***	Criterion revised to allow enrollment of adolescent patients in the study.
m. ***[Revision 1]*** Women of childbearing potential (see Appendix E) ***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 drugs and for the duration of the study and for 120 days after the last injection of study drug.	m. ***[Revision 1]*** Women of childbearing potential (see Appendix E) 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 drugs and for the duration of the study and for 120 days after the last injection of study drug.	Criterion revised to allow enrollment of adolescent patients in the study.
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	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	Clarification following enrollment option of adolescent patients in the study.

Original text with changes shown	New wording	Reason/Justification for change
patients may not donate sperm for the duration of the study and for 120 days after taking the study drug.	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.	
4.2. Patient Exclusion Criteria		
d. ***[Revision 1]*** 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 RNA 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.***	d. [Revision 1] 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 RNA 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.	Clarification regarding patient enrollment in case of positive hepatitis C serology result.
k. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results. • 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 ~~and~~ ***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.	k. The patient has clinically significant findings in biochemistry, hematology, ECG, or urinalysis results. • 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.	To clarify that discussion should take place in case of QTcF prolongation at either time point.
4.3.3. Pharmacokinetic Sampling in Case of Patient Withdrawal		
Note: Withdrawal under the above criteria (see Section 4.3.2.) 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.	Note: Withdrawal under the above criteria (see Section 4.3.2.) 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.	Correction of typos in text.
5. TREATMENTS		
5.1.1.1 Starting Dose and Dose Levels		
In general, TV-46000 will be administered to ~~the~~ ~~adult~~ patients in the abdomen (except as indicated below) by sc injection, at intervals of q1m or q2m, at a dose equivalent to oral risperidone 2 to 5 mg/day ***on which they were stabilized***	In general, TV-46000 will be administered to patients in the abdomen (except as indicated below) by sc injection, at intervals of q1m or q2m, at a dose equivalent to oral risperidone 2 to 5 mg/day on which they were stabilized in	Clarifications regarding administration of TV-46000.

Original text with changes shown	New wording	Reason/Justification for change
in Stage 1, per the conversion table below (Table 3). The maximal dose administered will be equivalent to an oral risperidone dose of 5 mg/day. ***Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized.*** Several investigational centers may be ~~pre-~~selected by the sponsor (based on the centers' capabilities, sponsor's considerations, and prior clinical experience with injectable medication) for injection of study drug in the back of the upper arm***,*** instead of the abdomen***,*** to all ***or some of the*** enrolled patients at these sites (approximately 20% of the study patient population).	Stage 1, per the conversion table below (Table 3). The maximal dose administered will be equivalent to an oral risperidone dose of 5 mg/day. Patients that require a stabilization dose below 2 mg/day will not be randomized in the study. Also, as a precautionary measure, adolescent patients that will require a stabilization dose of more than 4 mg during the stabilization stage will not be randomized. Several investigational centers may be selected by the sponsor (based on the centers' capabilities, sponsor's considerations, and prior clinical experience with injectable medication) for injection of study drug in the back of the upper arm, instead of the abdomen, to all or some of the enrolled patients at these sites (approximately 20% of the study patient population).	To allow for greater flexibility.
5.1.2. Placebo Investigational Medicinal Product		
[redacted]	[redacted]	[redacted]
5.2.1. Storage and Security		
The investigator or designee must confirm appropriate temperature conditions have been maintained for all ~~IMPs~~ ***medicinal products*** received, and any discrepancies must be reported and resolved before ***their*** use ~~of the IMPs~~. … Oral risperidone is to be stored and securely locked according to the storage conditions specified in the package insert (RISPERIDONE tablets, Teva Pharmaceuticals, US PI).	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. …	[redacted] Since it is not considered an IMP, the sentence on oral risperidone storage was moved to Section 5.4.
5.2.3. Accountability		
Used and partially used IMP (test or placebo) will ~~be destroyed by the study center. Unused IMP (test or placebo) will be Unused IMP (test or placebo).~~ ***All test or placebo IMP supplies (used, partially-used, and unused)*** will be returned to the sponsor or its designee according to	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.	Clarification that all IMP will be returned to the sponsor. Correction of text duplication.

Original text with changes shown	New wording	Reason/Justification for change
local and national regulations and the site's standard operating procedures (SOPs), following written authorization from the sponsor.		
5.3. Justification for Dose of Test Investigational Medicinal Product		
… Based on the pharmacokinetic performance and the safety profile of TV-46000 in Study TV46000-SAD-10055 and the population pharmacokinetic model-derived simulations, it is expected that TV-46000 provides sufficient coverage throughout 28 and 56 days in 4 doses [redacted] equivalent to 2-, 3-, 4-, and 5-mg oral risperidone based on total active moiety (Table 3). ***Adolescent patients will receive a maximal dose of TV-46000 equivalent to 4 mg oral risperidone.***	… Based on the pharmacokinetic performance and the safety profile of TV-46000 in Study TV46000-SAD-10055 and the population pharmacokinetic model-derived simulations, it is expected that TV-46000 provides sufficient coverage throughout 28 and 56 days in 4 doses [redacted]) equivalent to 2-, 3-, 4-, and 5-mg oral risperidone based on total active moiety (Table 3). Adolescent patients will receive a maximal dose of TV-46000 equivalent to 4 mg oral risperidone.	Clarification regarding maximal dose of TV-46000 for adolescents.
5.4. Other Medicinal Products/Non-Investigational Medicinal Products		
In the US, ~~***Oo***~~***oral*** risperidone ~~tablets~~ for stabilization (Table 4) will be a commercial product supplied by the study center. ***In Bulgaria, oral risperidone for stabilization (Table 4) will be a commercial product supplied centrally by the sponsor.*** The brand name of the oral risperidone supplied will be recorded on the source documentation. ***Oral risperidone is to be stored*** ~~***and securely locked***~~ ***according to the*** ~~storage conditions specified in the package insert (RISPERIDONE tablets, Teva Pharmaceuticals, US PI)~~ ***manufacturer's Summary of Product Characteristics (SmPC).***	In the US, oral risperidone for stabilization (Table 4) will be a commercial product supplied by the study center. In Bulgaria, oral risperidone for stabilization (Table 4) will be a commercial product supplied centrally by the sponsor. The brand name of the oral risperidone supplied will be recorded on the source documentation. Oral risperidone is to be stored according to the manufacturer's Summary of Product Characteristics (SmPC).	Correction for consistency with Table 4; all forms of oral risperidone are allowed. Clarification regarding oral risperidone sourcing. Since it is not considered an IMP, the sentence on oral risperidone storage was moved from Section 5.2.1 to this section and revised to encompass storage conditions for all forms of oral risperidone.
5.5 Treatment After the End of the Study		
When the study ends, eligible patients may be offered the opportunity to enter an extension study to assess the long-term safety and tolerability of extended-release risperidone. This ~~potential~~ extension study is beyond the scope of this protocol. A separate protocol will issued for the extension study as applicable.	When the study ends, eligible patients may be offered the opportunity to enter an extension study to assess the long-term safety and tolerability of extended-release risperidone. This extension study is beyond the scope of this protocol. A separate protocol will issued for the extension study as applicable.	Preparations for the feasibility and conduct of the extension study have begun.

Original text with changes shown	New wording	Reason/Justification for change
5.7. Prior and Concomitant Medication or Therapy		
Enrolled patients not already on oral risperidone or injectable risperidone (RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI) and on any antipsychotic (other than clozapine), will be converted to oral risperidone during Stage 1 of the study. The patients should start taking their oral risperidone beginning from Visit 2. However, they will be allowed to receive their down-titrated other antipsychotic medication together with a low dose of risperidone for the purpose of conversion only, and for as short a duration as possible. The previous antipsychotic must be completely stopped within four weeks of visit 2. It is highly preferable that the patients be transitioned to oral risperidone during the allowed screening period after eligibility has been established. … The following medications will be prohibited during this study: • antipsychotics other than the study treatments o ***Except during the conversion and stabilization stage (Stage 1), and only if required for conversion from the previous antipsychotics to oral risperidone***. …Allowed rescue medications will include zolpidem or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for EPS; and propranolol and benzodiazepines for akathisia. ***In addition, use of lorazepam (up to 6 mg/day) is permitted on an as needed basis for indications other than akathisia (anxiety etc.). Use in this context must be limited to no more than 72 consecutive hours, and lorazepam should not be taken within 8 hours of rating scale assessment.***	Enrolled patients not already on oral risperidone or injectable risperidone (RISPERDAL CONSTA, Janssen Pharmaceuticals, US PI) and on any antipsychotic (other than clozapine), will be converted to oral risperidone during Stage 1 of the study. The patients should start taking their oral risperidone beginning from Visit 2. However, they will be allowed to receive their down-titrated other antipsychotic medication together with a low dose of risperidone for the purpose of conversion only, and for as short a duration as possible. The previous antipsychotic must be completely stopped within four weeks of visit 2. It is highly preferable that the patients be transitioned to oral risperidone during the allowed screening period after eligibility has been established. The following medications will be prohibited during this study: • antipsychotics other than the study treatments o Except during the conversion and stabilization stage (Stage 1), and only if required for conversion from the previous antipsychotics to oral risperidone. … Allowed rescue medications will include zolpidem or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for EPS; and propranolol and benzodiazepines for akathisia. In addition, use of lorazepam (up to 6 mg/day) is permitted on an as needed basis for indications other than akathisia (anxiety etc.). Use in this context must be limited to no more than 72 consecutive hours, and lorazepam should not be taken within 8 hours of rating scale assessment.	Clarification regarding conversion of patients to oral risperidone and benzodiazepine use. Additional clarification regarding use of lorazepam.
5.8. Procedures for Monitoring Patient Compliance		
~~In Stage 1,~~ ***A patient with*** total compliance of less than 80%	A patient with total compliance of less than 80% in Stage 1	Compliance will be measured for

Original text with changes shown	New wording	Reason/Justification for change
in Stage 1~~(measured on Visits 2, 3, 4, and 5)~~ will be considered noncompliant.	will be considered noncompliant.	the overall stabilization period.
5.9. Randomization and Blinding		
In the event of an emergency (ie, where knowledge of the study drug assignment is needed to make treatment decisions for the patient), the treatment group and dose to which the patient has been allocated can be determined by accessing the IRT system. All investigational centers will be provided with details on how to access the system for code breaking at the start of the study. ~~The medical monitor or equivalent should be consulted before unblinding, whenever possible.~~ ***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.	In the event of an emergency (ie, where knowledge of the study drug assignment is needed to make treatment decisions for the patient), the treatment group and dose to which the patient has been allocated can be determined by accessing the IRT system. All investigational centers will be provided with details on 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.	Clarification per updated sponsor template to enhance patient safety and ensure that the patient's needs are first addressed.
5.10.2 Blinding and Unblinding		
In case of a serious adverse event, 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 each investigational center via the IRT, both via telephone and internet. ~~If possible, the sponsor should be notified of the event before breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's IMP assignment should not be given.~~ Breaking of the ~~randomization~~ ***treatment*** code can always be performed by the ~~investigational centers~~ ***investigator*** without prior approval by the sponsor***; however, the sponsor should be notified following the breaking of the treatment code. The patient's IMP assignment should not be revealed to the sponsor.***	In case of a serious adverse event, 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 each investigational center via the IRT, 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. The patient's IMP assignment should not be revealed to the sponsor.	Clarification per updated sponsor template to enhance patient safety and ensure that the patient's needs are first addressed.
5.10.3. Data Monitoring Committee		
The IDMC will perform 1 formal interim analysis of efficacy	The IDMC will perform 1 formal interim analysis of	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
in this study (when the number of events observed reaches 60% of the planned 207 relapse events ***in the ITT analysis set*** [Section 3.4] 3.4).	efficacy in this study (when the number of events observed reaches 60% of the planned 207 relapse events in the ITT analysis set [Section 3.4]).	
[redacted]		
[redacted]	[redacted]	[redacted]
6. ASSESSMENT OF EFFICACY		
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 is used to capture quality of life.	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 is used to capture quality of life.	Clarification in which patient population this scale will be assessed. Cross-link created to new table of assessments.
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 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.	Clarification in which patient population this scale will be assessed. Cross-link created to new table of assessments.
6.2.3. Drug Attitudes Inventory 10-item Version (DAI-10)		

Original text with changes shown	New wording	Reason/Justification for change
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.	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.	Clarification in which patient population this scale will be assessed. Cross-link created to new table of assessments.
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 et al 2000). ~~The scale consists of 100 items~~ ***The PSP is a 100-point single-item rating scale,*** divided in***to*** 10 equal intervals.	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 et al 2000). The PSP is a 100-point single-item rating scale, divided into 10 equal intervals.	Clarification in which patient population this scale will be assessed. Cross-link created to new table of assessments. Correction of PSP scale description.
6.2.5. Healthcare Resource Utilization		
Healthcare resource utilization will be assessed ***for both adult and adolescent patients*** approximately every 3 months (at the time points specified in Table 1 ***and Table 2***) for hospitalizations, emergency room (ER) visits, and outpatient visits (ie, not including protocol-mandated outpatient visits).	Healthcare resource utilization will be assessed for both adult and adolescent patients approximately every 3 months (at the time points specified in Table 1 and Table 2) for hospitalizations, emergency room (ER) visits, and outpatient visits (ie, not including protocol-mandated outpatient visits).	Clarificatin in which patient population this scale will be assessed. Cross-link created to new table of assessments.
7. ASSESSMENT OF SAFETY		
7.4. Clinical Laboratory Tests		
Table ~~6~~ *7* Header: Hematology ~~and coagulation~~	Table 7 Header: Hematology	Correction; coagulation samples are not collected in this study.
7.4.1. Serum Chemistry, Hematology and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology ~~and coagulation~~, and urinalysis) will be performed at the time points detailed in Table 1 ***and Table 2***.	Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 1 and Table 2.	Correction; coagulation samples are not collected in this study.
7.4.2.2. Human Chorionic Gonadotropin Tests		
A FSH test will be performed at the screening visit for any female who has been without menses for at least 12 months to confirm post-menopausal status. Women may be allowed	A FSH test will be performed at the screening visit for any female who has been without menses for at least 12 months to confirm post-menopausal status. Women may be	Clarification for whom the FSH test should be performed.

Original text with changes shown	New wording	Reason/Justification for change
not to use contraceptives during the study if they had no menses for at least 12 months (without an alternative medical cause) and the FSH concentration is above 35 U/L. A serum beta human chorionic gonadotropin (β-HCG) test will be performed for all women at screening, baseline, and the follow-up/exit visits (see Table 1 ***and Table 2***). ***At baseline, both a serum and a urine β-HCG test will be performed.*** Urine β-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 prior to study drug administration.***	allowed not to use contraceptives during the study if they had no menses for at least 12 months (without an alternative medical cause) and the FSH concentration is above 35 U/L. A serum beta human chorionic gonadotropin (β-HCG) test will be performed for all women at screening, baseline, and the follow-up/exit visits (see Table 1 and Table 2). At baseline, both a serum and a urine β-HCG test will be performed. Urine β-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 prior to study drug administration.	At the baseline visit, both types of pregnancy tests will be performed since the serum result may not be available that day prior to dosing. Clarification that a negative result must be obtained before study drug is administered.
7.4.2.3. Urine Drug Screen		
A urine drug screen will be performed at the time points specified in Table 1 ***and Table 2***. The urine drug screen detects the presence of drugs of abuse, including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol. ***Substance use disorder is exclusionary and will preclude the patient from enrollment/randomization. However, if per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a*** ~~A~~ positive result for any of the above drugs or their metabolites, without medical explanation, will ~~preclude the patient from randomization/enrollment or continued participation in the study~~. ***be discussed on a case-by-case basis between the site, the Medical Monitor and the sponsor to determine the patient's eligibility, based on the information available.*** The patients should be advised that use of these substances should be avoided during the study.	A urine drug screen will be performed at the time points specified in Table 1and Table 2. The urine drug screen detects the presence of drugs of abuse, including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol. Substance use disorder is exclusionary and will preclude the patient from enrollment/randomization. However, if per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a positive result for any of the above drugs or their metabolites, without medical explanation, will be discussed on a case-by-case basis between the site, the Medical Monitor and the sponsor to determine the patient's eligibility, based on the information available. The patients should be advised that use of these substances should be avoided during the study.	Clarification regarding a positive urine drug screen result due to the high prevlalence of recreational and medical use of various substances in this patient population.
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 et al 2011). The interview and rating for the C-SSRS ~~is~~ ***will be conducted***~~completed by~~	The C-SSRS is a semi structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors (Posner et al 2011). The interview and rating for the C-SSRS will be rater specifically trained	Corrected per Clarification Letter 01 (June2018). Any rater who meets the scale author's requirements may conduct the rating following

Original text with changes shown	New wording	Reason/Justification for change
~~a licensed clinician~~ ***rater specifically trained to rate the scale (per the minimum requirements outlined by the scale author), regardless of education level, who has appropriate clinical trial experience with C-SSRS administration*** ~~specifically trained to rate the scale~~, ***after review and approval by the Teva clinical project physician or designee***.	to rate the scale (per the minimum requirements outlined by the scale author), regardless of education level, who has appropriate clinical trial experience with C-SSRS administration, after review and approval by the Teva clinical project physician or designee.	approval from the Sponsor or designee.
8. ASSESSMENT OF PHARMACOKINETICS/PHARMACODYNAMICS/BIOMARKERS/PHARMACOGENOMICS		
8.1. Pharmacokinetic Assessment		
Blood samples will be collected from all patients for quantitation of the plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OHrisperidone) at weeks -12, -10, -8, and -4 in Stage 1, at baseline, q4w in Stage 2, and at the follow-up/exit visits. ***In case the patient is on a twice-daily (bid) oral risperidone dosing regimen, the patient can take the first out of the 2 daily oral doses at the clinic with a PK assessment taken within an hour prior to dosing, and the second dose can be taken at home in the afternoon/evening, per the patient's convenience at approximately the same hour every day.*** ***During Stage 2 of the study, blood samples for PK assessment will be taken within an hour prior to sc dose administration.*** ***Another pharmacokinetic sample will be collected from adolescent patients only at Week 14 (2 weeks after Visit 9 [Week 12]), approximately after steady state is reached. 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, respectively) at the sponsor's discretion. This may be considered, for example, if few adolescent patients will be enrolled. 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,***	Blood samples will be collected from all patients for quantitation of the plasma concentrations of risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OHrisperidone) at weeks -12, -10, -8, and -4 in Stage 1, at baseline, q4w in Stage 2, and at the follow-up/exit visits. In case the patient is on a twice-daily (bid) oral risperidone dosing regimen, the patient can take the first out of the 2 daily oral doses at the clinic with a PK assessment taken within an hour prior to dosing, and the second dose can be taken at home in the afternoon/evening, per the patient's convenience at approximately the same hour every day. During Stage 2 of the study, blood samples for PK assessment will be taken within an hour prior to sc dose administration. Another pharmacokinetic sample will be collected from adolescent patients only at Week 14 (2 weeks after Visit 9 [Week 12]), approximately after steady state is reached. 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, respectively) at the sponsor's discretion. This may be considered, for example, if few adolescent patients will be enrolled. The additional samples, if taken following another in-clinic visit, will be collected at the same intervals. If more than 1 additional	Clarification regarding oral risperidone dosing and collection of pharmacokinetic samples during Stage 1 of the study. New text describing collection of additional pharmacokinetic samples from adolescents to further characterize the PK profile in this patient population. Clarification that unscheduled pharmacokinetic samples are relevant for Stage 2 of the study.

Original text with changes shown	New wording	Reason/Justification for change
1 sample can be taken 3 weeks after Visit X and another can be taken 1 week after Visit Y). ***Thus, up to 3 additional pharmacokinetic samples may be taken from adolescent patients at supplementary in-clinic visits (without dosing) at varying time intervals following sc dose administration.*** … ***During Stage 2, u***~~U~~nscheduled 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 the 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.	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). Thus, up to 3 additional pharmacokinetic samples may be taken from adolescent patients at supplementary in-clinic visits (without dosing) at varying time intervals following sc dose administration. … 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 the 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.	
9. STATISTICS		
9.1. Sample Size and Power Considerations		
Median time to impending relapse was observed to be 7 months in the placebo group in a similarly designed study (Kane et al 2012). Assuming a similar placebo effect in this study, as well as a hazard ratio of 1.82 (placebo vs TV-46000), at a 2-sided alpha of ~~0.025~~***0.05***, and randomization ratio of 1:1:1 (q1m:q2m:placebo), a total of 207 relapse events will need to be observed during Stage 2 of the study for ~~the~~ the ITT analysis set (adult patients) in the 3 treatment groups (combined) to have a statistical power of approximately 90% (East 6 [Version 6.3] manual, 2014). ***The sample size rationale is based on the adult patients. There is no estimation of the sample size in the adolescent population, and their number is not known at this time.*** Assuming an accrual time of 6 months and a maximal treatment duration during the double-blind stage of approximately 13 months, approximately 139 ***adult*** patients will need to be randomized to each treatment group for a total of 417 ***adult*** patients randomized. Assuming that 30% of the patients enrolled in Stage 1 will not be randomized to the	Median time to impending relapse was observed to be 7 months in the placebo group in a similarly designed study (Kane et al 2012). Assuming a similar placebo effect in this study, as well as a hazard ratio of 1.82 (placebo vs TV-46000), at a 2-sided alpha of 0.05, and randomization ratio of 1:1:1 (q1m:q2m:placebo), a total of 207 relapse events will need to be observed during Stage 2 of the study for the ITT analysis set (adult patients) in the 3 treatment groups (combined) to have a statistical power of approximately 90% (East 6 [Version 6.3] manual, 2014). The sample size rationale is based on the adult patients. There is no estimation of the sample size in the adolescent population, and their number is not known at this time. Assuming an accrual time of 6 months and a maximal treatment duration during the double-blind stage of approximately 13 months, approximately 139 adult patients will need to be randomized to each treatment group for a total of 417 adult patients randomized. Assuming that 30% of the patients enrolled in Stage 1 will	Correction of typo. Additional details provided regarding the expected sample size in the adult and adolescent populations.

Original text with changes shown	New wording	Reason/Justification for change
double-blind phase (Stage 2), a total of 596 ***adult*** patients will need to be enrolled into Stage 1. As an event-driven study, depending on the actual recruitment rate and percentage of patients who are enrolled in Stage 1 and are randomized to Stage 2, it may be possible to randomize more than 417 ***adult*** patients, as long as Stage 2 of the study ends when the number of relapse events ***in the ITT analysis set*** reaches 207.	not be randomized to the double-blind phase (Stage 2), a total of 596 adult patients will need to be enrolled into Stage 1. As an event-driven study, depending on the actual recruitment rate and percentage of patients who are enrolled in Stage 1 and are randomized to Stage 2, it may be possible to randomize more than 417 adult patients, as long as Stage 2 of the study ends when the number of relapse events in the ITT analysis set reaches 207.	
9.2.2. Intent-toTreat Analysis Set		
The intent-to-treat (ITT) analysis set will include ~~all~~ ***adult*** patients randomized during the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	The intent-to-treat (ITT) analysis set will include adult patients randomized during the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	Clarification; the ITT analysis set is defined for adult patients only.
9.2.3. Extended Intent-toTreat Analysis Set		
[Not applicable]	The extended intent-to-treat (eITT) analysis set will include all patients (adults and adolescents) randomized to the double-blind maintenance stage (Stage 2), regardless if they have received treatment or not. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.	Newly-created sub-section and text to define this analysis set due to the option of adolescent enrollment.
9.4. Study Population		
The ***e***ITT analysis set (Section 9.2) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. ***The primary analysis will be conducted on the ITT analysis set, the first key secondary endpoint will be conducted on the complete eITT analysis set and the second key secondary endpoint will be conducted on the adolescent subsetof the eITT analysis set. The analysis set on which analysis for other end-points will be conducted will be specified on a case-by-case basis.*** The	The eITT analysis set (Section 9.2) will be used for all study population summaries of the double-blind treatment stage unless otherwise specified. Summaries will be presented by treatment group and for all patients. The primary analysis will be conducted on the ITT analysis set, the first key secondary endpoint will be conducted on the complete eITT analysis set and the second key secondary endpoint will be conducted on the adolescent subset of the eITT analysis set. The analysis set on which analysis for other end-points will be conducted will be specified on a case-by-case basis. The enrolled patients set will be used	Clarification regarding the endpoints and corresponding analysis sets with the newly-introduced option of adolescent enrollment.

Original text with changes shown	New wording	Reason/Justification for change
enrolled patients set will be used for data summaries before the double-blind treatment stage.	for data summaries before the double-blind treatment stage.	
9.4.1. Patient Disposition		
Data from patients screened and enrolled in Stage 1; patients who were enrolled in Stage 1 but not randomized for the double-blind stage and reason for not randomized; patients who were randomized; patients who were randomized but not treated; patients in the ITT, ***patients in the eITT,*** PP, safety, and pharmacokinetics analysis sets; patients who completed the study; and patients who withdrew from the study will be summarized using descriptive statistics. Data from patients who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics. ***Adolescent patient disposition may be summarized separately, if applicable.***	Data from patients screened and enrolled in Stage 1; patients who were enrolled in Stage 1 but not randomized for the double-blind stage and reason for not randomized; patients who were randomized; patients who were randomized but not treated; patients in the ITT, patients in the eITT, PP, safety, and pharmacokinetics analysis sets; patients who completed the study; and patients who withdrew from the study will be summarized using descriptive statistics. Data from patients who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics. Adolescent patient disposition may be summarized separately, if applicable.	Clarification regarding analysis sets used.
9.4.2. Demographic and Baseline Characteristics		
Treatment groups will be compared for all continuous variables, using an analysis of variance (ANOVA) with treatment group and investigational center as factors. The categorical variables of patient sex and race will be summarized using the descriptive statistics for each variable category. Missing categories will be presented if necessary. Treatment groups will be compared for all categorical variables using a Pearson's chi-squared test (or Fisher's exact test if cell sizes are too small). ***The ITT analysis set, the eITT analysis set, and the eITT subset of adolescents will be used for the summaries.***	The ITT analysis set, the eITT analysis set, as well as the eITT subset of adolescents will be used for the summaries.	The analysis methods will be detailed in the Statistical Analysis Plan. New text to clarify subsets used in the analysis.
9.5.1. Primary Endpoint		
… - an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of ≥->4 and an absolute	.. - an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an	Correction of typos for consistency with other protocol sections.

Original text with changes shown	New wording	Reason/Justification for change
increase of ~~>~~≥*4* on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization	absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization	
9.5.2. Key Secondary Endpoints		
[Not applicable]	The key secondary endpoints are: 1. time to impending relapse (as defined under the primary objective) in the eITT analysis set), and 2. time to impending relapse in adolescent patients with schizophrenia. **NOTE:** The assessment of time to impending relapse in adolescent patients is pending randomization of at least 10 adolescent patients with clinically sufficient exposure.	Newly-added sub-section defining the introduced key secondary endpoints.
9.5.3. Secondary Endpoints		
[Not applicable]	The eITT analysis set (Section 9.2) will be used for all summaries in this section, unless otherwise specified. For the endpoints that are evaluted only in the adult population, the analysis will be conducted on the ITT analysis set.	[Previously Section 9.5.2.] New text to clarify subsets used in the analysis.
[redacted]		
[redacted]	[redacted]	[redacted]
9.5.4.2. 5-Level EuroQol Five Dimensions Questionnaire		
~~The change from baseline to endpoint in total score will be calculated.~~***The change from baseline to each visit and to endpoint*** in ***each of the EQ-5D-5L domains will be calculated.***	The change from baseline to each visit and to endpoint in each of the EQ-5D-5L domains will be calculated.	Correction since there is no "total score" in this scale.
9.5.4.6. CGI-I Score at Endpoint		

Original text with changes shown	New wording	Reason/Justification for change
The change from baseline to endpoint in total score will be calculated. ***CGI-I at endpoint will be analyzed.***	CGI-I at endpoint will be analyzed.	Correction since there is no "total score" in this scale.
9.5.5. Planned Method of Analysis		
The ITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group. ***Analysis that will be conducted on the eITT analysis set or on the adolescent patient subset of the eITT will be described below.***	The ITT analysis set (Section 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group. Analysis that will be conducted on the eITT analysis set or on the adolescent patient subset of the eITT will be described below.	Re-numbering of section (instead of 9.5.4). Clarification.
9.5.5.2. Sensitivity Analysis		
A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment when the first relapse was observed ***via the interval censoring method***. ~~If the interval is ≥1.5 times the protocol planned assessment interval length, then the patient will be censored at the previous assessment visit.~~ Sensitivity analysis will also be conducted by classifying dropouts (for reasons other than relapse) as relapse events instead of censoring. The PP analysis set will also be used to assess the primary efficacy variable. ~~A sensitivity analysis to assess the impact of dropouts (for reasons other than relapse) will be conducted as well.~~ Details will be provided in the statistical analysis plan. ***Senstivity analysis will be conducted on the ITT analysis set.***	A sensitivity analysis will be conducted to assess the impact of large intervals between the previous assessment and the assessment when the first relapse was observed. Sensitivity analysis will also be conducted by classifying dropouts (for reasons other than relapse) as relapse events instead of censoring. The PP analysis set will also be used to assess the primary efficacy variable. Details will be provided in the statistical analysis plan. Senstivity analysis will be conducted on the ITT analysis set.	Section number changed from 9.5.4.2. due to addition of key secondary enpoints. Introduction of the **interval censoring method** instead of the previous description of method of sensitivity to the large inter assessment intervals. Deletion of redundant reference to dropout sensitivity analysis (mentioned 2 sentences before). Clarification regarding patient subset analyzed.
9.5.5.3. Subgroup Analysis		
Additional s~~S~~ubgroup analysis for the primary endpoint, including region, will be described in the statistical analysis plan.	Additional subgroup analysis for the primary endpoint, including region, will be described in the statistical analysis plan.	Clarification.
9.5.5.4. Key Secondary Analyses		
[Not applicable[]	**9.5.5.4.1. Key Secondary Analysis 1** Time to impending relapse in adult and adolescent patients will be assessed similarly to the Primary Efficacy Analysis using the eITT Analysis Set (Section 9.2.2.**)**. The Cox proportional hazard model will include patient age group	New sub-section describing the analysis of the newly-introduced key secondary endpoints.

Original text with changes shown	New wording	Reason/Justification for change
	(if applicable) along with treatment, and the aforementioned stratification variables as the factors. The details about the Type I statistical error control will be discussed in Section 9.6. **9.5.5.4.1. Key Secondary Analysis 1** Time to impending relapse in adolescent patients will be assessed if the number of randomized patients will be at least 10 with clinically sufficient exposure. The method will be similar to the Primary Efficacy Analysis, but will use the adolescent patients subset. The details about the Type I statistical error control will be discussed in Section 9.6.	
9.5.5.5. Secondary Efficacy Analysis		
[Not applicable]	The eITT analysis set (Section 9.2) will be used for all summaries in this section, unless otherwise specified.	[Previously Section 9.5.4.4] Information added regarding the analysis set to be used.
9.5.5.6. [redacted]		
[redacted]	[redacted]	[Previously Section 9.5.4.5] [redacted]
9.6. Multiple Comparisons and Multiplicity		

Original text with changes shown	New wording	Reason/Justification for change
There will be 1 interim analysis when the number of events observed reaches 60% of the planned 207 relapse events (125 events) ***in the ITT analysis set***. At this interim analysis, both primary efficacy tests will be tested at a 2-sided alpha of 0.0101. If both tests are significant at the interim analysis, the study may be stopped. If only 1 primary efficacy test (or none) is significant at the interim analysis, the study will continue until the required number of relapse events are observed. … ***Type-I error will be further controlled for the 2 key secondary endpoints by employing the hierarchical approach. Secondary endpoint #1 will be analyzed only in case the2 primary efficacy endpoints have p-value less than or equal to alpha of 0.0464. In that case, key secondary endpoint #1 will be tested for the 2 dosing regimens using the same approach. Namely, tests for the 2 dosing regimens will be conducted with 2-sided alphas of 0.0464; if one of the comparisons for the key secondary endpoint #1 is not significant at a 2-sided alpha of 0.0464, the other will be tested at 2-sided alpha of 0.0464 divided by 2.*** ***If secondary endpoint #1 is successful on both dosing regimens against placebo, and there are at least 10 adolescent patients in the study with clinically sufficient exposure, then the 2 dosing regimens in the adolescent study population will be tested against placebo in the same way as described for the primary efficacy endpoint and key secondary endpoint #1.***	There will be 1 interim analysis when the number of events observed reaches 60% of the planned 207 relapse events (125 events) in the ITT analysis set. At this interim analysis, both primary efficacy tests will be tested at a 2-sided alpha of 0.0101. If both tests are significant at the interim analysis, the study may be stopped. If only 1 primary efficacy test (or none) is significant at the interim analysis, the study will continue until the required number of relapse events are observed. … Type-I error will be further controlled for the 2 key secondary endpoints by employing the hierarchical approach. Secondary endpoint #1 will be analyzed only in case the2 primary efficacy endpoints have p-value less than or equal to alpha of 0.0464. In that case, key secondary endpoint #1 will be tested for the 2 dosing regimens using the same approach. Namely, tests for the 2 dosing regimens will be conducted with 2-sided alphas of 0.0464; if one of the comparisons for the key secondary endpoint #1 is not significant at a 2-sided alpha of 0.0464, the other will be tested at 2-sided alpha of 0.0464 divided by 2. If secondary endpoint #1 is successful on both dosing regimens against placebo, and there are at least 10 adolescent patients in the study with clinically sufficient exposure, then the 2 dosing regimens in the adolescent study population will be tested against placebo in the same way as described for the primary efficacy endpoint and key secondary endpoint #1.	Clarification. Details regarding Type I error control for the newly-introduced key secondary endpoints are provided.
9.7. Safety Analysis		
Allowed rescue medications will include zolpidem or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for EPS; and propranolol and benzodiazepines for akathisia. Descriptive statistics ***for***	Descriptive statistics for allowed rescue medications (see Section 5.75.7) will be presented by treatment group. Safety outcomes, including changes from baseline in EPS scale scores (BARS, AIMS, and SAS) and CDSS during	Details of the rescue medication were deleted since not relvant here. Cross-reference to concomitant medication section was created for

Original text with changes shown	New wording	Reason/Justification for change
allowed rescue medications (see 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 ~~and/or ANCOVA, with~~ treatment and stratification variables as factors and baseline as a covariate (LOCF will be used) ***by treatment group***. ***Adjustment to stratification factors may be conducted as appropriate.*** … Selected safety data will also be presented by site of injection (abdomen vs arm) ***and by age group (adolescents [ages 13-17] and adults [18 years of age and above]), as applicable***. ***Separate summaries for adolescent patients may be presented separately for some analyses, as applicable and will be described in the Statistical Analysis Plan.***	Stage 2, will be presented using descriptive statistics by treatment group. Adjustment to stratification factors may be conducted as appropriate. … Selected safety data will also be presented by site of injection (abdomen vs arm) and by age group (adolescents [ages 13-17] and adults [18 years of age and above]), as applicable. Separate summaries for adolescent patients may be presented separately for some analyses, as applicable and will be described in the Statistical Analysis Plan.	clarity. The safety analysis method(s) will be detailed in the Statistical Analysis Plan. Newly-introduced text regarding adolescent data.
9.8. Tolerability Analysis		
All-cause discontinuation rates and discontinuation rates due to adverse events (dropout rates) will be calculated as the number of patients who withdrew early for all reasons, and the number of patients who withdrew early due to adverse events, respectively, divided by number of patients in each treatment group, and will be ~~analyzed~~ ***presented*** using descriptive statistics.	All-cause discontinuation rates and discontinuation rates due to adverse events (dropout rates) will be calculated as the number of patients who withdrew early for all reasons, and the number of patients who withdrew early due to adverse events, respectively, divided by number of patients in each treatment group, and will be presented using descriptive statistics.	Correction.
[Not applicable]	Separate summaries for adolescent patients may be presented separately for some analyses, as applicable and will be described in the Statistical Analysis Plan.	Newly-introduced text regarding adolescent data.
9.9. Pharmacokinetic Analysis		
All concentration data will be summarized by ***age subset (adult, adolescent),*** treatment (q1m, q2m or oral), dose and	All concentration data will be summarized by age subset (adult, adolescent), treatment (q1m, q2m or oral), dose and	Clarifications regarding the pharmacokinetic modeling and

Original text with changes shown	New wording	Reason/Justification for change
visit using descriptive statistics (n, mean, standard deviation, median, minimum, geometric mean, and coefficient of variation). Drug concentrations over time [C(t)] reported by ***age subset,*** time (visit) and treatment will be presented for risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OH-risperidone). Additional pharmacokinetic parameters may be determined if data permit~~s~~ (see Section 2.2). In addition, the pharmacokinetics of TV-46000 (and if data permit~~s~~, also of oral risperidone) will be evaluated using a population pharmacokinetics approach. [redacted] Importantly, ~~pharmacokinetic concentration analysis and population pharmacokinetics analysis~~ ***independent pharmacokinetic modeling and population-based modeling*** analysis will take place during the study conduct, while maintaining the blind, as will be described in the pharmacokinetics analysis plan.	visit using descriptive statistics (n, mean, standard deviation, median, minimum, geometric mean, and coefficient of variation). Drug concentrations over time [C(t)] reported by age subset, time (visit) and treatment will be presented for risperidone, 9-OH-risperidone, and total active moiety (sum of risperidone and 9-OH-risperidone). Additional pharmacokinetic parameters may be determined if data permit (see Section 2.2). In addition, the pharmacokinetics of TV-46000 (and if data permit, also of oral risperidone) will be evaluated using a population pharmacokinetics approach. [redacted] Importantly, independent pharmacokinetic modeling and population-based modeling analysis will take place during the study conduct, while maintaining the blind, as will be described in the pharmacokinetics analysis plan.	analysis.
9.13. Planned Interim Analysis		
There will be 1 formal interim analysis when the number of events observed ***in the ITT analysis set*** reaches 60% of the planned 207 relapse events (125 events in adult patients).	There will be 1 formal interim analysis when the number of events observed in the ITT analysis set reaches 60% of the planned 207 relapse events (125 events in adult patients).	Clarification.
15. REFERENCES		
[Not applicable]	Asarnow R, Brown W, Strandburg R. Children with a schizophrenic disorder: neurobehavioral studies. Eur Arch Psychiatry Clin Neurosci. 1995;245:70-9. Bo S, Haahr UH. Early-onset psychosis and child and adolescent schizophrenia. Scandinavian J Child Adolescent Psychiatry and Psychology 2016;4(1):1-3. Ferrin M, Gosney H, Marconi A, Rey JM. Using	Newly-added references on diagnostics and treatment of schizophrenia in the pediatric patient population.

Original text with changes shown	New wording	Reason/Justification for change
	antipsychotic medication for the treatment of schizophrenia in children and adolescents. In Rey JM (ed), IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions 2016. Hollis C. Adult outcomes of child- and adolescent-onset schizophrenia: diagnostic stability and predictive validity. Am J Psychiatry 2000;157(10):1652-9. Lytle S, McVoy M, Sajatovic M. Long-acting injectable antipsychotics in children and adolescents. J Child Adolesc Psychopharmacol. 2017;27(1): 2-9. Pogge DL, Singer MB, Harvey PD. Rates and predictors of adherence with atypical antipsychotic medication: a follow-up study of adolescent inpatients. J Child Adolesc Psychopharmacol. 2005;15(6):901-12. Rapoport J, Addington A, Frangou S. The neurodevelopmental model of schizophrenia: what can very early onset cases tell us? Curr Psychiatry Rep. 2005;7:81–2. Weinberger D, Harrison PJ (Eds.) Schizophrenia. 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2011. Yazdi K, Unterlass G, Kemmler G, et al. Factors influencing adherence in children and adolescents treated with antipsychotics or antidepressants. Prim Care Companion J Clin Psychiatry 2008;10(2):160-1.	
Lindenmayer JP, Czobor P, Alphs L, Nathan AM, Anand R, Islam Z. et al. The InterSePT scale for suicidal thinking reliability and validity. Schizophr Res. 2003;63(1–2):161–~~1~~70. ~~1 9.~~	Lindenmayer JP, Czobor P, Alphs L, Nathan AM, Anand R, Islam Z. et al. The InterSePT scale for suicidal thinking reliability and validity. Schizophr Res. 2003;63(1–2):161–70.	Correction; the reference appears on pg 161-170 of the journal.
APPENDIX A . CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Legal Representative of the Sponsor in the European Union [redacted] Senior Director, Head of European Regulatory Affairs [redacted]	**Legal Representative of the Sponsor in the European Union** [redacted] [redacted]	This reflects a change in responsibilities at Teva; introduced in Local Am 01 for Bulgaria.

Original text with changes shown	New wording	Reason/Justification for change
Graf-Arco-Str. 3 89079 Ulm Germany ~~Tel.: +~~ [redacted] ~~E-mail:~~ [redacted]	Graf-Arco-Str.3 89079 Ulm Germany Telephone: [redacted] E-mail: [redacted]	
[Not applicable]	**Medical Monitor:** [redacted] Medical Director ICON PLC Mobile: + [redacted]	Addition of the medical monitor contact details to the protocol.
Electronic Data Capture: ~~Medidata Solutions Worldwide~~ ~~350 Hudson Street~~ ~~New York, NY 10014~~ ***ICON Clinical Research Services*** ***123 Smith Street*** ***Farmingdale, NY 11735*** ***United States***	**Electronic Data Capture:** ***ICON Clinical Research Services*** ***123 Smith Street*** ***Farmingdale, NY 11735*** ***United States***	Correction. The service is sub-contracted to and managed by ICON.
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
Procedures for Screening (Visit 1, Week -16+4 weeks) … • functional measures (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 – ***for all patients***	**Procedures for Screening (Visit 1, Week -16+4 weeks)** … • functional measures (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 – **for all patients**	Clarification regarding which patient population(s) will be analyzed for the quality of life and healthcare resource utilization endpoints. This change affects the other sub-sections in this appendix in which these scales are mentioned.

Original text with changes shown	New wording	Reason/Justification for change
• Drug Attitudes Inventory 10-item version (DAI-10) – ***for adult patients only*** …	• Drug Attitudes Inventory 10-item version (DAI-10) – **for adult patients only** …	
Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Baseline [Visit 6, Day 1 ±3 days]) … • 12-lead electrocardiography (in triplicate) • serum β-HCG tests (for women of childbearing potential) • ***urine β-HCG tests (for women of childbearing potential)*** • PANSS • CGI-S … • questions to assess ease of study drug administration – to be performed only in the event that prefilled syringes become available during the study (***assessed during 3 in-clinic visits for each patient)*** …	**Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Baseline [Visit 6, Day 1 ±3 days])** … • 12-lead electrocardiography (in triplicate) • serum β-HCG tests (for women of childbearing potential) • urine β-HCG tests (for women of childbearing potential) • PANSS • CGI-S … • questions to assess ease of study drug administration – to be performed only in the event that prefilled syringes become available during the study **(assessed during 3 in-clinic visits for each patient)** …	Addition of urine pregnancy test at the baseline visit. Clarification regarding which patient population(s) will be analyzed for the quality of life and healthcare resource utilization endpoints. Clarification; assessment of ease of study drug administration will only be performed for the first 3 visits for each patient after introduction of the PFS. o This change is also relevant for sub-section d (Visit 7) and sub-section e (Visit 8)
d. Stage 2: Relapse Prevention (Visit 7, Week 4±3 days) • questions to assess ease of study drug administration – **to be performed only in the event that prefilled syringes become available during the study *(assessed during 3 in-clinic visits for each patient)***	**d. Stage 2: Relapse Prevention (Visit 7, Week 4±3 days)** • questions to assess ease of study drug administration – **to be performed only in the event that prefilled syringes become available during the study (assessed during 3 in-clinic visits for each patient)**	Clarification
[Not applicable]	**f. Stage 2: Relapse Prevention (Visit 9, Week 12±3 days)** The following procedures and assessments will be performed at visit 9: • inquiry of concomitant medication • vital sign measurement • urine β-HCG test (for women of childbearing potential)	Newly-introduced text outlining Visit 9 procedures due to the time points for quality of life and healthcare utilization scales.

Original text with changes shown	New wording	Reason/Justification for change
	• PANSS • CGI-I • CGI-S • CGI-SS • AIMS • BARS • SAS • C-SSRS • PSP - ***and every 12 weeks thereafter (for adult patients only)*** • SQLS - ***and every 12 weeks thereafter (for adult patients only)*** • EQ-5D-5L - ***and every 12 weeks thereafter (for adult patients only)*** • CDSS • healthcare resource utilization - ***and every 12 weeks thereafter (for all patients)*** • blood samples for plasma drug concentration - will be taken within an hour prior to dosing • TV-46000 q1m/placebo administration – for patients randomized to those treatment groups • questions to assess ease of study drug administration – to be performed only in the event that prefilled syringes become available during the study (assessed during 3 in-clinic visits for each patient) • adverse event inquiry (including serious adverse event reporting, injection site-related events including pain) • inquiry about alchohol consumption and illicit drug use since previous visit	
NOTE: Patients will continue study visits and assessments as detailed above (ie, the same assessments performed at visits 7 and 8 will be repeated at visits 9 and 10, respectively).	**NOTE:** Patients will continue study visits and assessments as detailed above (ie, the same assessments performed at visits 7 and 8 will be repeated at visits 9 and 10,	Clarification regarding the repetition of the in-clinic visits (detailed in Table 2).

Original text with changes shown	New wording	Reason/Justification for change
However, note that functional measures (PSP, SQLS, and EQ-5D-5L) and the healthcare resource utilization will be performed every 12 weeks ***as of Visit 9, inclusive.*** ***Thus, the 24 week series from Visit 7 to Visit 12c (Visits 13-18c, Visits 19-24c, etc) repeats until patient completion of the study, relapse or early termination.*** ***Another pharmacokinetic sample will be collected from adolescent patients only 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, 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 one additional sample is taken, they do not need to be collected after the same injection (ie, one sample can be taken 3 weeks after Visit X and another can be taken 1 week after visit Y).***	respectively). However, note that functional measures (PSP, SQLS, and EQ-5D-5L) and the healthcare resource utilization will be performed every 12 weeks. ***Thus, the 24 week series from Visit 7 to Visit 12c (Visits 13-18c, Visits 19-24c, etc) repeats until patient completion of the study, relapse or early termination.*** Another pharmacokinetic sample will be collected from adolescent patients only 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, 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 one additional sample is taken, they do not need to be collected after the same injection (ie, one sample can be taken 3 weeks after Visit X and another can be taken 1 week after visit Y).	Newly-added text detailing the additional PK sampling in adolescents.
Stage 2: ~~Relapse Prevention~~ ~~(Visit 9, Week 12±3 days)~~ ~~(or~~ Early Termination (ET) Visit/End-of-Treatment Visit (EoT)~~)~~ The following procedures and assessments will be performed ~~at visit 9 or~~ at the ET/EoT visit: • urine drug screen – **will be performed if this is the patient's ET/EoT visit** • inquiry of concomitant medication • full physical examination, including weight – **will be performed if this is the patient's ET/EoT visit** • vital sign measurement • urine β-HCG test (for women of childbearing potential) • PANSS • CGI-S	**Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT)** The following procedures and assessments will be performed at the ET/EoT visit: • urine drug screen • inquiry of concomitant medication • full physical examination, including weight • vital sign measurement • urine β-HCG test (for women of childbearing potential) • PANSS • CGI-S • CGI-I • CGI-SS	The ET/EoT visit is now depicted as a separate visit, and therefore the clarifying comments are redundant. Clarification regarding the number of events at the end of the study. Clarification regarding performance of an ECG at this visit.

Original text with changes shown	New wording	Reason/Justification for change
• CGI-I • CGI-SS • AIMS • BARS • SAS • C-SSRS • PSP - **will be performed if this is the patient's ET/EoT visit** ***for adult patients only*** • SQLS - **will be performed if this is the patient's ET/ EoT visit** - ***for adult patients only*** • EQ-5D-5L - **will be performed if this is the patient's ET/EoT visit** - ***for adult patients only*** • CDSS • healthcare resource utilization **– and every 12 weeks thereafter (will also be performed if this is the patient's ET/EoT visit)** - ***for all patients*** • DAI-10 **– will be performed if this is the patient's ET/EoT visit** ***for adult patients only*** • blood sample for biomarker analysis – **will be performed if this is the patient's ET/ EoT visit** • blood samples for plasma drug concentration - will be taken within an hour prior to dosing • TV-46000 q1m/placebo administration – for patients randomized to those treatment groups ***study drug administration (for patients randomized to all treatment groups).*** • questions to assess ease of study drug administration – to be performed only in the event that prefilled syringes become available (~~in total~~ ***if this is one of the 3 visits in which it is assessed***) • adverse event inquiry (including serious adverse event reporting, injection site-related events including pain) • inquiry about alchohol consumption and illicit drug use	• 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 – **for all patients** • DAI-10 - **for adult patients only** • blood sample for biomarker analysis • blood samples for plasma drug concentration - will be taken within an hour prior to dosing • study drug administration (for patients randomized to all treatment groups). • questions to assess ease of study drug administration – **to be performed only in the event that prefilled syringes become available (if this is one of the 3 visits in which it is assessed**) • adverse event inquiry (including serious adverse event reporting, injection site-related events including pain) • inquiry about alchohol consumption and illicit drug use since previous visit **Note:** The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy at the interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set. **Note:** If per the investigator's judgement, the patient is at	

Original text with changes shown	New wording	Reason/Justification for change
since previous visit **Note:** The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free during the double-blind phase until the study is terminated for efficacy at the interim analysis or because 207 relapse events are recorded in the study in the ITT analysis set. ***Note: If per the investigator's judgement, the patient is at risk of not appearing to 1 or both of the follow-up visits, the investigator may also complete the unscheduled visit form and perform an ECG.***	risk of not appearing to 1 or both of the follow-up visits, the investigator may also complete the unscheduled visit form and perform an ECG.	
Unscheduled Visits ***During Stage 2,*** ~~U~~***u***nscheduled 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 the 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.	**Unscheduled Visits** 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 the 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.	Clarification; relevant only to Stage 2 of study.
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	**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,	Verbiage regarding assent was added following the introduction of the possibility to enroll adolescent patients in the study.

Original text with changes shown	New wording	Reason/Justification for change
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. … ***For adolescent patients, a personally signed and dated informed consent form 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.***	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. … For adolescent patients, a personally signed and dated informed consent form 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.	
APPENDIX G. LIST OF PROHIBITED MEDICATIONS		
… 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 o ***Except during the conversion and stabilization stage (Stage 1), and only if required for conversion from the previous antipsychotics to oral risperidone*** • dopamine reuptake inhibitors or prescription psychostimulants within 30 days prior to first oral risperidone dose	… 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 o Except during the conversion and stabilization stage (Stage 1), and only if required for conversion from the previous antipsychotics to oral risperidone • dopamine reuptake inhibitors or prescription psychostimulants within 30 days prior to first oral	Clarification regarding use of antipsychotics during Stage 1 of the study; for consistency with Section 5.7.

Original text with changes shown	New wording	Reason/Justification for change
• opiates or opiate-containing analgesics within 14 days prior to first oral risperidone dose medications	risperidone dose • opiates or opiate-containing analgesics within 14 days prior to first oral risperidone dose medications	
[redacted]		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change

Original text with changes shown

Pharmacogenetics	6	1*d*	6
Virology	***9***	***1***	***9***
Total	**37.5*53.5***	**40*45***	**~~217~~*297* (309 for adolescents)**

[a] Serum pregnancy test to be performed for women of childbearing potential only.

[b] Up to 3 additional samples will be collected from adolescent patients.

~~b~~***c*** Biomarker blood samples will be collected as follows: 6 mL each for plasma and serum, and ~~6.5~~ ***2.5*** mL for RNA (PAXgene).

[d] 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.

New wording

Pharmacogenetics	6	1[d]	6
Virology	9	1	9
Total	**53.5**	**45**	**297 (309 for adolescents)**

[a] Serum pregnancy test to be performed for women of childbearing potential only.

[b] Up to 3 additional samples will be collected from adolescent patients.

[c] Biomarker blood samples will be collected as follows: 6 mL each for plasma and serum, and 2.5 mL for RNA (PAXgene).

[d] 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.

[redacted]

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX J. PHARMACOGENETIC ASSESSMENTS		
A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent for pharmacogenetic assessments at the time point detailed in ~~Table 1~~ ***Table 2***. Genetic variability in the metabolizer gene, cytochrome P450 2D6 (CYP2D6), will be evaluated for an association with drug concentrations of TV-46000 and oral risperidone.	A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent for pharmacogenetic assessments at the time point detailed in Table 2. Genetic variability in the metabolizer gene, cytochrome P450 2D6 (CYP2D6), will be evaluated for an association with drug concentrations of TV-46000 and oral risperidone.	Table of Assessments has been divided into 2 to reflect Stage 1 and Stage 2; therefore, the cross-link was corrected to appropriate table.

16.7. Letter of Clarification 01 (26 June 2018)

teva

LETTER OF CLARIFICATION 01

Study number: TV46000-CNS-30072 (The RISE study)

Clinical Study Protocol with Revision 01, 15 February 2018

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult Patients with Schizophrenia

26 June 2018

Dear Investigator:

The purpose of this letter of clarification is to alert you to the following changes in the above-referenced protocol:

1. **C-SSRS Administration**

Section 7.9.1 currently states that the interview and rating for the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed by a licensed clinician specifically trained to rate the scale. However, the minimum requirements determined by the scale author, 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. Hence, the text will be revised to allow raters with appropriate prior clinical trial experience with the C-SSRS administration and meet the aforementioned requirements to be eligible to administer this scale to patients participating in the TV46000-CNS-30072 study, after review and approval by the Teva clinical project physician or designee. Details regarding C-SSRS rater requirements and training can be found in the Columbia Lighthouse Project website, (http://cssrs.columbia.edu/training/training-research-setting/), ©2016.

2. **Correction of Typo in Primary Endpoint Description**

In Section 9.5.1 (Primary Endpoint), the second sub-bullet of the first relapse criterion (which begins with CGI-I of ≥5) in the primary endpoint description currently states:

- an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of ≥4 and an absolute increase of >4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization

This is a typographical error; for consistency with other protocol sections (ie, protocol synopsis, Section 2.1) in which these criteria are accurately described, the symbols should be reversed and the text should read as follows:

Teva Pharmaceutical
2 West Liberty Blvd, Suite 300 | Malvern, PA 19355 | Tel. 610.344.0200 | www.tevapharm.com

- an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization

3. Addition of New Study Name

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

The **RISE** Study – The **RI**speridone **S**ubcutaneous **E**xtended-release Study (TV46000-CNS-30072)

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

These aforementioned changes are **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.

If you have any questions or concerns regarding this letter, please feel free to contact your ICON CRA or the Teva Clinical Program Manager, [redacted] at +[redacted]

Sincerely,

[redacted]

Senior Director, Global Clinical Development, Neuropsychiatry
Teva Branded Pharmaceutical Products R&D, Inc.

CC: [redacted], Study File

Teva Pharmaceutical
2 West Liberty Blvd, Suite 300 | Malvern, PA 19355 | Tel. 610.344.0200 | www.tevapharm.com

16.8. Local Amendment 01 for Bulgaria (Dated 28 May 2018)

The primary reason for this local amendment is to allow inclusion of Bulgarian investigational centers and patients in this study. The amended protocol was submitted as part of the Clinical Trial Authorization (CTA) Application in Bulgaria.

To adhere with local regulations, the European Union Drug Regulating Authorities Clinical Trials (EudraCT) number has been added to the protocol. A few additional revisions have been made to clarify various aspects of the planned study conduct in this country.

The revisions listed below have been made to the protocol and protocol synopsis, as appropriate, and are considered non-substantial and administrative by the Teva Authorized Representative.

A comparison table showing the changes from the Protocol with Revision 01 to the Local Amendment 01 for Bulgaria is provided below. Previous text with changes indicated is presented in the column titled “Original text with changes shown,” and the final text is presented in the column titled "New wording". Revised or new text is shown in bold italics and deletions are shown with strike-throughs.

Changes to the Protocol

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">TITLE PAGE (Other sections affected by this change: Investigator Agreement; Coordinating Investigator Agreement)</td></tr>
<tr><td>Clinical Study Protocol with <s>Revision</s> Local Am 01for Bulgaria</td><td>Clinical Study Protocol with Local Am 01for Bulgaria</td><td>To denote the country-specific local amendment.</td></tr>
<tr><td>EudraCT number: <s>Not applicable</s> 2018-001619-65</td><td>EudraCT number: 2018-001619-65</td><td>Number added for study conduct in EU.</td></tr>
<tr><td colspan="3">AMENDMENT HISTORY</td></tr>
<tr><td>[Not applicable]</td><td>AMENDMENT HISTORY
The protocol for Study TV46000-CNS-30072 (original protocol dated 14 December 2017) has been amended and reissued as follows:
<table><tr><td>Local Amendment 01 for Bulgaria</td><td>28 May 2018 (6 patients enrolled to date)</td></tr><tr><td>Protocol with Revision 01</td><td>15 February 2018 (0 patients enrolled to date)</td></tr></table>
The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.</td><td>This page was added in the amendment for tracking history.</td></tr>
<tr><td colspan="3">LIST OF ABBREVIATIONS</td></tr>
<tr><td>[Not applicable]</td><td>SmPC = Summary of Product Characteristics</td><td>Newly-added abbreviation.</td></tr>
<tr><td colspan="3">3. STUDY DESIGN</td></tr>
<tr><td colspan="3">3.2. Planned Number of Patients and Countries</td></tr>
<tr><td>Approximately 795 patients will be screened to achieve enrollment of approximately 596 patients in Stage 1, including approximately 57 patients in Bulgaria.
The number of randomized patients in Stage 2 is planned to be approximately 417, including approximately 40 patients in</td><td>Approximately 795 patients will be screened to achieve enrollment of approximately 596 patients in Stage 1, including approximately 57 patients in Bulgaria.
The number of randomized patients in Stage 2 is planned to be approximately 417, including</td><td>Information added regarding study projection in Bulgaria.</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
Bulgaria. Details on the definition of evaluable patients and determination of the sample size are given in Section 9.1. The study is planned to be conducted in approximately 80 investigational centers in North America and possibly other regions ***(eg, Bulgaria)*** as well.	approximately 40 patients in Bulgaria. Details on the definition of evaluable patients and determination of the sample size are given in Section 9.1. The study is planned to be conducted in approximately 80 investigational centers in North America and possibly other regions (eg, Bulgaria) as well.	
5. TREATMENTS		
5.2.1. Storage and Security		
The investigator or designee must confirm appropriate temperature conditions have been maintained for all ~~IMPs~~ ***medicinal products*** received, and any discrepancies must be reported and resolved before ***their*** use ~~of the IMPs~~. … ~~Oral risperidone is to be stored and securely locked according to the storage conditions specified in the package insert (RISPERIDONE tablets, Teva Pharmaceuticals, US PI).~~	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. …	[redacted] Since it is not considered an IMP, the sentence on oral risperidone storage was moved to Section 5.4.
5.2.3. Accountability		
~~Used and partially used IMP (test or placebo) will be destroyed by the study center.~~ Unused ***and partially used*** IMP (test or placebo) will be ~~Unused IMP (test or placebo) 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.	Unused and partially used IMP (test or placebo) 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.	Clarification that the IMP will be returned to the sponsor. Correction of text duplication.
5.4. Other Medicinal Products/Non-Investigational Medicinal Products		
Oral risperidone ~~tablets~~ for stabilization (Table 4) will be a commercial product supplied ***centrally*** by ~~the study center~~ ***the sponsor***. The brand name of the oral risperidone supplied will be recorded on the source documentation. ***Oral risperidone is to be stored*** ~~***and securely locked***~~ ***according to the*** ~~storage conditions specified in the package insert (RISPERIDONE tablets, Teva Pharmaceuticals, US PI)~~ ***manufacturer's Summary of Product Characteristics (SmPC).***	Oral risperidone for stabilization (Table 4) will be a commercial product supplied centrally by the sponsor. The brand name of the oral risperidone supplied will be recorded on the source documentation. Oral risperidone is to be stored according to the manufacturer's Summary of Product Characteristics (SmPC).	Correction for consistency with Table 4; all forms of oral risperidone are allowed. In Bulgaria, oral risperidone will be sourced by the sponsor. Since it is not considered an IMP, the sentence on oral risperidone storage was moved from Section 5.2.1 to this section and revised to encompass storage conditions for all

Original text with changes shown	New wording	Reason/Justification for change
		forms of oral risperidone.
9. STATISTICS		
9.5.1. Primary Endpoint		
… - an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of ~~≥~~>4 and an absolute increase of ~~≥~~ ***≥4*** on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization	.. - an increase in any of the following 4 individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥4 on the combined score of these 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization	Correction of typos for consistency with other protocol sections.
APPENDIX A . CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
Legal Representative of the Sponsor in the European Union [redacted] [redacted]-***Merckle GmbH*** Graf-Arco-Str. 3 89079 Ulm Germany ~~Tel.~~ [redacted] ~~E-mail:~~ [redacted]	**Legal Representative of the Sponsor in the European Union** [redacted] Merckle GmbH Graf-Arco-Str.3 89079 Ulm Germany Telephone: [redacted] E-mail: [redacted]	This reflects a change in responsibilities at Teva.

16.9. Protocol with Revision 01 (Dated 15 February 2018)

The Clinical Study Protocol with Revision 01 includes updates to the original protocol dated 14 December 2017.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Vice President, Therapeutic Area Head, Neurology and Psychiatry Specialty Clinical Development Teva Branded Pharmaceutical Products R&D, Inc. Tel [redacted] Cell: [redacted]
Legal Representative of the Sponsor in the European Union	[redacted] Merckle GmbH Graf-Arco-Str.3 89079 Ulm Germany Telephone [redacted] E-mail: [redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. Tel: [redacted] Cell: [redacted] Email: [redacted]
Study Principal Investigator	[redacted] Professor of Psychiatry, Neurology and Neuroscience; Chairman, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Tel: [redacted] Email: [redacted]
Medical Monitors	**For US:** [redacted] Medical Director ICON PLC Mobile: [redacted] **For Bulgaria:** [redacted]) Medical Director ICON PLC Mobile: [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance **For serious adverse events:** 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.	[redacted] Director, Safety Physician Global Patient Safety and Pharmacovigilance Teva Pharmaceutical Industries, [redacted]

Contract Research Organization	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Central Clinical Laboratory	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Rater Training for Clinical Scales and Utilization Measures	Signant Health (formerly Bracket) 575 E. Swedesford Road, Ste 200 Wayne, PA 19087 United States
Electronic Data Capture	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Central Electrocardiogram Evaluation	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA, 19103 United States
Interactive Response Technology	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Bioassay and Pharmacokinetic Sample Analysis	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)

The screening visit (visit 1) will take place not more than 4 weeks before Stage 1 (visits 2, 3, 4, and 5). The following procedures will be performed at visit 1:

- obtain written informed consent 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
- review prior medication history
- review inclusion and exclusion criteria
- clinical laboratory tests (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 electrocardiography (in triplicate)
- serum beta human chorionic gonadotropin (β-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)
- functional measures (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 – **for all patients**
- Drug Attitudes Inventory 10-item version (DAI-10) **– for adult patients only**
- inquiry about adverse events (including serious adverse event reporting)
- inquiry about alchohol consumption and illicit drug use

2. Procedures Before Administration of Investigational Medicinal Product (Stage 1: Oral Conversion and Stabilization Stage)

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 measurement
- urine β-HCG test (for women of childbearing potential)
- PANSS
- Clinical Global Impression–Improvement (CGI-I)
- Clinical Global Impression of Severity (CGI-S)
- CGI-SS
- AIMS
- BARS
- SAS
- C-SSRS
- CDSS
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- oral risperidone dispensing (for qd intake)
- inquiry about adverse events (including serious adverse event reporting)
- dosage review and adjustment
- inquiry about alchohol 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 alchohol 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. A list of suggested questions will be provided to the investigator.

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:

- review inclusion and exclusion criteria (including randomization-specific criteria)
- clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- urine drug screen
- inquiry of concomitant medication
- full physical examination (including weight)
- vital sign measurement
- 12-lead electrocardiography (in triplicate)
- serum β-HCG tests (for women of childbearing potential)
- urine β-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 sample for pharmacogenetic analysis, unless the patient declines testing or local regulations prohibit testing.
- blood sample for biomarker analysis, unless the patient declines testing or local regulations prohibit testing.
- assessment of stability (based on the defined criteria)
- randomization
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- TV-46000 every month (q1m)/placebo administration – for patients randomized to those treatment groups
- TV-46000 every 2 months (q2m) administration – for patients randomized to that treatment group
- questions to assess ease of study drug administration **– to be performed only in the event that prefilled syringes become available during the study (assessed during 3 in-clinic visits for each patient).**
- inquiry about adverse events (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alchohol consumption and illicit drug use since previous visit

Procedures During Double-blind Maintenance Stage Administration of Investigational Medicinal Product (Stage 2: Relapse Prevention)

c. Stage 2: Relapse Prevention (Visit 6a, Week 1±3 days; Visit 6b, Week 2±3 days; and Visit 6c, Week 3±3 days [Telephone Contacts]) (Visit 7a, Week 5±3 days; Visit 7b, Week 6±3 days; and Visit 7c, Week 7±3 days [Telephone Contacts], 8a-8c, 9a-9c, etc.)

Note: Telephone contacts 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 visits 6a, 6b, and 6c (telephone contacts) and the other 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, injection site-related events including pain)
- inquiry about alchohol 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. A list of suggested questions will be provided to the investigator.

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

d. Stage 2: Relapse Prevention (Visit 7, Week 4±3 days)

The following procedures and assessments will be performed at visit 7:

- inquiry of concomitant medication
- vital sign measurement
- urine β-HCG test (for women of childbearing potential)
- PANSS
- CGI-I
- CGI-S
- CGI-SS
- AIMS
- BARS
- SAS
- C-SSRS
- CDSS
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- [redacted]

- vital sign measurement
- 12-lead electrocardiography
- urine β-HCG test (for women of childbearing potential)
- PANSS
- CGI-I
- 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
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- TV-46000 q1m/placebo administration – for patients randomized to those treatment groups
- TV-46000 q2m administration – for patients randomized to that treatment group
- questions to assess ease of study drug administration **– to be performed only in the event that prefilled syringes become available during the study (assessed during 3 in-clinic visits for each patient)**
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alchohol consumption and illicit drug use since previous visit

f. Stage 2: Relapse Prevention (Visit 9, Week 12±3 days)

The following procedures and assessments will be performed at visit 9:

- inquiry of concomitant medication
- vital sign measurement
- urine β-HCG test (for women of childbearing potential)
- PANSS
- CGI-I

- CGI-S
- CGI-SS
- AIMS
- BARS
- SAS
- C-SSRS
- PSP - **and every 12 weeks thereafter (for adult patients only)**
- SQLS - **and every 12 weeks thereafter (for adult patients only)**
- EQ-5D-5L - **and every 12 weeks thereafter (for adult patients only)**
- CDSS
- healthcare resource utilization - **and every 12 weeks thereafter**
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- TV-46000 q1m/placebo administration – for patients randomized to those treatment groups
- questions to assess ease of study drug administration **– to be performed only in the event that prefilled syringes become available during the study (assessed during 3 in-clinic visits for each patient)**
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alchohol consumption and illicit drug use since previous visit

NOTE: Patients will continue study visits and assessments as detailed above (ie, the same assessments performed at visits 7 and 8 will be repeated at visits 9 and 10, respectively). However, note that functional measures (PSP, SQLS, and EQ-5D-5L) and the healthcare resource utilization will be performed every 12 weeks after visit 9.

Thus, the 24 week series from Visit 7 to Visit 12c (Visits 13-18c, Visits 19-24c, etc) repeats until patient completion of the study, relapse or early termination.

Another pharmacokinetic sample will be collected from **adolescent patients only** 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, 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).

g. Stage 2: Early Termination (ET) Visit/End-of-Treatment Visit (EoT)

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

- urine drug screen
- inquiry of concomitant medication
- full physical examination, including weight
- vital sign measurement
- urine β-HCG test (for women of childbearing potential)
- PANSS
- CGI-S
- CGI-I
- 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 sample for biomarker analysis, unless the patient declines testing or local regulations prohibit testing.
- blood samples for plasma drug concentration - will be taken within an hour prior to dosing
- study drug administration (for patients randomized to all treatment groups) - This is applicable only for the EoT visit, not the ET visit.
- questions to assess ease of study drug administration **– to be performed only in the event that prefilled syringes become available (if this is 1 of the 3 visits in which it is assessed)**
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- inquiry about alchohol consumption and illicit drug use since previous visit

Note: The double-blind maintenance stage will be variable in duration, with patients continuing until they experience a relapse event and complete all end-of-study assessments; meet 1 or more of the study discontinuation or withdrawal criteria; or remain relapse-free at the time of study termination.

Note: If per the investigator's judgement, the patient is at risk of not appearing to 1 or both of the follow-up visits, the investigator may also complete the unscheduled visit form and perform an ECG.

Follow-up/Exit Period (Follow-up Visit 1 [4 weeks after last dosing visit] and Follow-up Visit 2 [8 weeks after the last dosing visit, End-of-Study (EoS) Visit])

The following procedures and assessments will be performed at follow-up visit 1 and follow-up visit 2:

- clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- inquiry of concomitant medication
- full physical examination (including weight)
- vital sign measurement
- 12-lead electrocardiography
- serum β-HCG tests (for women of childbearing potential)
- PANSS
- CGI-I
- CGI-S
- CGI-SS
- AIMS
- BARS
- SAS
- C-SSRS
- PSP - **at Follow-up Visit 2 only**
- SQLS - **at Follow-up Visit 2 only**
- EQ-5D-5L - **at Follow-up Visit 2 only**
- CDSS
- healthcare resource utilization - **at Follow-up Visit 2 only**
- DAI-10 - **at Follow-up Visit 2 only**
- blood sample 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 alchohol consumption and illicit drug use since previous visit

Note: Eligible patients who choose to enter the long term TV46000-CNS-30078 extension study will not need to complete the follow-up/exit visits in this study.

Unscheduled Visits

An unscheduled visit may be performed at any time during the study as deemed necessary by the investigator (eg, in case of psychiatric adverse events or suspicion of a 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:

- concomitant medication review;
- inquiry about changes in use of alcohol and illicit drugs
- vital sign measurements
- adverse event inquiry (including serious adverse event reporting, injection site-related events including pain)
- C-SSRS ("Since Last Visit" version) (if visit scheduled to assess psychiatric adverse events)
- PANSS and review of relapse criteria

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 the 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.

Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as these may compromise the scientific value of the trial. All 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 discontinue 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. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If the 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 protocol deviation. A deviation from the eligibility criteria will always result in study drug discontinuation in case the patient has not been dosed. In case a patient who was wrongly randomized has already started taking the study drug, a risk/benefit evaluation has to take place, and a strong clinical justification must be provided in case the patient is not withdrawn from the study drug. 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 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 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 (CRFs 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 informed consent form 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 product (IMPs) as well as non-IMPs, eg, background therapy, and the measures to be followed should be based on the medicinal product with 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 P4504A inducers. In case 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:

- 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] 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. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, 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, 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 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.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, 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, MHRA).

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.

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 record.
- 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 drugs that are either strong/moderate inhibitors of cytochrome P450 (CYP) 2D6 or strong inducers of CYP3A4 and/or P-glycoprotein (P-gp) are presented below:

Table 9: List of Prohibited Medications Affecting Cytochrome P450

Therapeutic class	Strong and moderate CYP2D6 inhibitors[a]	Strong CYP3A4 and/or P-gp inducers[b]
Anti-arrhythmics	Quinidine, dronedarone	
Antidepressants[c]	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

[a] 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.

[b] 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.

[c] These antidepressants are permitted if the patient was on a stable dose for at least 3 months prior to screening (no dose changes or new administrations will be permitted during the study).

CYP2D6=cytochrome P450 2D6; CYP3A4=cytochrome P450 3A4; 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 the previous antipsychotics 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 medications

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.

[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]

APPENDIX J. PHARMACOGENETIC ASSESSMENTS

A blood sample (6 mL) for pharmacogenetic assessment will be collected from all patients who signed the informed consent for pharmacogenetic assessments at the time point detailed in Table 2, unless the patient declines testing or local regulations prohibit testing. All blood tubes will be labeled with the patient code number. If required by local regulations, following DNA extraction from the pharmacogenetic blood sample, the DNA sample will be labeled with a new code (ie, double coding).

[redacted]. The candidate genes may be related to pharmacokinetics, safety features, drug mechanism of action, schizophrenia, or related diseases. The final list of genes that will be investigated will be selected at a later stage before the analysis to allow for updating with the latest scientific evidence. Genetic analysis could also include sequencing of the whole genome, if warranted.

The planned pharmacogenetic analysis and results of other potential genetic factors will be detailed in a separate document.

Pharmacogenetic assessment will be performed only for investigations related to schizophrenia, related diseases, or various aspects of understanding response to the test drug or related drugs (other antipsychotics).

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

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:

- 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
- excessive force to inject

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 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.

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.

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 of the protocol, respectively).

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, 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, 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. 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, electronic patient-reported outcome [ePRO] 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 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:

- 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, 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 the 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). 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 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 countries/sites.

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 Coronavirus disease 2019 [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 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;

[redacted]

Section 5.2.3 Accountability

Any [redacted] IMP transported for home administration will be returned to the clinic to maintain accountability. Used syringes 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 9.5.4.2. Sensitivity Analysis

Sensitivity and supplementary analyses will be conducted to evaluate the impact of the change to remote monitoring (VC visits) and the impact of the COVID-19 pandemic on the impending relapse and rating scales. The analysis will include subgroup analysis (eg, pre, during and post COVID-19 pandemic outbreak, where each patient will be classified into one of the levels), a multivariate model (eg, Cox model with time dependent covariate for COVID-19), and/or imputation methodology for patients' attrition due to the COVID-19 pandemic, as appropriate and if data permit. Details of the supplementary and sensitivity analyses will be presented in the statistical analysis plan or addendum thereof, following a blinded review meeting prior to database lock.

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

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."