Statistical Analysis Plan

A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy, Safety, and Tolerability of Olanzapine for Extended-Release Injectable Suspension (TV-44749) for Subcutaneous Use as Treatment of Adult Patients with Schizophrenia

Study Number TV44749-CNS-30096

NCT05693935

SAP Approval Date: 17 April 2024

Statistical Analysis Plan

Study TV44749-CNS-30096 with Protocol Amendment 01

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Phase 3

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV44749-CNS-30096

Study Title: A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy, Safety, and Tolerability of Olanzapine for Extended-Release Injectable Suspension (TV-44749) for Subcutaneous Use as Treatment of Adult Patients with Schizophrenia

Statistical Analysis Plan for:

☐ ☐ **Integrated Summary of Efficacy**

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

Amendment: 01

Approver: [redacted] **Date**

[redacted]

Approver: [redacted] **Date**

[redacted]

Executed signature pages are maintained separately within the Trial Master File

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AMENDMENT HISTORY

The Statistical Analysis Plan for study TV44749-CNS-30096 (original study protocol amendment dated 15 February 2024) has been amended and reissued as follows:

Amendment number	Date	Author(s)	Summary of changes	Reason for amendment
01	17 April 2024	[redacted] SCD Statistics [redacted] Statistics [redacted] Statistics	**Estimands:** Provide clearer language regarding estimands. Introduce an estimand using the treatment policy strategy. Introduce another estimand using the modified treatment policy strategy. Deleting the while on treatment strategy **Simplification of Secondary and Exploratory Endpoints Analyses**. **Imputations Methodology and Tipping Point Analyses**: Clarify the methodology for imputations. Provide details on tipping point analyses. **Analysis of SQLS and [redacted]**: Clarification on the analysis of SQLS. Describe the analysis approach for [redacted]. **Omitting Conditional Power Analysis**: Exclude conditional power analysis from the study. **Provide clarifications in regards to:** the safety analyses section the pain and tolerability section the pharmacokinetics section the biomarker and pharmacogenetic section **Update Appendices**: Ensure that the appendices are updated accordingly.	Response to FDA's comments on the SAP. Requests from clinical programming to clarify language
Original Statistical Analysis Plan	23 October 2023	[redacted] SCD Statistics [redacted] SCD Statistics	Not applicable	Not applicable

Amendment number	Date	Author(s)	Summary of changes	Reason for amendment
		[redacted] SCD Statistics		

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
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-Severity
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
EOT	end-of-treatment
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up (period)
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	investigational medicinal product
ISR	injection site reaction
ITT	Intent-to-Treat
MAR	missing at random

MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MM	medical monitor
MMRM	mixed-model repeated measures
MNAR	missing not at random
n	number
PANSS	Positive and Negative Syndrome Scale
PDAESI	protocol-defined adverse event of special interest
PDSS	Post-injection Delirium/Sedation Syndrome
PGI-I	Patient Global Impression-Improvement
PK	pharmacokinetics
PSP	Personal and Social Performance Scale
PT	preferred term
q1m	once monthly
R&D	Research and Development
RDQ	Readiness for Discharge Questionnaire
RTSM	Randomization and Trial Supply Management
SAS	Simpson-Angus Scale
sc	subcutaneous
SD	Standard Deviation
SE	Standard Error
SI	standard international
SOC	system organ class
SOP	Standard Operating Procedure
SQLS	Schizophrenia Quality of Life Scale
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States (of America)
WHO	World Health Organization
β-HCG	Beta-human chorionic gonadotropin

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, study TV44749-CNS-30096, (A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy, Safety, and Tolerability of Olanzapine for Extended-Release Injectable Suspension (TV-44749) for Subcutaneous Use as Treatment of Adult Patients with Schizophrenia), and was written in accordance with standard operating procedure (SOP) GSD-SOP-702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol with amendment 01 (approved on February 15, 2024) for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, this SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g., other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report.

1. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

This section describes the estimands and endpoints in the study. For a tabulated presentation of the efficacy endpoints with respect to the estimands see Appendix D.

1.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** is to evaluate the efficacy of TV-44749 in adult patients with schizophrenia**.**	The primary efficacy endpoint is as follows: • The change from baseline to week 8 in the Positive and Negative Syndrome Scale (PANSS) total score.
A **key secondary objective** is to further evaluate the efficacy of TV-44749 based on additional parameters in adult patients with schizophrenia.	The secondary efficacy endpoints are as follows: • Change in Clinical Global Impression-Severity (CGI-S) scale score from baseline to week 8 • Change in Personal and Social Performance Scale (PSP) score from baseline to week 8
A **secondary objective** is to evaluate the safety and tolerability of TV-44749 in adult patients with schizophrenia.	The safety and tolerability endpoints will include, where appropriate, the following: adverse events (including serious adverse events, extrapyramidal symptoms, injection pain and other injection site reactions [local tolerability]), vital signs (blood pressure, pulse and orthostatic changes, and temperature), body weight, laboratory tests, electrocardiogram (ECG), concomitant 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)
A **secondary objective** of this study is to evaluate the efficacy of TV-44749 from baseline to endpoint in Period 1 in adult patients with schizophrenia.	• Change from baseline to weeks 1, 2, 4 and 8 in the PANSS total score • Clinical Global Impression-Improvement (CGI-I) scale at weeks 4 and 8 • Clinical Global Impression-Severity (CGI-S) scale at weeks 1, 2, 4 and 8 • Patient Global Impression-Improvement (PGI-I) scale at weeks 2, 4 and 8 • Change from baseline to weeks 4 and 8 in the Schizophrenia Quality of Life Scale (SQLS) • Change from baseline to weeks 4 and 8 in the PSP score

1.1.1. Justification of Primary Endpoint

The primary efficacy endpoint of the study is the change from baseline to week 8 in the PANSS total score. The PANSS is a well-characterized standardized measurement used for rating

presence and severity of positive and negative symptoms in patients with schizophrenia and is widely used in the research of antipsychotic treatment.

The 30-item PANSS is used to identify the presence and severity of psychopathology symptoms, the relationship of these symptoms to one another, and global psychopathology (Kay 1987). This instrument measures the severity of positive symptoms (7 items), negative symptoms (7 items), and general psychopathology symptoms (16 items) and is the most widely used measure of symptom severity in schizophrenia drug trials. Each of the items is scored from 1 (absence of symptoms) to 7 (severe symptoms presentation). The sum of the 30 items provides the PANSS total scores, which ranges from 30 to 210 (the lower, the better the outcome). The PANSS has been shown to have high internal validity, reliability, and sensitivity to change in both short- and long-term trials (Gopalakrishnan et al 2021, Curson et al 1986, Wyatt et al 1999).

The PANSS will be administered by the investigator/trained rater who will evaluate a patient's current severity level of each symptom (item).

1.2. Estimands for Primary and Secondary Objectives and Endpoints

1.2.1. Primary Estimand

The purpose of the primary estimand is to evaluate the efficacy of TV-44749 compared to placebo as if patients do not withdraw and adhere to treatment as instructed (see Section 3.2.1 in the Study Protocol). Patients who withdrew from the treatment/study due to lack of efficacy or did not adhere to the investigator instructions will be regarded as if they share the slope of the placebo group from that intercurrent event (ICE) time point until week 8 (see White et al 2019). Use of prohibited antipsychotic medications is considered non-adherence to the investigator instructions unless it is short term oral use.

The clinical question of interest is as follows: "What will be the treatment benefit if a patient adheres to treatment for 8 weeks?".

For the primary efficacy objective, the following estimand attributes will be employed:

a. **Treatment**: The treatment of low (318 mg monthly [q1m]), medium (425 mg q1m), or high (531 mg q1m) dose of TV-44749 compared to placebo, separately, will be evaluated according to the randomization assignment in Period 1.

b. **Population**: All randomized adult patients who have a confirmed diagnosis of schizophrenia, present with acute exacerbation of disease, and are eligible for olanzapine treatment.

c. **Endpoint**: Change from baseline to week 8 in the PANSS total score.

d. **Population-level summary**: Difference in the means between each individual dose arm of TV-44749 and placebo for the endpoint described above.

In this study any use of antipsychotic concomitant medications is regarded as prohibited per protocol (see Section 6.7 in the protocol). However, short term oral antipsychotic medications prohibited by the protocol may be occasionally used as part of the management of acute agitation of schizophrenia exacerbation in real-life clinical practice. If such case of use of oral antipsychotic occurs, it would not be considered as effecting the primary endpoint when:

- The treatment use end date was > 14 days prior to the week 8 (Visit 11) and
- Treatment duration was ≤ 3 consecutive days and
- There were only ≤ 2 treatment episodes (where a treatment episode is defined as ≤3 consecutive days of treatment followed by at least 7 days without treatment) from baseline to Visit 11.

In addition, any use of prohibited antipsychotics after early termination is not considered an ICE. Prior antipsychotic medications without a defined end-date are not deemed as ICE of "prohibited concomitant antipsychotic medication" since these cases occur before randomization and initiation of treatment.

Table 1: Classification of Intercurrent Events

Intercurrent Event	Strategy	Handling of Intercurrent Events

• Early discontinuation of treatment due to:
  ○ lack of efficacy
  ○ disease progression
• Prohibited antipsychotic (with the exception above)
	Hypothetical	Measurements after ICE will be removed and replaced with imputed data using reference-based (CIR) imputation (assuming MNAR)

• Early discontinuation of treatment due to other reasons (including due to adverse event)	Hypothetical	Measurements after ICE will be removed and replaced with imputed data based on randomized treatment group (assuming MAR)
• Allowed concomitant medications • Adverse event that did not lead to treatment discontinuation • Use of prohibited medications that are not antipsychotic • Short term use of prohibited antipsychotic (see meeting the definition above) • Injection site reaction • Out of window safety assessments	Treatment policy	Measurements after ICE will be included in the primary analysis

ICE=intercurrent event; MAR=missing at random; MNAR=missing not at random; CIR = copy increments in reference

Any data collected after the intercurrent event (ICE) of taking prohibited antipsychotic medications (except as described above) or withdrawal from randomized treatment due to insufficient clinical response (i.e., lack of efficacy) will be treated in the analysis as MNAR. An ICE of early discontinuation for other reasons will be treated in the analysis as if the patient fully complied and completed the study (i.e., assuming missing at random [MAR]); see Table 1 for further details on the classification and handling of ICEs. This complies with the hypothetical approach.

For ICEs that were not foreseen at the time of writing the protocol and that require the use of the hypothetical strategy, classification as MAR/MNAR and revisiting this classification will be done in a blinded manner on a case-by-case basis prior to database lock for efficacy and will be

documented in the blinded statistical data review meeting minutes (see Section 5.7). Likewise, the classification of ICEs as stated in Table 1 will be conducted in a blinded manner before database lock for efficacy and documented accordingly. The reference-based CIR approach (White et al 2019) is described in Section 6.2.3 of this document.

1.2.2. Key Secondary Efficacy Estimand

For the key secondary efficacy objectives, attributes "a" and "b" will be implemented in the same manner as planned for the primary estimand:

a. Treatment: The treatment of low, medium, or high dose of TV-44749 compared to placebo, separately, will be evaluated according to the randomization assignment at Period 1.

b. Population: All randomized adult patients who have a confirmed diagnosis of schizophrenia, present with acute exacerbation of disease, and are eligible for olanzapine treatment.

c. Endpoint: Change in Clinical Global Impression-Severity (CGI-S) scale score from baseline to week 8 and change in Personal and Social Performance Scale (PSP) score from baseline to week 8.

d. Population-level summary: Details are described in Section 6.4.

Any data collected after the ICE of taking prohibited antipsychotic medications (that is not short term) or withdrawal from randomized treatment due to insufficient clinical response (lack of efficacy) will be regarded as patients not reaching the optimal treatment effect (ie, MNAR). The ICE of early discontinuation for other reasons will be regarded as if the patient fully complied and completed the study (assuming MAR); see Table 1 for further details on the classification and handling of ICEs. This complies with the hypothetical approach.

1.2.3. Estimand Using the Treatment Policy Strategy

As supplementary analyses (Section 10.5.6.3 in the Protocol), the primary and key secondary objectives will be evaluated where all ICEs are handled using the Treatment Policy strategy (i.e., all available data will be analyzed regardless of ICE). *The estimand attributes for treatment, population, endpoint and population-level summary will be the same as described in the Primary Estimand and Key Secondary Efficacy Estimand sections*, respectively. This estimand addresses the following clinical question of interest: "What is the treatment benefit of a patient regardless of treatment adherence or early discontinuation over 8 weeks?".

In addition to the primary and key secondary endpoints, the other secondary efficacy endpoints in Period 1 will also be analyzed according to this estimand: PANSS, CGI-I, CGI-S, PGI-I, SQLS, PSP, and [redacted] (Section 6.4 and Appendix D).

1.2.4. Estimand using a Modified Treatment Policy Strategy

As additional supplementary analyses, the primary and key secondary objectives will be evaluated using the Treatment Policy strategy except that efficacy data after the ICE for use of antipsychotic medication during Period 1 will not be used (i.e., they will be defined as missing in the analysis dataset). *The estimand attributes for treatment, population, endpoint and population-level summary will be the same as described in the Primary Estimand and Key Secondary*

Efficacy Estimand sections, respectively. The clinical question of interest is as follows: "What is the treatment benefit of a patient diagnosed with schizophrenia who did not receive any other antipsychotic medication regardless of early discontinuation for 8 weeks?". The rationale for this estimand is to evaluate the treatment effect of TV-44749 versus placebo on efficacy endpoints, which is not confounded by concomitant use of other antipsychotics from baseline to week 8.

In addition to the primary and key secondary endpoints, the other secondary efficacy endpoints in Period 1 will also be analyzed according to this estimand: PANSS, CGI-I, CGI-S, PGI-I, SQLS, PSP, and [redacted] (Section 6.4 and Appendix D).

1.2.5. Estimand for Assessing Safety and Tolerability

For safety and tolerability objectives, the following estimand attributes will be employed:

a. **Treatment**: the treatment of low, medium, or high dose of TV-44749 and placebo, separately, will be evaluated according to treatment actually initially received.

b. **Population**: all randomized adult patients who have a confirmed diagnosis of schizophrenia, present with acute exacerbation of disease at randomization and received at least 1 administration of IMP, and are eligible for olanzapine treatment.

c. **Endpoint**: see Section 1.1 "Primary and Secondary Objectives and Endpoints" above; these safety and tolerability endpoints will be evaluated without regard to any ICE.

d. **Population-level summary**: details are described in Section 8 and Section 9 .

1.3. Exploratory Objectives and Endpoints

Exploratory objectives are:

Objectives	Endpoints
[redacted]	[redacted]

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

Objectives	Endpoints
[redacted]	[redacted]

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a Phase 3, multinational, multicenter, randomized, double-blind, -parallel group, placebo-controlled study with an open-label, long-term safety phase to evaluate the efficacy, safety, and tolerability of olanzapine for extended release- injectable suspension (TV-44749) for subcutaneous (sc) use as treatment of adult patients with schizophrenia.

The study will be composed of 2 periods (Figure 1): Period 1 (the double-blind, placebo controlled, efficacy and safety period [acute treatment phase]) and Period 2 (open-label safety period [long-term safety phase]). For each patient, the duration of Period 1 will be 8 weeks, and the duration of Period 2 will be up to 48 weeks-.

Patients will be randomized to the 8-week efficacy and safety period (acute treatment phase; Period 1) to 1 of 3 active treatment groups (low dose [318 mg q1m], medium dose [425 mg q1m], or high dose [531 mg q1m]) or the placebo group in a 1:1:1:1 ratio.

Period 2 will be open-label and will not include a placebo group. Period 1 will remain blinded until database lock for Period 1. In order to maintain the masking of Period 1, all patients will be randomized again between Period 1 and Period 2; patients who were previously assigned to the active treatment groups will retain their Period 1 treatment assignment (the re-randomization of patients in the TV-44749 groups is being done only to maintain blinding of Period 1, and de facto is a deterministic assignment and not randomization), and patients who were previously assigned to the placebo group will be randomized to one of the active treatment groups in a 1:1:1 ratio. Revealing of the treatment assignment in Period 2 will be performed only after completion and reporting of the relevant study procedures related to assessment of efficacy and safety endpoints in Period 1 (for more detail see Section 6.9.1 in the protocol), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (Visit 11) by authorized site staff according to a process predefined in the relevant study plans, provided that all requirements stipulated in this process were met. Therefore, the dosing at week 8, although assigned to Period 2, will be handled in a blinded manner by all parties, similarly to the dosing in Period 1. The sites are encouraged to complete the revealing of the treatment assignment procedure before IMP administration in week 12 (Visit 12).

After approximately 440 patients complete the week 8 visit, depending on the need for additional data on exposure or safety, the placebo treatment group may be discontinued and additional patients may be randomized to the study (ie, to Period 1) to the TV-44749 active treatment groups only. For further details, see Section 2.2.2 Discontinuation of the Placebo Treatment Group.

During the conduct of this study, an Independent Data Monitoring Committee (IDMC) will review accumulated unblinded safety, pharmacokinetic, and efficacy data on a regular basis, as detailed in the IDMC charter, to evaluate the safety of the product for the purpose of ensuring the continuing safety of the study patients and overseeing study conduct issues, as applicable. The IDMC will not evaluate efficacy for early efficacy or early futility.

Once all patients completed Period 1, and Period 2 is ongoing, an analysis of the full efficacy data will be performed.

Screening (up to 8 days Prior to Randomization to Period 1):

Patients will undergo screening procedures and assessments up to 8 days prior to randomization to Period 1. Patients will provide informed consent at the screening visit before any study-related procedures are performed. Patients will be asked to consent to share their information with a vendor that will verify that they are not currently participating or have not recently participated in another clinical study, unless prohibited by local requirements. [redacted]

Patients with exacerbation that started ≤8 weeks prior to screening (the investigator should confirm the exacerbation based on the patient's medical records and/or based on anamnesis) and who would benefit from psychiatric hospitalization or continued hospitalization for symptoms of schizophrenia may be included in this study.

The patient's total Positive and Negative Syndrome Scale (PANSS) score should be between 80 and 120, inclusive, at screening with a score ≥4 on at least 2 of the following 4 items of the PANSS positive sub-scale: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution.

Patients must have an identified responsible person (referred to as the caregiver) who has agreed to provide information about the patient's location, condition, and overall status during outpatient portions of the study during Period 1. The patient's caregiver will be asked to sign a caregiver ICF during the screening period.

Patients who are not already in an inpatient setting will be hospitalized during the screening period (see details pertaining to hospitalization duration and discharge criteria in the description of "Period 1" below).

Patients will taper off their prior oral antipsychotic medications at rates per the investigator's discretion. The tapering-off process should be completed prior to randomization.

Patients entering the study who have not previously received oral olanzapine will receive 2 oral doses of olanzapine for 2 consecutive days during the screening period (the second dose should be administered at least 24 hours prior to randomization) to assess patient tolerability (oral olanzapine 10 mg/day or higher [but not exceeding 20 mg/day] per investigator decision). The PANSS and Clinical Global Impression-Severity (CGI-S) should be completed prior to oral olanzapine administration.

Patients who received olanzapine within the last year will not be required to receive the 2 doses of oral treatment. The investigator will verify the previous use, tolerability, and duration of olanzapine treatment to assure prior tolerability.

In the event that a patient meets all study inclusion criteria and does not meet any of the study exclusion criteria, but results of screening blood and urine samples taken within the 8-day screening period are not available by day 8 of screening, the screening period may be extended by 2 days (until day 10 of screening) to allow the receipt of the results to confirm patients'

eligibility. In case results are not available by day 10, the patient will be considered a screening failure and may be considered for rescreening. In addition, the screening period may be extended by 2 days (until day 10 of screening), in exceptional cases, due to special conditions (e.g. extreme weather) after receiving approval from the MM or sponsor.

Period 1 (8 weeks):

Period 1 is an 8-week double-blind, placebo-controlled, efficacy and safety period (acute treatment phase).

Randomized patients should have a PANSS total score between 80 and 120, inclusive, at baseline (prior to randomization) with a score ≥4 on at least 2 of the following 4 items of the PANSS positive subscale: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution.

Patients demonstrating a reduction in the total PANSS score of ≥20% between screening and the baseline (randomization) visit will not be eligible for randomization into the study.

Randomized patients will be treated with sc injections of TV-44749 (low [318 mg q1m], medium [425 mg q1m], or high dose [531 mg q1m]) or placebo at visit 2 (week 0) and visit 7 (week 4).

At visits 2 and 7, the PANSS, Columbia Suicide Severity Rating Scale (C-SSRS), CGI-S, and Clinical Global Impression-Improvement (CGI-I; visit 7 [week 4] only) scales should be completed prior to investigational medicinal product (IMP) administration; all other scales and questionnaires may be completed either prior to IMP administration or after. Any assessments performed after IMP administration must be completed on the day of IMP administration.

Prior to screening, patients can be either outpatients or inpatients. All patients will be hospitalized upon study entry (screening) and will remain hospitalized during the screening period and for the first 4 weeks after randomization (until the second IMP administration). After the second injection, patients may be discharged if all discharge criteria are met and if, in the opinion of the investigator, discharge is appropriate. During the hospitalization period (ie, before the patient is discharged), a short-term leave from the site may be allowed if requested by the patient. Patient's eligibility for such leave will be determined by the investigator clinical judgment, in accordance with the study conduct and with the patient's best interest. During the leave, the patient will be escorted by a caregiver or another individual per investigator approval. The patient will return to the site on the same calendar day. In exceptional cases, an overnight stay outside the site may be approved by the investigator. Upon return to the site, after any period of leave, the patient will undergo a urine drug screen, an abbreviated physical examination (including weight), and a concomitant medication and alcohol consumption/illicit drug use inquiry. The results of these assessments, along with the date and time of site leave and return, will be captured in a dedicated case report form (CRF).

The Readiness for Discharge Questionnaire (RDQ) will be used to assess a patient's readiness for discharge (Potkin et al 2005) and should be completed. Once discharge criteria are met, and in the opinion of the investigator discharge is appropriate, the patient can be discharged to a suitable supervised environment or to the responsibility of the patient's caregiver.

If the patient is discharged before week 8, the patient will return to the clinic for weekly visits from the time of discharge and until the end of Period 1. If discharge criteria are not met, the

patient will remain in the clinic. Patients may remain as inpatients for the full duration of Period 1 if they do not meet the discharge criteria.

If at any point after discharge during Period 1 the patient no longer has a caregiver, lacks a supervised environment, or lacks stable housing and the site cannot provide frequent monitoring via telephone contact, the patient may be discontinued from study treatment and will be asked to complete ET and FU visits.

For the entire duration of Period 1 (including the inpatient and outpatient setting), a window of ±3 days will be allowed around the scheduled visit dates for dosing visits; a window of ±2 days will be allowed for all other visits (during the inpatient period, every effort will be made to maintain the assessments on the scheduled dates). Visit dates should be calculated from the date of previous IMP administration. In exceptional cases, per the discretion of the investigator and with permission from the medical monitor (MM) or sponsor, dosing visits may take place up to 5 days before the scheduled visit date (and recorded accordingly).

Period 2 (up to 48 weeks):

Following completion of Period 1 (8 weeks), eligible patients will continue to Period 2, the safety period (long-term safety phase; up to 48 weeks). During this period, patients will receive monthly sc injections of TV-44749.

In order to enter Period 2, the patient should meet the following eligibility criteria:

1. Patient has completed Period 1.
2. Patient is considered sufficiently clinically stable per the investigator's judgment.
3. Patient is an outpatient (ie, met RDQ criteria and was discharged prior to Period 2).

   Note: Patients who do not meet RDQ criteria, but in the opinion of the investigator show sufficient clinical stabilization for transition to Period 2 and may benefit from continuation of participation in the study, may continue to Period 2 as inpatients for up to an additional 8 weeks. For such patients, RDQ can be assessed periodically according to investigator discretion; if RDQ criteria are not met by the end of the additional 8-week hospitalization period (week 16), then the patient will be discontinued from study treatment and will be asked to complete ET and FU visits.

Visit 11 (week 8) will be the last visit of Period 1 and the first visit in Period 2. In order to maintain the blind in Period 1, all patients will be randomized again between Period 1 and Period 2; patients who were previously assigned to the active treatment groups will retain their Period 1 treatment assignment (the re-randomization of patients in the TV-44749 groups is being done only to maintain blinding of Period 1, and de facto is a deterministic assignment and not randomization), and patients who were previously assigned to the placebo group will be randomized to one of the active treatment groups in a 1:1:1 ratio. The treatment with TV-44749 at this visit will be assigned to Period 2 and will be performed according to the re-randomization treatment assignment. Scales and questionnaires and other assessments will be completed only once. Revealing of the treatment assignment in Period 2 will be performed only after completion and reporting of the relevant study procedures related to assessment of efficacy and safety endpoints in Period 1 (Section 6.9.1 of the protocol), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (Visit 11) by the sites according to a process predefined in the relevant study plans, provided that all requirements

stipulated in this process were met. Therefore, the dosing at week 8, although assigned to Period 2, will be handled in a blinded manner by all parties, similarly to the dosing in Period 1.

The study will continue on an outpatient basis (or inpatient basis for patients who remain hospitalized for up to an additional 8 weeks), and telephone contacts (or other comparable form of remote communication) will take place weekly between the monthly in-clinic visits. If, in the judgment of the investigator, the patient is likely to experience an exacerbation or pose a danger to himself/herself or others, that patient should be invited for an unscheduled visit (per assessments specified in Table 2 of the study protocol) and/or hospitalized if needed, and the patient should be treated per the investigator's judgment. If treatment with disallowed medications is required, including antipsychotics other than TV-44749, the patient will be discontinued from study treatment and will be asked to complete ET and FU visits.

The PANSS, C-SSRS, CGI-S, and CGI-I scales should be completed prior to IMP administration; all other scales and questionnaires may be completed either prior to IMP administration or after (except for visit 11 [week 8], where all assessments must be completed prior to IMP administration). Any assessments performed after IMP administration must be completed on the day of IMP administration.

For the entire duration of Period 2 (including any phone visits), a window of ±3 days will be allowed around the scheduled visit dates for dosing visits; for any patients who are inpatients at the beginning of Period 2, every effort will be made to maintain the assessments on the scheduled dates during the inpatient period. Visit dates should be calculated from the date of previous IMP administration. In exceptional cases, per the discretion of the investigator and with permission from the MM or sponsor, dosing visits may take place up to 5 days before the scheduled visit date (and recorded accordingly).

Patients entering Period 2 will be treated for up to 48 weeks. An end-of-treatment (EOT) visit will be completed 4 weeks after the patient's last injection. The time window for the EOT visit is ±1 week.

Dose Adjustment:

During Period 2, the investigator may perform dose adjustments of TV-44749 (to one of the doses offered in the protocol) from visit 12 (week 12) and onward, based on clinical judgment. Dose adjustment will be documented in the CRF.

Detailed procedures regarding dose adjustments will be provided in the pharmacy manual and in any other study plans as applicable.

Procedures for Potential Post-injection Delirium/Sedation Syndrome (PDSS)

[redacted]

[redacted]

Early Termination and Follow-up Period

Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria should be invited to perform the ET visit as soon as possible. An EOT visit will be conducted at 4 weeks after the last dose of IMP, and a FU visit for safety evaluation will be conducted at 8 weeks after the last dose of IMP. The time window for the EOT visit is ±1 week, and the time window for the FU visit is -1/+2 weeks. Since TV-44749 is an LAI, additional antipsychotic treatment is not required for 4 weeks following the last dosing visit (unless clinically indicated), whereas during the subsequent 4 weeks (FU period), patients may be treated for schizophrenia according to the investigator's judgment. In case the ET visit is conducted during the time window of the EOT visit, the ET and EOT visits may be conducted on the same day (ie, the visits will be combined, and all assessments listed in the Study Procedures and Assessments tables [Table 1 or Table 2 of the study protocol] for the ET and EOT visits must be performed). Patients who discontinue study treatment should be encouraged to complete the remaining visits until completion of the study (ie, ET, EOT, and FU visits).

In case the sponsor decides to stop the study, active randomized patients will be asked to complete the EOT visit 4 weeks after the last dose of IMP and a FU visit 8 weeks after the last dose of IMP.

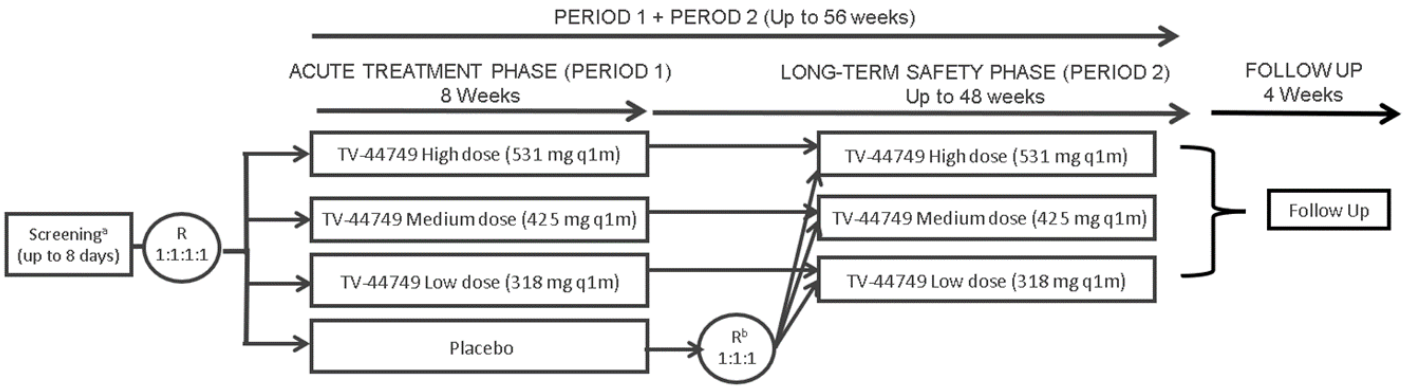
The total duration of patient participation in the study will include up to 8 days of screening, during which oral olanzapine will be administered for 2 consecutive days (to establish tolerability), 8 weeks of treatment with TV-44749 or placebo (Period 1 [acute treatment phase]), up to 48 weeks of treatment with TV-44749 (Period 2 [long-term safety phase]), and 4 weeks of FU.

The end of study is defined as the last visit of the last patient.

The study duration will be from Q1 2023 (first patient screened) to Q2 2025 (last patient last visit).

The study schematic diagram is presented in Figure 1. Study procedures and assessments with their time points are presented in Table 1 (Period 1) and Table 2 (Period 2) of the study protocol. Study procedures and assessments by visit are listed in Appendix B of the study protocol.

Figure 1: Overall Study Schematic Diagram



q1m=once monthly; R=randomization.

2.2. Randomization and Blinding

Period 1: Patients will be randomized to receive 1 of 3 doses of TV-44749 (low [318 mg q1m], medium [425 mg q1m], or high dose [531 mg q1m]) sc injection or placebo sc injection in a 1:1:1:1 ratio. Randomization will be stratified by sex (male or female) and geographical region (North America; Europe and Asia, namely, the continent of Europe and India; Far East, namely China; and the rest of the world). The doses of TV-44749 will be comparable to low, medium, and high dose of oral olanzapine (10, 15, and 20 mg, respectively). Patients randomized to TV-44749 or placebo sc will receive a sc injection of TV-44749 or placebo, respectively, at baseline (randomization) and visit 7 (week 4).

During Period 1, patients and investigators will remain blinded to the identity of the treatment administered to each patient. Due to the differences between TV-44749 and placebo, unblinded study personnel, not associated with rating the patient and assessments of safety and independent of the study team, will be required at each site to reconstitute and administer the IMP. The sponsor's clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the Period 1 database is locked for final efficacy analysis. The sponsor (and/or delegates) will assign designated unblinded personnel who will be responsible to oversee unblinded activities performed at the site during Period 1. This includes but is not limited to unblinded monitoring at the site and supporting the unblinded site staff as required during Period 1. During Period 1, the sponsor's (and delegates) unblinded personnel will not be involved with managing the study and will not take part in any discussions or decisions related to it.

Period 2: Period 2 will be open-label and will not include a placebo group. Period 1 will remain blinded until database lock for Period 1. In order to maintain the blind in Period 1, all patients will be randomized again between Period 1 and Period 2.

Patients will be randomized to receive 1 of 3 doses of TV 44749 sc injection (low [318 mg q1m], medium [425 mg q1m], or high dose [531 mg q1m]). After completing all visit 11 (week 8) scales and assessments, eligible patients who were on active treatment in Period 1 will retain their Period 1 treatment assignment, and eligible patients who were on placebo in Period 1 will be randomized to one of the active treatment groups in 1:1:1 ratio. To maintain the blind in

Period 1, this procedure will be performed as patients enter Period 2 via the randomization system.

Revealing of the treatment assignment in Period 2 will be performed only after completion and reporting of the relevant study procedures related to assessment of efficacy and safety endpoints in Period 1 (see Section 6.9.1 of the study protocol; Procedures and Assessments to be Performed Before and After Randomization into Period 1 at Visit 11), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (Visit 11) by authorized site staff according to a process predefined in the relevant study plans, provided that all requirements stipulated in this process were met. Therefore, the dosing at week 8, although assigned to Period 2, will be handled in a blinded manner by all parties, similarly to the dosing in Period 1.

The randomization lists for both Period 1 (double blind period) and Period 2 (open label period) will be assigned to the relevant treatment groups through a qualified service provider, eg, via a Randomization and Trial Supply Management (RTSM) system. The generation of the randomization list and management of the RTSM system will be done by a qualified service provider. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

2.2.1. Blinding Procedures

The unblinded pharmacist/study team member at the investigational center who will prepare and administer the IMPs will know the IMP assignments for each patient. In addition, during Period 1, up to 2 other unblinded individuals from the investigational center will know the IMP assignments to serve as backup staff or to provide quality assurance and oversight in their preparation and administration, as necessary. These individuals will not be involved in the conduct of any study procedures and assessment of any adverse events and must not discuss any unblinding information with the blinded site staff.

Additional details about the IMP preparation and injection procedure (including measures to mitigate the risk of unblinding) can be found in the pharmacy manual. In order to avoid nonintentional unblinding, the dosing procedure described in the pharmacy manual (including masking measures such as covering the IMP syringe contents, etc) will remain unchanged throughout the study, although after week 8 IMP administration, the treatment in Period 2 allocation will be revealed.

2.2.2. Discontinuation of the Placebo Treatment Group

After approximately 440 patients complete the week 8 visit, depending on the need for additional data on exposure or safety, the placebo treatment group may be discontinued and additional patients may be randomized to the study (ie, to Period 1) to the TV-44749 treatment groups only. Patients randomized to the study from that time point will not be included in the primary efficacy analyses, as there will be no concurrent placebo group. The sponsor will notify the sites and the IDMC once the placebo treatment group is discontinued, and new patients from that time point will sign an updated ICF reflecting the actual available treatment groups.

Once all patients who were still ongoing in Period 1 at the time of the placebo group discontinuation will either complete or early terminate from Period 1, and are randomized into

Period 2 (if applicable), randomization into Period 2 will no longer be performed, as at that point, all patients in Period 1 will be assigned to TV-44749 treatment groups and will continue their treatment assignment in Period 2 as well.

Period 1 will remain blinded until database lock for efficacy, including for patients randomized after the discontinuation of the placebo treatment group as long as they are still in Period 1. After the data are locked for efficacy analyses, the study may continue in an unblinded manner.

Period 1 efficacy data collected from patients randomized after discontinuation of the placebo treatment group will not be included in the primary analysis. Therefore, revealing of Period 1 treatment assignment (ie, since patients will be continuing their treatment assignment in Period 2) for patients who were randomized to the study after discontinuation of the placebo treatment group will not be considered unblinding.

Additional details regarding maintenance of randomization and blinding are described in Section 6.10 of the study protocol.

2.3. Independent Data Monitoring Committee

During the conduct of this study, an Independent Data Monitoring Committee (IDMC) will review accumulated unblinded safety, pharmacokinetic, and efficacy data on a regular basis, as detailed in the IDMC charter, to evaluate the safety of the product for the purpose of ensuring the continuing safety of the study patients and overseeing study conduct issues, as applicable.

The IDMC will be composed of independent physicians with expertise in the relevant therapeutic area and other relevant experts, such as a statistician and a pharmacokinetic expert. The IDMC will receive safety data periodically in an unblinded fashion.

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 and the unblinded statistician to provide the necessary data for review.

Based on the IDMC interim reviews, the IDMC can make recommendations on study conduct including study termination. After at least 50% of patients who were randomized completed Period 1 PANSS assessment in Week 8 visit, a conditional power estimation may be provided to the IDMC as part of the interim reviews. The conditional probabilities for each of the 3 active treatment groups compared to placebo will be incorporated into the benefit-risk evaluation and decision-making if the IDMC considers study termination. Further details can be found in Section 15.

In addition, the IDMC will review each case of suspected Post injection Delirium/Sedation Syndrome (PDSS) and adjudicate it based on the diagnosis criteria for PDSS, as detailed in the IDMC charter, and agreed upon between the FDA and Teva.

Further details regarding the IDMC roles and responsibilities and the data transfer process are given in the IDMC charter and the unblinded PK analysis plan. Details regarding the analysis and the conditional power approach are described in Section 15.

2.4. Stopping Rules for the Study

During the conduct of the study, all safety data will be reviewed 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 that invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

Based on the IDMC interim reviews, the IDMC can make recommendations on study conduct including study termination. After at least 50% of patients complete Period 1, conditional power may be provided to the IDMC as part of the interim reviews. This information will be incorporated into the benefit-risk evaluation and decision-making by the IDMC, if IDMC considers terminating the study. Further details regarding the conditional power approach can be found in Section 15.

In case the entire study or arms of the study will be stopped, the patients who are terminated early will be followed according to Withdrawal Criteria and Assessments/Procedures for the Patient (Section 5.4 of the study protocol).

2.5. Sample Size and Power Considerations

The following assumptions are made for the sample size determination:

1. Standardized mean difference of [redacted]
2. Homogenous variance
3. Overall 2-sided alpha of 0.05
4. Power of [redacted]
5. Randomization ratio of 1:1:1:1
6. Truncated Hochberg adjustment for multiplicity

For the sample size calculation, a 2-sample t-test and a [redacted] correction (ie, 2-sided alpha of [redacted]) were used. A simulation study with the above assumptions was conducted to evaluate the power using mixed-model repeated measures (MMRM) with truncated Hochberg as a multiplicity control method; the power to demonstrate statistically significant superiority in the 3 active treatment groups versus placebo for the primary endpoint was about [redacted].

Approximately 440 patients completing week 8 are needed to achieve the above power, per comparison. Despite the fact that missing data after discontinuation will be imputed, for simplicity, it is assumed that the ET rate in Period 1 will be [redacted], and the overall sample size is adjusted for that; hence, the number of patients to be randomized is approximately 640.

Once 440 patients complete week 8 in Period 1, randomization to placebo may be stopped, and new patients will then be randomized to the active treatment groups only (Section 2.2.2 above). The efficacy analysis will include all patients randomized until the time point at which

randomization to placebo was stopped. Patients randomized after the randomization to placebo group was stopped will not be included in the efficacy analyses.

2.6. Sequence of Planned Analyses

2.6.1. Planned Interim Analyses

Interim safety and efficacy data will be analyzed and reviewed periodically by an IDMC. Interim analyses will be performed by an unblinded analyses group independent of the sponsor (eg, unblinded statistician). The sponsor will remain blinded to the results of the interim analyses.

Data review meetings will take place according to a set schedule:

- The initial data review meeting will be triggered approximately six months after the first patient is enrolled, when approximately 40 patients will complete two months of treatment in Period 1 of the study. This meeting will include review of data collected during Period 1.
- Thereafter, data review meetings will occur on a quarterly basis and include data collected in Period 1 and Period 2.
- Unscheduled meeting or ad hoc meeting are called by the IDMC chairperson or the CSP or designee when a safety concern arises.
- If a suspected PDSS event occurs, the IDMC will review the case and meet ad-hoc to determine if it fulfills all 5 criteria in the clinical definition of PDSS (further details can be found in the IDMC charter and in the study protocol).

Each meeting is composed of an open session and a closed session (if applicable). In the closed session, unblinded data may be reviewed. Further details are depicted in the IDMC charter.

2.6.2. Final Analyses and Reporting

Final Analysis for efficacy will be performed once approximately 440 patients have completed Period 1, and completed assessment 8 weeks after the first IMP administration of the primary and key secondary efficacy endpoints (PANSS, CGI-S, PSP). At the time for the efficacy database lock, all data available (including safety assessments) from period 1will be included in the analysis and will be presented. Topline results analysis of the efficacy and safety of period 1 will be conducted according to GSCD-SOP-905 (Top-Line Results Dissemination).

Final Analysis for safety will be performed after the study completion.

This Statistical Analysis Plan and any corresponding amendments will be approved prior to the first database lock, in accordance to GSD-SOP-702 (Statistical Analysis Plan).

The randomization codes for period 1 will be maintained blinded to Teva until this Statistical Analysis Plan has been approved and until the database lock for efficacy analysis will be conducted, in accordance to GSCD-SOP-703 (Release of Blinded Randomization Codes for a Randomized Clinical Study). During the study, the randomization lists (including the patients treatment assignments) will be shared by the Randomization Code Generator vendor with an external unblinded statistician, for the purpose of generating unblinded TLGs for IDMC safety

reviews. The transfer process will be according to the Unblinding Plan (GSCD-SOP-703-FRM02) and will follow all the required steps and instructions described in this plan.

Any change prior to unblinding along with the reasons for the change will be described in the statistical analysis plan. After unblinding of Period 1, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR). In the event of any contradiction between the study protocol and the statistical analysis plan, the statistical analysis plan will prevail.

3. ANALYSIS SETS

3.1. Full Analysis Set

The full analysis set will include all patients randomized to Period 1 regardless of the actual treatment the patients received.

The treatment assignment for this analysis set will be according to the randomization assignment in the opening of each Period (Visit 2 for Period 1 and Visit 11 for Period 2).

This analysis set will be used for selected exploratory efficacy analyses and supplementary analyses, unless otherwise specified.

3.2. Efficacy Analysis Set

The efficacy analysis set will include all patients randomized to Period 1 while patients are randomized to either one of the three TV-44749 doses or placebo, regardless of the treatment the patients actually received. As. The efficacy analysis set will not include patients randomized to Period 1 after the randomization to placebo group was stopped (Section 2.2.2).

This analysis set will be used for the primary efficacy estimand and other efficacy type-I error controlled endpoints analyses specified below.

3.3. Safety Analysis Set

The safety analysis set for Period 1 will include all randomized patients who received at least 1 dose of TV-44749 or placebo. The safety analysis set for Period 2 will include all randomized patients to Period 2 who received at least 1 dose of TV-44749. For the integrated study periods summary tables (see Section 8) the safety analysis set will include all patients in the safety analysis set of period 1 that received 1 of the 3 TV-44749 treatments groups, or all patients that meet the definition of the safety analysis set of Period 2.

In each of the safety analysis sets, treatment will be assigned based on the initial treatment patients actually received in the corresponding period, regardless of the treatment to which they were randomized, and regardless of dose adjustments, unless otherwise specified. For the integrated periods summary tables, patients randomized in Period 1 to 1 of the 3 TV-44749 groups will be counted according to the initial dose they actually received in Period 1. Patients that were randomized to Placebo in Period 1 will be counted according to the initial dose of TV-44749 they actually received after the re-randomization of those patients to the 1 of the 3 TV-44749 treatment groups in Period 2, regardless of dose adjustment that may occur during Period 2.

In cases of dosing error, a decision of what is the treatment assignment for these patients will be made in a blinded manner prior to unblinding of Period 1, as applicable. The decision will be made during the statistical data review meeting and will be documented in the statistical data review document.

For IDMC monitoring during the study, the safety analysis set will use the treatment based on the randomization assignment in the opening of each period.

3.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include those patients from the safety analysis set of the integrated study periods (see Section 4.1) who received at least one dose of TV44749 and have ≥1 Olanzapine plasma concentration value available.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), median, minimum, and maximum. When appropriate, least squares means and standard errors (SE) are presented. Descriptive statistics for categorical variables include patient counts and percentages. Missing categories will be displayed as appropriate.

For the CSR and IDMC closed reports, summary tables by treatment groups will have 2 versions – (a) summary tables for Period 1; (b) summary tables for the integrated periods including patients from both Periods (Period 1 & Period 2), unless otherwise specified. For IDMC open reports, a summary tables for Period 1 and Period 2 will be generated and will only be presented overall (total).

4.2. Specification of Baseline Values

For Period 1, the baseline value for a patient is the last observed data that was collected for this patient prior to the first IMP dose administration, unless otherwise noted.

For Period 2, the baseline value for a patient is the last observed data that was collected for a patient prior to the third IMP administration (i.e., first administration in period 2, at visit 11, week 8), unless otherwise specified (see procedures and assessments which may be performed after the re-randomization to Period 2 at visit 11 in Section 6.9.1 in the study protocol).

For the integrated periods to be presented in the CSR and during the IDMC closed (in an unblinded manner) and open (in a blinded manner) sessions, the baseline values of patients initially randomized in Period 1 to TV-44749 groups will be defined as the last observed data that was collected prior to the first TV-44749 dose administration. For patients that were assigned to placebo group in Period 1, the baseline value is the baseline value for Period 2 (see above paragraph).

It should be noted that the baseline values of placebo patients will differ between tables presented in the integrated periods summaries and those presented in Period 1 summaries.

4.3. Handling Withdrawals and Missing Data

Despite the best efforts to obtain complete data, missing data is unavoidable. Unless otherwise specified, only observed patient data will be used in the statistical analyses.

According to the definition of the primary efficacy estimand, it is planned to assign multiple possible values to each missing efficacy data point (i.e., missing primary and secondary efficacy endpoints) by employing multiple imputation methodology (see Section 4.3.1 and Section 6.2.2), in addition a multiple imputation procedure is planned to assess the robustness of the underlying assumption for the primary efficacy analysis using the tipping point approach (see Section 17 and Appendix A below).

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

4.3.1. Imputation for Primary Efficacy Analysis

[redacted]

4.3.2. Ad-hoc Imputation for Safety Data

[redacted]

4.3.3. Missing items in the Quality of Life Questionnaires

[redacted]

4.3.4. Handling of Adverse Events with Missing Dates

For the purpose of this study, oral olanzapine is not considered an IMP. Any adverse event with incomplete start dates will be handled as described below, and end dates will not be imputed.

- If only the start day of an adverse event (but not the month) is missing, then the start day will be imputed as the first day (01) of the month, unless otherwise specified. If the adverse event month is not missing and it is the same month as that of randomization, the start date will be imputed as the first IMP administration date during that month.
- If both the day and month are missing and the year is the year of the date of first study treatment then the date will be imputed as the date of first IMP administration, unless the adverse event end date occurred prior to the date of first study treatment, in which case the start day-month will not be imputed. In addition, if the date of first IMP administration year is < the year of the adverse event start year then the start day-month will be imputed as 01 and January, respectively.

4.3.5. Handling of Concomitant Medication with Missing Dates

For determination of prior vs. concomitant medication, missing start or end month are imputed to January or December, respectively, and missing start or end days are imputed to day 01 and 30, respectively, unless the month is not missing then a missing day is imputed to 28. Missing dates for oral Olanzapine administered in the screening period (as part of the predefined study procedures, in accordance to the description in the study protocol) will not be imputed.

4.4. Study Days and Visits

Study days will be numbered relative to the first day of IMP administration (i.e., the first administration in Period 1). The start of treatment (Day 1) is defined as the date for which a patient receives the first dose of study drug, as recorded on the Case Report Form (CRF). Days will be numbered relative to treatment start (i.e., ..., –2, –1, 1, 2, ...; with Day 1 being the first day of study drug administration and day –1 being the day before the first day of study drug administration).

In case the Early Termination (ET)/End-of-Treatment (EOT) visit occurred on the allowed time window for any scheduled visit (according to Table 1 and Table 2 of the study protocol), and the scheduled visit results are missing, the results from the overlapping ET/EOT visit will be mapped to the scheduled visit.

In case the EOT or Follow-up visit assessments were collected out of the allowed time window, assessment results will be excluded from the by-visit summary tables but will be included in relevant listings. In addition, if there are multiple assessments at a post-baseline visit day, then the last non-missing assessment at that visit will be used, unless otherwise specified.

For the by-visit summary tables, only scheduled visits, EOT and follow-up visits will be presented. The ET visit will not be presented, and unscheduled visits will not be mapped or presented. For the 'at any time' summary statistics in the shift tables and in the presentation of Potentially Clinically Significant (PCS) summaries, all visits will be used (including unscheduled visits).

5. STUDY POPULATION

5.1. General

The full analysis set (Section 3.1) will be used for all study population summaries, unless otherwise specified. Summaries will be presented by treatment group, by period (Period 1or Integrated periods, as specified) and overall (i.e., including a total column).

5.2. Patient Disposition

Definition	Disposition/Completion status
Randomized, not treated	A patient who was randomized but did not receive any injection
Period 1 Completer	A patient who completed all Period 1 scheduled injections and Visit 11 or completed Visit 10 and has PANSS total score in allowed window of Visit 11.
Period 1+2 Completer	A patient who completed all Period 2 scheduled injections and completed EOT visit assessments. If the sponsor decides to terminate the study earlier, patients who are terminated early due to this decision and has already received at least one injection in Period 2 and completed EOT visit, will be considered as Period 1+2 completers.
Study completer	Period 1+2 completer who completed FU visit
Early Terminated in P1	A patient who received at least one injection but terminated the study before week 8 (Visit 11).
Early Terminated in P2	A patient who was randomized to P2, received at least one injection, but terminated the study before Visit 22 or before the time point at which the sponsor decides to terminate the study, the earlier of the two dates.
Discontinued before EOT	Patient who received at least one injection and did not complete EOT visit
Discontinued before FU	A patient who received at least one injection, completed EOT, and did not complete follow-up visit
Follow-up Completer	A patient who received at least one injection and completed follow-up visit assessments

In the IDMC sessions, counts and percentages of ongoing patients in Period 1 and in Period 2 will be presented (i.e., Patients who did not terminate the study at the time of the data cut-off date).

Summary table of patient disposition will include the following:

- patients screened
- patients screened but not randomized and reason(s) for not being randomized
- patients who are randomized (full analysis set)
- patients randomized but not treated
- randomized and treated (safety analysis set)
- patient completion status as defined above; patients who were early terminated in Period 1 or in Period 2 or discontinued the study as described above will also be summarized by reason for discontinuation using descriptive statistics.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics (eg age, sex, race, ethnicity, height, weight, BMI, disease length, prior use of olanzapine, PANSS score at baseline, and region) will be summarized using descriptive statistics for the full and safety analysis sets. 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.

5.4. Medical History

All medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 26.0 or later version). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients will be counted only once in each PT and SOC category. Summaries will be presented by treatment group and overall (total) using the safety analysis set.

5.5. Prior Therapy and Medication

Any prior therapy, medication, or procedure a patient has had within 30 days before IMP administration and up to the end of study, including FU, will be recorded on the CRF. The trade name and international non-proprietary name (if available), indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will code all medication according to the World Health Organization drug dictionary (WHODRUG GLOBAL B3 March 1, 2023 or later version).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once for each therapeutic class category, and only once for each preferred term category. Prior therapies and medications will include all medications taken and therapies administered before the first day of study drug administration.

5.6. Childbearing Potential and Methods of Contraception

For female patients, data related to childbearing potential and reproductive status is collected at the screening and FU visits (see Table 1 and Table 2 of the study protocol). For female and male

patients, methods of contraception is collected at the screening visit. All of the childbearing and methods of contraception data will be presented in listings.

5.7. Study Protocol Deviations

Important protocol deviations as reported in [redacted] (external vendor) Clinical Trial Management System (CTMS) will be summarized overall and for each category using descriptive statistics. All protocol deviations will also be included in a listing.

Protocol deviations pertaining to study conduct due to emergency situations (eg, COVID-19 outbreaks), including implemented contingency measures and their impact (eg, patient discontinuation from treatment with IMP 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.

In addition, it should be noted that data pertaining to protocol deviations including potential ICEs will be reviewed in a planned Statistical Data Review meeting prior to unblinding of the treatment codes. Important protocol deviations and ICEs determined by the study team in this meeting will be subsequently documented in the Statistical Data Review meeting minutes.

5.8. Hospitalization and Re-hospitalization

Hospitalization/re-hospitalization data is collected during Period 1. Patients discharge status, discharge criteria, time duration (in days) of hospitalization from first IMP dose, and whether patients were re-hospitalized will be summarized using descriptive statistics. Hospitalization will include the full extent of its duration, i.e. if hospitalization continued to period 2 then the duration of hospitalization will include the time in period 2 as well.

6. EFFICACY ANALYSIS

6.1. General

Per protocol, the efficacy analysis set (Section 3.2) was planned to be used for the primary efficacy estimand and other efficacy type-I error controlled endpoint analyses. The full analysis set (Section 3.1) will be used for exploratory efficacy analyses and supplementary analyses, unless otherwise specified. However, since the option to enroll patients into Period 1 randomization following the cessation of the enrollment to placebo (Section 6.9.3, the Study Protocol) was not exercised the efficacy and full analysis sets are indistinguishable. Thus, all analyses will be conducted on the full analysis set.

Summaries will be presented for Period 1 and for the integrated study periods (including randomization through Period 2), but only data from Period 1 will be used for the primary and secondary efficacy analysis.

6.2. Primary Efficacy Endpoint and Analysis

The primary estimand is defined in Section 1.2.1. Three pairwise comparisons of low (318mg q1m), medium (425mg q1m), or high dose (531mg q1m) of TV-44749 compared to placebo will be evaluated according to the randomization assignment in Period 1, regardless of the actual treatment received.

6.2.1. Definition of Endpoint

The primary efficacy endpoint is change from baseline to week 8 in the PANSS total score. This instrument is a 30-item scale used to identify the presence and severity of psychopathology symptoms related to Schizophrenia. Each of the items is scored from 1 (absence of symptoms) to 7 (severe symptoms presentation). The sum of the 30 items, provides the PANSS total scores, which ranges from 30 to 210.

6.2.2. Estimand

The primary efficacy estimand is described in Section 1.2.1 in accordance with the estimand framework detailed in ICH E9R1. As noted in that section, intercurrent events will be handled using the hypothetical or hypothetical-treatment policy approach, as appropriate.

6.2.3. Multiple Imputation Methods

For ICEs using the hypothetical strategy (Section 1.2.1), data collected after the ICE will be handled as analysis missing, and a multiple imputation method will be used to handle this missing data.

For ICEs of early discontinuation of randomized treatment due to lack of efficacy/disease progression, or use of prohibited antipsychotic medication that are not part of the management of patients with schizophrenia (see Section 1.2.1), imputations will be performed assuming Copy Increment from Reference (CIR) in order to estimate what would have happened if patients who discontinued early had remained in the study and had a similar ('trend') slope to patients on placebo group from the time of ICE onward (White et al 2019).

For ICEs of early discontinuation of randomized treatment due to a reason that is not lack of efficacy, imputations will be performed using MAR, i.e., assuming that the clinical effect in these patients is similar to those in the same treatment arm that did not experience an ICE during the study.

[redacted]

[redacted]

6.2.4. Primary Analysis

For each of the 200 complete datasets, a mixed model repeated measures (MMRM) analysis will be performed using the change in PANSS score from baseline to week 8 as the dependent variable, and treatment arm, study visit, treatment-by-visit interaction, stratification variables (sex and geographic region), age, and PANSS total score at baseline as covariates. An unstructured covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors. If the group size of stratification factors is small, groups may be pooled together for modeling purposes. Such a decision will be made prior to unblinding and documented in the statistical data review meeting.

[redacted]

Least squares means will be calculated of the change from baseline to week 8 in the PANSS total score for each of the 4 treatment arms and for the differences between each of the TV-44749 arms and the placebo arm. In addition, the 95% confidence intervals, and the nominal p-values

for the comparisons between each of the 3 dose strengths of TV-44749 and placebo will be calculated using PROC MIANALYZE using Rubin's rules (see Appendix B for further details and example code). The nominal p-values will be adjusted for multiplicity (see Section 7).

6.2.5. Sensitivity Analyses of the Primary Efficacy Analysis

6.2.5.1. Sensitivity Analysis #1: Assuming MAR missing data mechanism for all ICE's

In order to assess the robustness of the underlying assumptions with respect to the ICEs and ET occurring during the efficacy period (Period 1), analysis of the primary efficacy estimand will be repeated assuming MAR for all ICEs.

6.2.5.2. Sensitivity Analysis #2: 'Tipping Point' analysis

To assess the robustness of the underlying missing data assumptions, a tipping point analysis will be conducted under a range of missing data assumptions, to determine how extreme assumptions would need to be for any conclusion of superiority of active treatment compared to placebo to change. Assumptions about missing values on active and placebo arms will vary independently and will include scenarios where subjects with missing data on the active treatment group have worse outcomes than subjects with missing data on placebo group and vice versa.

For each pair of offset values applied to active treatment and placebo groups, a point estimate, 95% CI and p-value will be calculated, to obtain a combination of offset values at which the overall analysis becomes non-significant (i.e., the "tipping point").

[redacted]

6.2.6. Sub-Group Analysis

Subgroup analyses of the primary efficacy endpoint will be performed by region, sex and time from diagnosis of schizophrenia (<5 year, 5-10 year and 10 years or more), race, ethnicity and prior use of Olanzapine. The subgroup analyses will be performed on the primary efficacy estimand. For a given subgroup analysis, each group must have at least 16 patients.

6.3. Key Secondary and Other Secondary Efficacy Endpoints and Analysis

This section will describe the secondary efficacy endpoints and methods used for analysis of each of the secondary efficacy endpoints. As describes in Section 1.1 the following key secondary endpoints will be analyzed:

- Change in Clinical Global Impression-Severity (CGI-S) scale score from baseline to week 8
- Change in Personal and Social Performance Scale (PSP) score from baseline to week 8

And the following other secondary efficacy endpoints:

- Change from baseline to weeks 1, 2, 4 and 8 in the PANSS total score
- Clinical Global Impression-Improvement (CGI-I) scale at weeks 4 and 8
- Clinical Global Impression-Severity (CGI-S) scale at weeks 1, 2, 4 and 8
- Patient Global Impression-Improvement (PGI-I) scale at weeks 2, 4 and 8
- Change from baseline to weeks 4 and 8 in the Schizophrenia Quality of Life Scale (SQLS)
- Change from baseline to weeks 4 and 8 in the PSP score

The definition of each of the endpoints described above and the analysis method are described in detail in the following sections (Section 6.3.1 - Section 6.3.8)

The methods that will be used for secondary efficacy endpoints are described in Section 6.2.

By-visit analyses for the PANSS, CGI-S and PSP endpoints will be performed based on their respective estimands in addition to using the treatment policy and modified treatment policy estimands shown in Appendix D.

All other secondary efficacy endpoints will be analyzed using only the treatment policy and modified treatment policy estimand shown in Appendix D .

6.3.1. Clinical Global Impression-Severity (CGI-S) – Change from Baseline to Week 8

6.3.1.1. Definition

The investigator/trained rater will complete the CGI-S at the time points specified in Table 1 and Table 2 of the study protocol. The CGI-S allows the rater to assess the patient's current severity of illness on a scale of 1 to 7, where 1=normal/not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients.

6.3.1.2. Analysis

Model Specification

Analysis will be conducted following the same steps as described in Section 6.2.4 except that the outcome variable will instead be the change from baseline in CGI-S score.

6.3.2. Personal and Social Performance Scale (PSP) Score – Change From Baseline to Week 8

6.3.2.1. Definition

The PSP will be administered to patients at the time points specified in Table 1 and Table 2 of the study protocol. The PSP is a clinician-rated instrument that measures personal and social functioning in patients with schizophrenia. The PSP is a 100-point single-item rating scale, divided into 10 equal intervals. The score is based on the assessment of patient's functioning in 4 categories: 1) socially useful activities, including work and study; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. Higher scores represent better personal and social functioning, with ratings from 91 to 100 indicating more than adequate functioning, while scores under 30 indicate functioning so poor that intensive supervision is required.

6.3.2.2. Analysis

Analysis will be conducted following the same steps as described in Section 6.2.4 except that the outcome variable will instead be the PSP score.

6.3.3. PANSS Total Score – Change From Baseline to Weeks 1, 2, 4 and 8

By visit analysis of change from baseline will be conducted based on the treatment policy, in addition to the by visit analyses based on the primary efficacy estimand. A mixed model repeated measures (MMRM) analysis will be performed using the PANSS total score and change in PANSS total score from baseline as the dependent variable, and treatment arm, study visit, treatment-visit interaction, stratification variables (sex and geographic region), age, and PANSS total score at baseline (only for the change from baseline model) as covariates. An unstructured covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors.

6.3.4. Clinical Global Impression-Improvement (CGI-I) scale – At Weeks 4 and 8

6.3.4.1. Definition

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

The CGI-I will be administered by the investigator/trained rater at time points specified in the protocol. For this endpoint, change from baseline is not calculated because the scale scores measure change ('improvement') over time. The CGI-I during Periods 1 and 2 will be adjusted to the CGI-S score at the baseline visit (visit 2 in Period 1).

6.3.4.2. Analysis

Least squares mean and least squares means difference at endpoint will be calculated using a mixed model repeated measures (MMRM) analysis will be performed on CGI-I score as the dependent variable, and treatment arm, study visit, treatment-visit interaction, stratification variables (sex and geographic region), age, and CGI-S at baseline as covariates. An unstructured

covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors, if convergence problems occur, the steps described in Section 6.2.4 will be employed.

6.3.5. Clinical Global Impression-Severity (CGI-S) scale – At Weeks 1, 2, 4 and 8

Data will be analyzed as described in Section 6.3.1.

6.3.6. Patient Global Impression-Improvement (PGI-I) scale – At Weeks 2, 4 and 8

6.3.6.1. Definition

The PGI-I scale is a 1-item patient-rated instrument that measures improvement of the patient's disease; the patient rates the perceived change in his/her condition in response to therapy (see time points specified in the protocol). It should be noted that for this endpoint, change from baseline is not calculated because the scale scores measure change ('improvement') over time.

The patient is instructed to select a response option on a scale of 1 to 7, where 1=very much better, 2=much better, 3=a little better, 4=no change, 5=a little worse, 6=much worse, 7=very much worse.

6.3.6.2. Analysis

Least squares mean and least squares means difference at endpoints will be calculated using a mixed model repeated measures (MMRM) analysis will be performed on PGI-I score as the dependent variable, and treatment arm, study visit, treatment-visit interaction, stratification variables (sex and geographic region), age as covariates. An unstructured covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors, if convergence problems occur, the steps described in Section 6.2.4 will be employed.

6.3.7. Schizophrenia Quality of Life Scale (SQLS) – Change From Baseline to Weeks 4 and 8

6.3.7.1. Definition

The Schizophrenia Quality of Life Scale (SQLS) Revision 4 will be administered at the time points specified in the protocol and will be used to capture quality of life. The 33-item measure yields subscales pertaining to psychosocial and cognition/vitality factors. The items for each subscale are as follows:

- Psychosocial subscale (20 items - Items 3, 4, 5, 6, 8, 10, 11,13, 15, 16, 17, 18, 19, 21, 22, 24, 25, 27, 29, 30)
- Cognition/vitality subscale (13 items – Items 1, 2, 7, 9, 12, 14, 20, 23, 26, 28, 31, 32, 33).

The items are scored on a five-point scale (1 - never, 2 - rarely, 3 - sometimes, 4 - often, 5 - always). For all items, except the specific 4 items discussed below, higher scores indicate comparatively lower quality of life.

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

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

12. I felt that I could cope;

14. I slept well;

26. I felt happy.

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

Therefore, the total score, namely TS, is calculated as the total of all items minus the number of items answered, divided by the maximum possible total score, namely, and multiplied by 100.

$$TS = \frac{R4S_{tot}}{RS_{max}} \times 100$$

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

6.3.7.2. Analysis

By visit analysis of change from baseline will be conducted based on the treatment policy estimand, in addition to the by visit analyses based on the primary efficacy estimand. A mixed model repeated measures (MMRM) analysis will be performed using the change in SQLS score from baseline as the dependent variable, and treatment arm, study visit, treatment-by-visit interaction, stratification variables (sex and geographic region), age, and SQLS total score at baseline as covariates. An unstructured covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors.

Only SQLS scores recorded while the subject was receiving randomized treatment will be included in the analysis. Any values recorded after withdrawal from randomized treatment will be set to missing. No multiple imputation will be used.

6.3.8. PSP Score – Change From Baseline to Weeks 4

A mixed model repeated measures (MMRM) analysis for Period 1 will be performed using the change in PSP score from baseline as the dependent variable, and treatment arm, study visit, treatment-by-visit interaction, stratification variables (sex and geographic region), age, and PSP score (if applicable, if the model does not converge this covariate will not be used) at baseline as covariates. An unstructured covariance matrix will be used in all models. Analyses will be performed in SAS using the Kenward-Roger option to estimate the denominator degrees of freedom and standard errors. Least squares mean and 95% CI of change in PSP Score from baseline to Week 4 and Week 8 will be generated.

Only PSP scores recorded while the subject was receiving randomized treatment will be included in the analysis. Any values recorded after withdrawal from randomized treatment will be set to missing. No multiple imputation will be used.

6.4. Other Efficacy Endpoints Analysis

[redacted]

6.4.1. Positive and Negative Symptom Scale (PANSS) – Change From Baseline to End of Treatment Period in Period 2

6.4.1.1. Definition

See Section 6.2.1.

6.4.1.2. Analysis

MMRM model will be repeated for this endpoint

```
proc mixed data=data method=reml;
  class trt01pn avisitn subjid;
  model [variable] = trt01pn avisitn trt01pn*avisitn sex region age
baseline/ddfm=kr cl;
  repeated avisitn/subject=subjid type=un;
  lsmeans trt01pn*avisitn/cl;
run;
```

Results Presentation

Summary statistics will be produced for absolute and change from period 2 baseline, by timepoint and treatment (TV-44749 318mg, TV-44749 425mg, TV-44749 531mg and former placebo assignment, i.e., overall 6 groups for period 2)

Least-square means of absolute value and change from baseline, including standard errors and 95% CI, will be presented at each timepoint by treatment group.

6.4.2. Clinical Global Impression-Severity (CGI-S) – Change From Baseline to End of Treatment Period in Period 2

6.4.2.1. Definition

See Section 6.3.1.1.

6.4.2.2. Analysis

MMRM model will be repeated for this endpoint, see Section 6.4.1.2.

6.4.3. Personal and Social Performance Scale (PSP) score – Change From Baseline to End of Treatment Period in Period 2

6.4.3.1. Definition

See Section 6.3.2.1.

6.4.3.2. Analysis

MMRM model will be repeated for this endpoint, see Section 6.4.1.2.

6.4.4. Clinical Global Impression-Improvement (CGI-I) scale at End of Treatment Period in Period 2

6.4.4.1. Definition

See Section 6.3.4.1.

6.4.4.2. Analysis

Analysis will be performed on the actual values (AVAL) that represent the improvement in the CGI-S at baseline as a covariate similar way presented inSection 6.3.4.2, on the treatment policy estimand. For this endpoint, change from baseline is not calculated because the scale scores measure change (‘improvement’) over time,

6.4.5. Patient Global Impression-Improvement (PGI-I) scale at End of Treatment Period in Period 2

6.4.5.1. Definition

See Section 6.3.6.1.

6.4.5.2. Analysis

Analysis will be performed on the actual values (AVAL) that represent the improvement in a similar way presented inSection 6.3.4.2, on the treatment policy estimand. For this endpoint, change from baseline is not calculated because the scale scores measure change (‘improvement’) over time.

6.4.6. Schizophrenia Quality of Life Scale (SQLS) – Change From Baseline to End of Treatment Period in Period 2

6.4.6.1. Definition

See Section 6.3.7.1.

6.4.6.2. Analysis

MMRM model will be repeated for this endpoint, see Section 6.4.1.2.

6.4.7. [redacted]

6.4.7.1. Definition

[redacted]

6.4.7.2. Analysis

[redacted]

7. MULTIPLE COMPARISONS AND MULTIPLICITY

[redacted] any p-value associated with these comparisons will be considered as nominal and will not be used for inference.

[redacted]

- [redacted]
- [redacted]

Multiplicity adjustments will be made to p-values obtained using Rubin's rules (see Section 6.2.3). [redacted]

8. SAFETY ANALYSIS

8.1. General

Safety analyses will follow the safety estimand approach using the safety analysis sets.

Safety will be assessed by qualified study personnel by evaluating reported adverse events (including serious adverse events, extrapyramidal symptoms, injection pain, injection site findings and Injection Site Reactions [ISRs]), vital signs (blood pressure, pulse and orthostatic changes, and temperature), body weight and BMI, laboratory tests, ECG, concomitant medication use, time to all-cause discontinuation, all-cause discontinuation rates and discontinuation rates due to adverse events (tolerability), time to all discontinuation by reason, and safety rating scales (including Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson-Angus Scale [SAS], C-SSRS, and CDSS).

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

The safety analysis will be performed separately for Period 1 and for the integrated study periods.

The safety analysis for Period 1 will be performed by treatment group and overall (total).

The safety analysis for the integrated study periods that will be presented in the CSR and in the IDMC closed reviews, will be performed by treatment group. Specifically, for IDMC closed reviews, patients rolling over from Placebo group will be distinguished from patients who continued their active treatment assignment from Period 1. Data from Period 1 for placebo patients will not be included in the integrated summaries.

For the open sessions of the IDMC reviews, data from Period 1 and from Period 2 will be presented separately. Summary tables will be generated for each period and will only be presented as a single total column.

For the following safety variables: Adverse events, Clinical laboratory results, ECG, weight and BMI and Vital signs, a separate safety summary will be presented for the 'While on Treatment' period, defined as the period between the first IMP administration visit until and including the End of Treatment visit (including the Early Termination visit if conducted during this period). In addition a separate safety summary table and listing will be presented for the Follow-Up period, defined as the period after the End of Treatment/Early Termination visit until the end of the study.

In the case of dose adjustment (which is allowed from Visit 12 during Period 2), the patient will be regarded according to the *initial* dose they actually received in the corresponding period. In addition, separate safety summaries will be generated for AEs, SAEs, exposure to study treatment, potential clinically significant safety measures, excluding the patients with at least one dose adjustment during Period 2. Analysis may also be initiated if the results of those summaries are judged to be significantly different from the results of the safety measurements according to the *initial* actual dose. A separate set of safety tables may be generated in which the patient will be regarded according to the actual dose, by the following exposure duration: ≤6 months, >6 and ≤12 months, >12months. Each patient may be calculated more than once, according to the exposure duration at each dose.

Analyses will be conducted on the raw values and changes from baseline at each time point, as appropriate. Summaries will be presented by treatment group and overall (total), unless otherwise stated.

8.2. Duration of Exposure to Study Drug

Duration of exposure to study drug (days) for individual patients will be calculated during the integrated study periods as the number the days patient was exposed to treatment (last day of TV-44749 administration – first day of TV-44749 administration + 28). For patients randomized to placebo in Period 1 who were re-randomized to Period 2, the first TV-44749 injection is at Visit 11 (week 8), the day of re-randomization for Period 2.

Duration of treatment (days) will be summarized for integrated study periods using descriptive statistics. Summaries of the total exposure toTV-44749, will be presented by treatment group, and for overall (total) for patients on active treatment. For an individual patient who was assigned to the placebo group in Period 1, the total duration of exposure will be counted only in Period 2 (the exposure to placebo in the first 8 weeks will not be included in the summary).

Duration of exposure (days) will also be presented by number of injections for the integrated periods using the mutually exclusive categories:

- 0 injections
- 1 injection
- 2 injections
- ≥3 to ≤6 injections
- ≥7 to ≤9 injections
- ≥10 to ≤12 injections
- >12 injections

In addition, summary of exposure to study TV-44749 doses will be calculated using the categories:

- <6 months
- ≥6 to <12 months,
- ≥12 months.

The total number of TV-44749 injections by dose and overall (total) will be presented. Exposure categories including at least 6 and 12 months are defined as at least 6 and 12 injections plus 28 days following the last injection, respectively.

All summary tables for duration of exposure will be presented by treatment group and overall (total).

Unless otherwise specified, in cases where there was a dose adjustment, exposure will be calculated according to the *initial* actual dose received in Period 1 (or the initial actual dose received in Period 2) regardless of dose adjustments. In addition, separate safety summaries will be generated, excluding the patients with at least one dose adjustment event during the study.

If the results of those summaries are judged to be significantly different from the results of duration of exposure summaries according to the randomized dose, additional analyses will be conducted. These analyses may include shift tables of randomized dose to dose adjustments. If the proportion of patients with dose adjustment will be high, additional table according to the actual cumulative exposure by dose will be presented. For this table a patient may contribute to more than 1 dose level, and the duration of exposure at each dose will be determined by the time from 1st administration of the dose to the day of the dose adjustment minus 1 or the last administration, as appropriate. For example if a patient that was re-randomized to medium dose following placebo in Period 1, and then underwent a dose adjustment to the high dose for the 3rd injection, this dose will be used until the end of study. Thus, assuming that all injections are administered exactly 28 days apart, the patient will contribute 2*28-1= 55 days to the medium dose group, and 28*10 =280 days to the high dose group.

8.3. Study Drug Compliance

Not applicable for the current study. Drug compliance during study duration will not be assessed.

8.4. Adverse Events

Adverse events will be collected and recorded from the time a patient signs the informed consent to the end of follow-up period.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 26.0 or later). Unless otherwise specified, adverse events will be summarized by SOC and preferred term, with preferred terms within SOCs presented in descending order of patient incidence. Multiple records with the same PT or SOC category and adverse event onset date for the same patient, or with overlapping or consecutive dates, are counted only once for the adverse event with the highest severity and seriousness.

Adverse events summaries will be presented for Period 1 separately and for the integrated study periods separately. Adverse events that started in Period 1 and ended in Period 2 will be reported only in Period 1, and will be presented only once in the integrated summary table.

Summaries will include treatment-emergent adverse events that are defined as adverse events that occurred at or after the first IMP injection was administered through the end of the treatment (including the assessment collected in the End-of-Treatment/ Early Termination visit). Additional summaries will be presented for the follow-up period (after the End of Treatment/Early Termination visit and until the end of the study).

Summaries will be presented for all adverse events (overall and by severity), including adverse events defined by the investigator as related or with missing relationship to IMP treatment and/or device (overall and by severity), serious adverse events, serious adverse device events and adverse events and adverse device events causing withdrawal from the study and withdrawal from the treatment. All summaries will be presented by treatment group and overall (total), using exposure categories.

Protocol defined adverse event of special interest (PDAESI) (section 8.1.7 of the study protocol) will also be summarized and presented by treatment group and by visit..

The summary tables for adverse events will be presented by the treatment group to which the patient were assigned according to the safety analysis set. A separate summary tables will be presented, excluding the patients with at least one dose adjustment. Additional analysis may be initiated if the results of those summaries will judged by the study team to be significantly different.

Patient listings of serious adverse events, adverse events leading to treatment discontinuation and study withdrawal, and adverse events leading to death will be presented. Patient's dose at the time of the Adverse Event onset will be included in all listings.

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

8.5. Deaths

A summary table and detailed listing will be provided of deaths by treatment group.

8.6. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, urinalysis) are detailed in Table 9 of the study protocol. Central laboratory value and changes from baseline will be summarized. Laboratory test results will be presented in standard international (SI) units. Listings will include all laboratory values (central and local laboratories).

Laboratory test results will be presented for Period 1 and for the integrated study periods.

Summary statistics for chemistry, hematology and urinalysis laboratory tests will be presented at time points detailed in the Schedule of Assessment Table 1 and Table 2 of the study protocol.

Laboratory values and changes from baseline to each scheduled visit will be summarized using descriptive statistics.

Shifts (below, within, and above the normal range) from baseline to each scheduled visit including "at any visit" assessment (as a separate visit) will be summarized using patient counts. Summaries of potentially clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics with the criteria specified in Table 2 below.

Summaries will be presented for the While on treatment period (starting from the baseline visit in Period 1 to the EOT visit, including ET visit if conducted during this period). A separate summary will be presented for the Follow-Up period (any visit conducted after EOT visit and until the end of the study).

Table 2: Criteria for Potentially Clinically Significant Laboratory Values

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

8.6.1. Laboratory Values Meeting Hy's Law Criteria

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

- ALT or AST increase of >3x the ULN
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)

All incidences will be listed.

8.6.2. Other Clinical Laboratory Tests

8.6.2.1. Virology and Thyroid Screening Tests

At the timepoints defined in Table 1 and Table 2 of the study protocol, patients will be tested for HIV, hepatitis B surface antigen and hepatitis C antibody, thyroid stimulating hormone (TSH), triodothyronine (T_3) and thyroxine (T_4). Virology is only performed at screening. Thyroid tests will be performed at screening and at the pre-defined time points due to potential effects on clinical psychiatric symptoms.

The data will be presented as listings.

8.6.2.2. Human Chorionic Gonadotropin and Follice-Stimulating Hormone Tests

A serum β-HCG test will be performed for all women of childbearing potential at screening and the FU visit (see Table 1 and Table 2 of the study protocol). Urine β-HCG (dipstick) test will be performed for women of childbearing potential at all visits where study drug is administered (prior to study drug administration) and at the ET and EOT visits.

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.

Note: Urine β-HCG (dipstick) test will not be performed for Both Postmenopausal women (no menses for at least 12 months [without an alternative medical cause] prior to screening and with follicle-stimulating hormone (FSH) concentration above 35 U/L) and women who are sterile (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or congenitally sterile).

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

8.6.2.3. Urine Drug Screen

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

Any findings will be listed.

8.6.2.4. Prolactin

Blood samples will be obtained for prolactin test at the time points specified in Table 1 and Table 2 of the study protocol. The test results will remain blinded to the sponsor until the database lock for efficacy analysis.

Note: in order to maintain the blind, prolactin level results, other the ones obtained before the first IMP administration per protocol, will not be available for review by the sponsor or the sites until visit 13 (8 weeks into Period 2).

The test results will be presented as described for all the clinical laboratory test results outlined in Section 8.6 above. In addition, summaries of potentially clinically significant abnormal values from baseline - from normal to 2x ULN and 5x ULN - will be presented.

8.7. Physical Examinations

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 of the study protocol. Full physical examination will be conducted at the screening visit and unscheduled visits only; the rest of the visits will include an abbreviated physical examination (including weight). 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. An abbreviated physical examination (general appearance, head, eyes, ears, nose, throat, lung, heart, skin, and extremities) will be conducted at the other time points and will include a brief neurological examination that includes examination of a subset of cranial nerves controlling vision and motor examination of a subset of larger muscle groups, including an assessment of muscle tone, reflexes, gait, and involuntary movements.

Any new 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 8.5 of the study protocol.

Descriptive statistics for weight will be provided. The values and percent changes from baseline to each visit in period 1 and for the integrated study periods will be presented for the safety analysis set. Weight shifts from reference to each visit by treatment group will be presented, where the reference is the screening measurement, using the following limits: '<0', '(0-7%]', '(7-10%]' and '≥10%

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

In addition, BMI values and changes from baseline to each visit (which weight was collected) in period 1 and for the integrated study periods will be presented for the safety analysis set.

8.8. Vital Signs

Vital signs (blood pressure [systolic/diastolic], pulse and orthostatic changes, respiratory rate, and temperature) will be measured at each in-clinic visit pre-injection. [redacted] Vital signs will also be measured in the event of an injection site pus-containing lesion (abscess, infection, or inflammation), ulceration, or necrosis (Table 1 and Table 2 of the study protocol).

[redacted]

[redacted]

Table 3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

8.9. Electrocardiography

A standard 12-lead ECG will be recorded at the time points detailed in Tables 1 and 2 of the study protocol. Triplicate measurements (approximately 5 minutes apart) will be performed at screening and baseline and single measurements at other in-clinic visits, as specified at the study protocol.

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

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

1. If ERT interpretation is 'normal' then investigator interpretation on the same date will be derived as 'normal';
2. Otherwise investigator interpretation will not be derived.

Shifts (normal and abnormal) from baseline to overall result interpretation at each scheduled visit including "at any visit" assessment (as a separate visit) will be summarized using patient counts.

For overall result interpretation the worst post baseline finding for the patient (the abnormal finding if there are both normal and abnormal findings) will be used in the summaries.

[redacted]

8.10. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored and recorded during the study. Details of prohibited medications may be found in Section 6.7 of the study protocol. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant therapies and medications will be summarized by therapeutic class category and preferred term using descriptive statistics. Patients are counted only once in each therapeutic class, and only once in each preferred term category. Concomitant therapies and medications will include all medications up to the end of study as defined in the study protocol. This will also include medication that a patient had started taking before entering the study as long as the patient had continued to take this medication during the study.

A separate summary will be presented for Period 1 and for the integrated study periods. A separate safety summaries will be presented for the On Treatment period (baseline visit until EOT visit, including ET if conducted during this period) and for the Follow-Up period (any visit after the End of Treatment/Early Termination visit until the end of the study).

8.11. Post-injection Delirium/Sedation Syndrome

If any PDSS event will occur during the study, the event will be presented as part of the AEs, PDAESI, SAE (if relevant) by Treatment Group. In addition, suspected PDSS cases will be listed.

8.12. Other Safety Assessments

8.12.1. Columbia-Suicide Severity Rating Scale (C-SSRS) - Assessment of Suicidality

The C-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior (Posner et al 2011). The C-SSRS is a semi-structured interview that captures the

occurrence, severity, and frequency of suicide-related thoughts and behaviors. Any positive answer to the behavior sub- components at screening or baseline identifies a patient with "Suicidal Behavior at Screening" or "Suicidal Behavior at Baseline" respectively. The C-SSRS interview will be administered at screening (baseline/screening version), and the "Since Last Visit" version will be administered at all other time points, as described in Table 1 and Table 2 of the study protocol).

For post-screening/post-baseline visits, any positive answer to the behavior subcomponents in any of the post screening or baseline assessments, identifies a patient as with "Suicidal Behavior Post Dosing". Same derivation will be done also for "Suicidal Ideation post Dosing". A patient identified with either "Suicidal Behavior Post Dosing" or with "Suicidal Ideation Post Dosing" is also classified as with "Suicidal Behavior or Ideation Post Dosing", the derivation should be done separately for period 1 and for the integrated study periods.

Frequency counts and percentages of the C-SSRS outcomes: Suicidal Behavior at Baseline in Period 1 and integrated periods, Suicidal Ideation at Baseline in Period 1 and integrated periods, Suicidal Behavior or Ideation at Baseline in Period 1 and integrated periods, Suicidal Behavior Post Dosing, Suicidal Ideation Post Dosing, Suicidal Behavior or Ideation Post Dosing, and shifts from baseline for Period 1 and integrated periods will be summarized.

8.12.2. Abnormal Involuntary Movement Scale (AIMS)

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

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

The AIMS total score and the individual score for each of the AIMS items 8-10 and changes from baseline will be presented, separately for Period 1 and for the integrated study periods, using descriptive statistics. Shift from baseline analysis of AIMS items 11-14 during Period 1 and during integrated study period will be presented.

Safety analysis set will be used as appropriate.

8.12.3. Simpson-Angus Scale (SAS)

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

The SAS mean score and changes from baseline during Period 1 separately and during the integrated study periods will be presented using descriptive statistics by treatment group using safety analysis set.

8.12.4. Barnes Akathisia Rating Scale (BARS)

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

BARS total score, global clinical assessment of severity values, and changes from baseline to each visit will be summarized using descriptive statistics - during Period 1 and integrated study periods by treatment group.

8.12.5. Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS will be performed at the time points specified in Table 1 and Table 2 of the study protocol. The CDSS is specifically designed to assess the level of depression separate from the positive, negative, and extrapyramidal symptoms in schizophrenia. This clinician-administered instrument consists of 9 items, each rated on a 4-point scale from 0 (absent) to 3 (severe) that are added together to form the CDSS depression score for the patient.

Descriptive statistics of CDSS depression score values and changes from baseline to each visit will be presented - during Period 1 and integrated study periods by treatment group.

9. LOCAL TOLERABILITY VARIABLES AND ANALYSIS

[redacted]

Table 4: Assessment of Local Tolerabilty (Injection Site Findings)

Test	Response
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

9.1. Assessment of Local Tolerability and Pain

[redacted]

9.2. All-cause Discontinuation Rate Assessment

All-cause discontinuation rates and discontinuation from treatment 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. The randomization date for the integrated study periods will be defined in accordance with treatment assignment in period 1; for patient who was randomized to placebo in period 1, the randomization day is the day of randomization to period 2, and for patient who was randomized to one of the three active treatment group in period 1, the randomization date is the day of randomization to period 1.

Kaplan-Meier curves for the time to discontinuation as a result of all causes will be plotted by treatment group, for period 1, and for the integrated study period.

The safety analysis set will be used for the analysis.

10. PHARMACOKINETIC ANALYSIS

[redacted]

11. PHARMACODYNAMIC ANALYSIS

Pharmacodynamic analysis is not planned this study.

12. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The pharmacokinetic/pharmacodynamic analysis will be detailed in a separate analysis plan, and results will be reported separately from the main study results.

13. BIOMARKER AND PHARMACOGENETIC ANALYSIS

[redacted]

14. [redacted]

[redacted]

15. INDEPENDENT DATA MONITORING COMMITTEE - EFFICACY EVALUATION

15.1. General

There is no interim analysis in this study to demonstrate early efficacy or futility. However, a presentation of summary statistics for primary endpoint will be displayed as part of the general risk benefit evaluation that the IDMC might require.

The efficacy analysis set (Section 3.1) will be used for the interim analysis. Summaries will be presented by treatment group as randomized and for overall (total), unless specified otherwise. Only data from Period 1 will be considered for efficacy purposes.

15.2. Conditional Power Evaluation

Due to the ultra-fast recruitment to the study in the first IDMC meeting where the criterion of randomizing at least 50% of patients was met, enrollment was nearly complete. Consequently, conditional power deemed unnecessary.

16. STATISTICAL SOFTWARE

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

17. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

17.1. Primary Efficacy Estimand

The primary efficacy estimand was modified after protocol approval to allow the use of measurements after a short use of prohibited oral antipsychotic medication during the first 6 weeks in Period 1. This change was based on the understanding of the study team that there are few cases of patients that received prohibited antipsychotic medication early after randomization, and that a short term use of prohibited antipsychotics as part of the management of acute agitation in schizophrenia exacerbation during the first 6 weeks of the study is not expected to affect the treatment effect at week 8 nor the interpretation of the results. Moreover, this approach reflects more accurately the real world management of patients with schizophrenia experiencing an exacerbation and thus would support the principle of intention to treat.

17.2. Conditional Power Evaluation for IDMC

Initially this study's accrual period was expected to be 19 months, however at the time of writing this SAP, the revised expected accrual period is 11 months. As stated in the protocol, a conditional power calculation was planned to be provided to the IDMC when 50% of patients completed Visit 11 as a means of evaluating whether termination of the study was warranted if safety concerns arose. However, since the accrual rate is much higher than anticipated, it is now expected that at the time of reaching 50% accrual, the additional information gained for the remainder of the study would be limited. In fact, at the next planned IDMC meeting, there was only approximately 10% of person-time remaining before the end of accrual in Period 1 (i.e., the time at which efficacy will be evaluated).

Therefore, given these calculations that support an unexpected fast accrual rate, it has been decided that the conditional power analysis will not be conducted as planned. This decision was vetted with the IDMC and the final arbitration will be documented in the IDMC meeting minutes.

17.3. While on Treatment Estimand

This estimand for analyzing efficacy endpoints using the treatment policy strategy replaces the while on treatment estimand.

17.4. Estimand Using the Modified Treatment PolicyStrategy

This estimand is planned to extend the understanding of the treatment effect estimated by the treatment policy strategy for evaluating the 'true' treatment effect of TV-44749 versus placebo on efficacy endpoints, not confounded by concomitant use of other antipsychotics from baseline to week 8.

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APPENDIX A. LIST OF DISALLOWED MEDICATIONS

The following list describes the restricted medications for the study due to interactions with cytochrome P450 1A2. Several medications may require dose adjustments or specific monitoring when combined with olanzapine. This should be assessed based on the ZYPREXA official label.

For any questions about prohibited medications, the sponsor or medical monitor should be contacted.

Medication class	**Drug name**
Antidepressants	Fluvoxamine
Antipsychotics	Any known antipsychotics besides oral olanzapine at screening and TV-44749
Antibiotics	Rifampin
Antiepileptics	Carbamazepine

APPENDIX B. MULTIPLE IMPUTATION DETAILS

Primary Analysis

Data preparation

Intercurrent events (ICEs) are defined in Table 1 (Section 1.2.1). Visits where an ICE occurred will be labelled with the appropriate ICE type:

USUBJID	TRT01P	AVISITN	AVISIT	ADY	AVAL	CNSRDT	EVNTDESC
[redacted]	Placebo	4		Visit 4/ Week 1		[redacted]	
[redacted]	Placebo	5	[redacted]	Visit 5/ Week 2	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	6		Visit 6/ Week 3	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	7		Visit 7/ Week 4	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	8		Visit 8/ Week 5	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	9		Visit 9/ Week 6	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	10		Visit 10/ Week 7	2	[redacted]	Prohibited antipsychotic
[redacted]	Placebo	11		Visit 11/ Week 8	2	[redacted]	Prohibited antipsychotic

The classification of intercurrent events (ICEs) will be performed as follows:

Event	CNSR	EVNTDESC
Early termination from randomized treatment due to "Lack of Efficacy" or an Adverse Event of “Exacerbation of schizophrenia”	1	ET due to lack of efficacy
An oral antipsychotic use was documented in the CRF (Concomitant Medication or Protocol Deviations) and reviewed in a blinded manner in the statistical data review meeting and does not meet the conditions in Section 1.2.1	2	Prohibited antipsychotic
Early termination from randomized treatment due to other reasons	3	ET due to other reasons

Multiple Imputation Method

Parameter Estimation Model

[redacted]

Imputation of ICE data under MAR

[redacted]

Imputation of ICE data under MNAR

[redacted]

Analysis model

[redacted]

[redacted]

[redacted]

Tipping Point Analysis (Two dimensional)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Tipping Point Analysis (One dimensional)

The above process will be repeated, but the delta value for the placebo group will be held at zero. The range of delta values and increments may be adjusted post hoc depending on the observed treatment effect in order to most effectively characterize the “tipping point”.

[redacted]

APPENDIX C. MULTIPLE COMPARISONS DETAILS

APPENDIX D. SUMMARY OF ENDPOINTS BY ESTIMAND STRATEGY FOR PERIOD 1

Family of Endpoint	Variable	Primary Estimand	Key Secondary Estimand	Sensitivity using MAR	Treatment Policy	Modified Treatment Policy
Primary	Change from baseline to week 8 in PANSS score	√		√	√	√
Key secondary	Change from baseline to week 8 in CGI-S score		√	√	√	√
	Change from baseline to week 8 in PSP score		√	√	√	√
Other Secondary	[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]

Additional analyses may be conducted (e.g., testing other scheduled visit or analyses extending the use of estimands not as outlined in the table); these analyses will be considered as exploratory.