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

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

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.

Objectives	Endpoints
[redacted]	[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 (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

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	**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	

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.

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

- 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

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]	

  - 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

- 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])

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)

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.

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).

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

2.2. [redacted]

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

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.

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”).

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]

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.)

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.

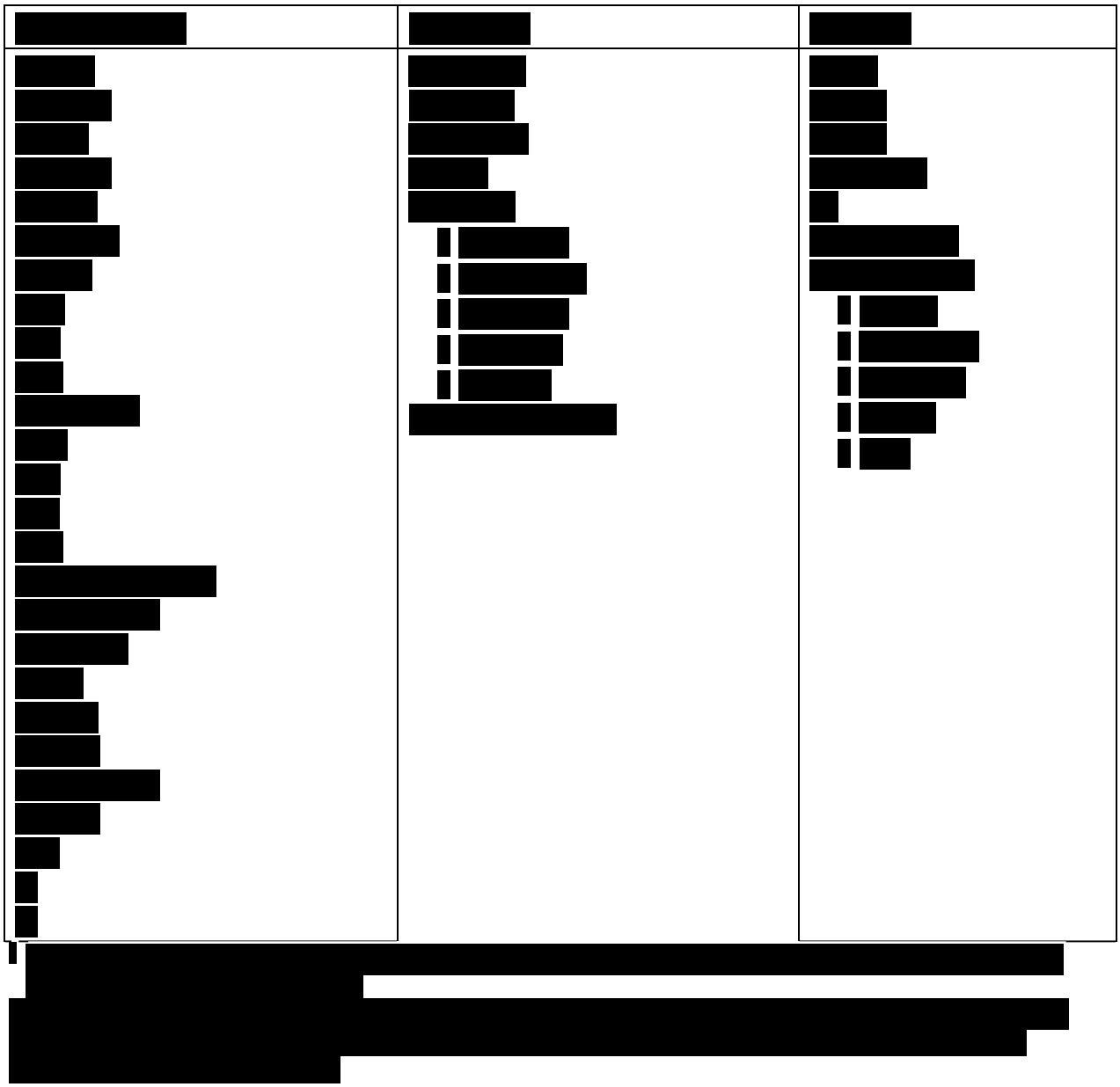
All female patients (or female partners of men participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including 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.

Table 7: [redacted]



For COVID-19 updates, refer to Appendix N.

7.4.1. [redacted]

Table 7.

8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/ BIOMARKERS/ PHARMACOGENOMICS

8.1. [redacted]

[redacted]

For COVID-19 updates, refer to Appendix N.

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

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

- 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.

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