Clinical Study Protocol

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

Protocol with Amendment 01 Approval Date: 15 February 2024

Clinical Study Protocol with Amendment 01

Study Number 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

***Brief Title*: A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy and Safety of TV-44749 in Adults with Schizophrenia**

***Lay Title:* A Study to Test if TV-44749 is Effective in Relieving Schizophrenia**

(The SOLARIS Study - Subcutaneous OLAnzapine Extended-Release Injection Study)

Efficacy and Safety Study (Phase 3)

IND number: 128851; NDA number: N/A; BLA number: N/A; EudraCT number: 2022-001865-11

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Version Date: 15 February 2024

Sponsor

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

Sponsor's Authorized Representative

[redacted]

Teva Pharmaceutical Industries Ltd.

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; the protocol; and the sponsor's Standard Operating Procedures (SOPs).

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INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 01

Version Date: 15 February 2024

IND number: 128851; NDA number: N/A; BLA number: N/A; EudraCT number: 2022-001865-11

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

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

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

Principal Investigator	Signature	Date

Executed signature pages are maintained within the Investigator Site File and the Trial Master File

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted] Teva Pharmaceutical Industries Ltd.		

Executed signature pages are maintained within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 01

Version Date: 15 February 2024

IND number: 128851; NDA number: N/A; BLA number: N/A; EudraCT number: 2022-001865-11

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Article 45 or 46 of 1901/2006 does not apply

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

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

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

Coordinating Investigator _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

Coordinating Investigator	Signature	Date

Executed signature pages are maintained within the Trial Master File

PROTOCOL AMENDMENT DETAILS

Document History	
Administrative Letter 05	05 September 2023
Administrative Letter 04	31 July 2023
Administrative Letter 03	21 March 2023
Administrative Letter 02	15 February 2023
Administrative Letter 01	27 November 2022
Original Protocol	01 September 2022

Current Amendment 01 15 February 2024

As of 29 January 2024, 675 participants have been randomized to the trial.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary reason for this amendment is to describe the course of action for Period 2 participants following the completion of the Period 1 efficacy analyses and the top line results availability. This amendment also provides clarity to assessments and processes in several sections and incorporates all changes from 5 prior administrative letters (see Appendix N for details).

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

Section Number and Name	Description of Change	Brief Rationale
1.2. Study Scheme 1.3. Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1 Table 2. Study Procedures and Assessments for Period 2 4.1. General Study Design and Study Schematic Diagram: Period 2 (up to 48 weeks) 6.9. Randomization and Blinding 6.9.2. Blinding Procedures	Updated timeframe of the revealing of treatment assignment (Administrative Letter 04)	To provide clarification
1.3 Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1 Table 2. Study Procedures and Assessments for Period 2 Table 3. Study Procedures and Assessments for a Potential Post-injection Delirium/Sedation Syndrome Event 4.1. General Study Design and Study Schematic Diagram: Procedures for Potential Post-injection Delirium/Sedation Syndrome 6.11. Total Blood Volume 8.10. Post-injection Delirium/Sedation Syndrome Monitoring	Added option of urine drug screen in certain cases (Administrative Letter 02)	To provide clarification
1.3 Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1 Table 2. Study Procedures and Assessments for Period 2 4.1. General Study Design and Study Schematic Diagram: Period 2 (up to 48 weeks) Early Termination and Follow-up Period	Updated end of treatment (EOT) and follow-up (FU) allowed visit windows (Administrative Letter 03)	To provide clarification
1.3 Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1, footnotes f and k Table 2. Study Procedures and Assessments for Period 2, footnotes a and f	Updated footnote text	To correct inconsistences and provide clarification

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1, footnote a	Updated the allowed duration of the screening period under special circumstances (Administrative Letter 03)	To provide clarification
4.1, General Study Design and Study Schematic Diagram: Screening (up to 8 days Prior to Randomization to Period 1)		
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT: Procedures for Screening/Visit 1 (Day -8, Weeks -2 to -1)		
1.3 Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1, footnote dd	Update the Readiness for Discharge Questionnaire (RDQ) rater qualifications (Administrative Letter 03)	To provide clarification
4.1 General Study Design and Study Schematic Diagram: Period 1 (8 weeks)		
1.3 Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1 Table 2. Study Procedures and Assessments for Period 2	Updated Injection site reactions to injection site findings (local tolerability assessments) (Administrative Letter 04)	To provide clarification
6.9.1. Procedures and Assessments to be Performed Before and After Randomization into Period 2 at Visit 11 (Week 8)		
8. ASSESSMENT OF SAFETY		
8.8. Assessment of Local Tolerability and Pain		
8.8. Assessment of Local Tolerability and Pain: Table 10. Assessment of Local Tolerability (Injection Site Findings and Pain), Title		
APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
1.3. Schedule of Study Procedures and Assessments: Table 1. Study Procedures and Assessments for Period 1, footnote h	Updated safety laboratory tests during visit 3 (Administrative Letter 04)	To provide clarification

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Study Procedures and Assessments: Table 2. Study Procedures and Assessments for Period 2	Updated the timing of assessments before and after randomization at visit 11 (Administrative Letter 04)	To provide clarification
4.1. General Study Design and Study Schematic Diagram: Period 2 (up to 48 weeks)		
2.1.3 Olanzapine for Subcutaneous Use (TV-44749)	Updated description of TV-44749 as a combination product (Administrative Letter 04)	To provide clarification
6.1.1. Test Investigational Medicinal Product		
3.2.2. Other Efficacy Estimand	Added text regarding estimand for key secondary endpoints	To align with final statistical analysis plan
4.1 General Study Design and Study Schematic Diagram: Screening (up to 8 days Prior to Randomization to Period 1)	Updated Positive and Negative Syndrome Scale (PANSS) [redacted] requirement and analysis (Administrative Letter 03)	To provide clarification
5.1. Patient Inclusion Criteria, criterion b		
7.1.1. Positive and Negative Syndrome Scale		
APPENDIX D. ETHICS: Informed Consent		
4.1. General Study Design and Study Schematic Diagram: Screening (up to 8 days Prior to Randomization to Period 1)	Updated timing of providing informed consent by the caregiver (Administrative Letter 04)	To provide clarification
5.1. Patient Inclusion Criteria, criterion h		
4.1. General Study Design and Study Schematic Diagram	Added text for dose adjustment following outcome of primary endpoint analysis	To describe the course of action following the outcome of primary efficacy analysis
6.9.4 Treatment of Study Participants Following Period 1 Efficacy Topline Results Availability		
5.1. Patient Inclusion Criteria, criterion a	Updated age limit (Administrative Letter 01)	To correct an error and provide clarification.
5.2. Patient Exclusion Criteria, criteria n and w	Updated exclusion criteria language (Administrative Letter 01, Administrative Letter 03)	To correct an error and provide clarification
6.1.1 Test Investigational Medicinal Product	Updated text to indicate the injection will be rotated between quadrants.	To provide additional clarification and align with the pharmacy manual

Section Number and Name	Description of Change	Brief Rationale
6.1.2. Placebo Investigational Medicinal Product	Updated description of TV-44749 placebo as a combination product	To provide clarification
6.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products		
6.7. Prior and Concomitant Medication or Therapy	Added non-pharmacological treatment and updated allowed concomitant medications (Administrative Letter 01)	To provide clarification
	Updated text regarding allowed antidepressants	To provide clarification
6.7.1.2. Antidepressants and Mood Stabilizers: Period 2	Updated text to indicate that only antidepressants approved according to the study protocol are allowed to be used during the study (Administrative Letter 05)	To provide clarification
6.9 Randomization and Blinding	Updated text for blinding and unblinding	To provide clarification
6.9.3 Discontinuation of the Placebo Treatment Group		
6.10.2. Blinding and Unblinding	Updated timing of unblinding of prolactin levels during the study (Administrative Letter 01)	To provide clarification
	Added a back-up process to unblind a patient in case of internet connection issues (Administrative Letter 01)	To provide clarification
6.11. Total Blood Volume	Updated text for total blood volume (Administrative Letter 01, Administrative Letter 04)	To correct an error and to provide clarification
7.1.1. Positive and Negative Syndrome Scale	Updated the data sources for PANSS, including informant data recording (Administrative Letter 04)	To provide clarification

Section Number and Name	Description of Change	Brief Rationale
8.1.1. Definition of an Adverse Event	Updated assessment of adverse events related to device (Administrative Letter 04)	To provide clarification
8.1.2. Recording and Reporting of Adverse Events		
8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product		
8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product: Table 8. The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device		
8.1.5.1. Definition of a Serious Adverse Event		
10.7. Safety Analysis		
11. QUALITY CONTROL AND QUALITY ASSURANCE		
APPENDIX I. PRODUCT COMPLAINTS		
8.4 Clinical Laboratory Tests	Added text for clinical laboratory tests during Visit 3	To provide clarification
8.4. Clinical Laboratory Tests: Table 9. Clinical Laboratory Tests	Updated source of glomerular filtration rate calculation in footnote a (Administrative Letter 01)	To correct an error
	Removed unneeded clinical laboratory tests (Administrative Letter 01, Administrative Letter 03)	To correct an error
8.7. Electrocardiography	Updated interpretation of ECGs to assess patient eligibility for enrollment (Administrative Letter 04)	To provide clarification
8.8.1. Procedures for Injection Site Pus-Containing Lesion (Abscess, Infection, or Inflammation), Ulceration, Necrosis, or Atrophy	Added text regarding the follow-up questionnaire (Administrative Letter 05)	To provide clarification
8.9. Assessment of Suicidality	Updated the C-SSRS rater qualifications (Administrative Letter 03)	To provide clarification
9.1. Pharmacokinetic Assessment	[redacted] (Administrative Letter 03)	To provide clarification

Section Number and Name	Description of Change	Brief Rationale
9.3. Assessment of Exploratory Biomarkers	[redacted] (Administrative Letter 01)	To provide clarification
10.2.4 Per Protocol Analysis Set	Deleted section	To align with final statistical analysis plan
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized

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LIST OF ABBREVIATIONS

Abbreviation	Term
β-HCG	Beta-human chorionic gonadotropin
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the plasma drug concentration-time curve over dosing interval
BARS	Barnes Akathisia Rating Scale
C-SSRS	Columbia Suicide Severity Rating Scale
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
C_{max}	maximum observed drug concentration
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
EOT	end-of-treatment
[redacted]	[redacted]
EU	European Union
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up (period)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HIV	human immunodeficiency virus

Abbreviation	Term
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
IEC	Independent Ethics Committee
im	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
LAI	long-acting injectable
LSO	local safety officer
MAR	missing at random
MM	medical monitor
MMRM	mixed-model repeated measures
MNAR	missing not at random
n	number
NCA	noncompartmental analysis
OLAI	olanzapine long-acting injection
PANSS	Positive and Negative Syndrome Scale
PDAESI	protocol-defined adverse event of special interest
PDSS	Post-injection Delirium/Sedation Syndrome
PFS	prefilled syringe
PGI-I	Patient Global Impression-Improvement
PP	per-protocol
PSP	Personal and Social Performance Scale
q1m	once monthly
RDQ	Readiness for Discharge Questionnaire
RNA	ribonucleic acid
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SAS	Simpson-Angus Scale
sc	subcutaneous

Abbreviation	Term
SCID-5-CT	Structured Clinical Interview for DSM-5, Clinical Trials Version
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SQLS	Schizophrenia Quality of Life Scale
SUSAR	suspected unexpected serious adverse reaction
TC	Teleconference
ULN	upper limit of normal
US	United States (of America)
USPI	United States Prescribing Information
VC	videoconference

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol 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

Brief Title: A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label, Long-Term Safety Phase to Evaluate the Efficacy and Safety of TV-44749 in Adults with Schizophrenia

Rationale: Schizophrenia is a severely debilitating psychotic disorder characterized by positive and negative symptoms and a worldwide lifetime morbidity risk of approximately 1%. For most patients, the disease follows a chronic course requiring long-term treatment with antipsychotic agents. Noncompliance and nonadherence to long-term oral medication regimens are the most significant therapeutic issues in treating schizophrenia and related disorders, resulting in many of these patients suffering frequent relapses or exacerbations and not experiencing the full benefit of antipsychotic drug therapy. Extended-release injectable antipsychotic agents may increase adherence in patients with schizophrenia. Currently, oral, long-acting intramuscular (im), and rapid-acting im formulations of olanzapine are approved for the treatments of adults affected by schizophrenia. A new formulation of olanzapine as an extended-release injectable suspension (TV-44749) for subcutaneous (sc) use is intended for the treatment of schizophrenia.

Objectives and Endpoints:

Objectives	Endpoints
The **primary objective** is to evaluate the efficacy of TV-44749 in adult patients with schizophrenia.	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.	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, 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, Simpson-Angus Scale, Barnes Akathisia Rating Scale, Columbia Suicide Severity Rating Scale, and Calgary Depression Scale for Schizophrenia.
A **secondary objective** of this study is to evaluate the efficacy of TV-44749	Change in total PANSS score from baseline to weeks 1, 2, and 4; Change in Clinical Global Impression-Improvement scale score from baseline to weeks 4 and 8; Change in CGI-S scale score from baseline

Objectives	Endpoints
from baseline to endpoint in Period 1 in adult patients with schizophrenia.	to weeks 1, 2, and 4; Change in Patient Global Impression-Improvement (PGI-I) scale score from baseline to week 8; Change in PGI-I scale score from baseline to weeks 2 and 4; Change in Schizophrenia Quality of Life Scale score from baseline to weeks 4 and 8; Change in PSP score from baseline to week 4

Exploratory objectives and endpoints will be assessed as well.

Overall 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 for sc use as treatment of adult patients with schizophrenia. Patients with exacerbation of schizophrenia that started ≤8 weeks prior to screening and who would benefit from psychiatric hospitalization or continued hospitalization for symptoms of schizophrenia may be included. The study will be composed of 2 periods: Period 1 (the double-blind, placebo-controlled, efficacy and safety period) and Period 2 (open-label safety period). For each patient, the duration of Period 1 will be 8 weeks, and the duration of Period 2 will be up to 48 weeks. Screening is up to 8 days prior to randomization. In Period 1, patients will be randomized to one of 3 TV-44749 treatment groups (318 mg once monthly [q1m], 425 mg q1m, or 531 mg q1m) or a placebo group q1m in a 1:1:1:1 ratio. 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 for Period 2, 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 for Period 2. The end-of-treatment and follow-up visits will be at 4 and 8 weeks after the last dose of investigational medicinal product administration, respectively.

Study Intervention and Intervention Form: The purpose of this study is to assess the efficacy, safety, and tolerability of olanzapine extended-release injectable suspension for sc use compared with placebo in patients with schizophrenia. Total study duration is up to 61 weeks, and treatment duration is up to 56 weeks, with weekly visits during the first 8 weeks and then monthly in-clinic visits with weekly calls during the remainder of the treatment period.

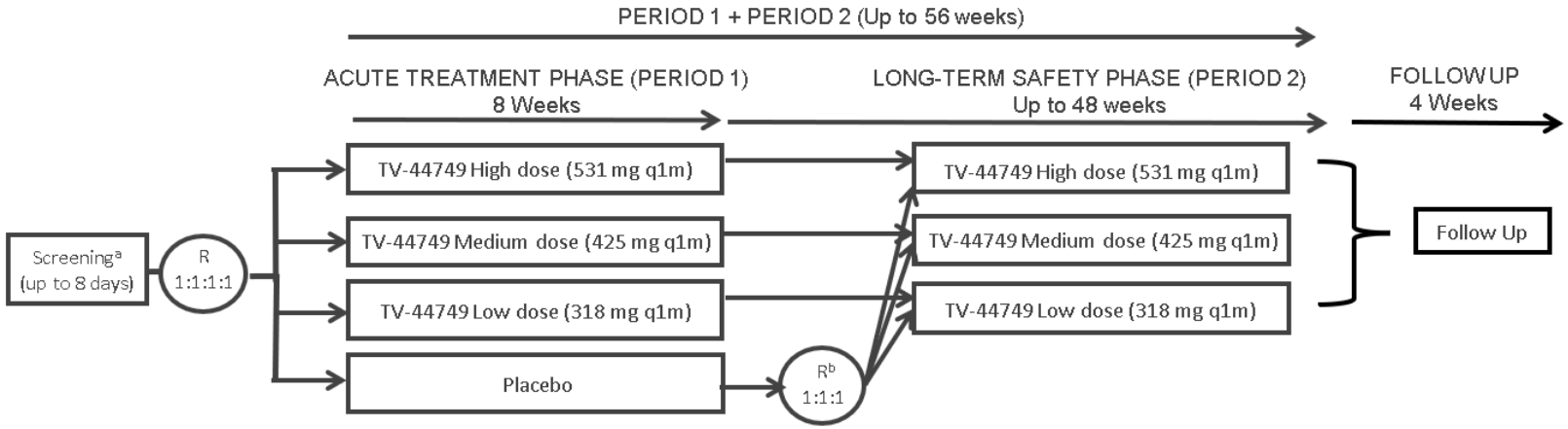
Number of Participants: Approximately [redacted] patients will be screened to achieve approximately 640 randomized patients.

Intervention Groups and Duration: The screening period includes treatment with 2 consecutive daily doses of oral olanzapine to establish tolerability (for patients who were not previously treated with oral olanzapine in the past year) prior to randomization into Period 1. During Period 1 (8 weeks), patients will receive 2 monthly sc injections of TV-44749 (318 mg, 425 mg, or 531 mg) or placebo. During Period 2 (up to 48 weeks), all patients will receive up to 12 monthly injections of TV-44749.

Data Monitoring: 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.

1.2. Study Scheme

Figure 1: Overall Study Schematic Diagram



[a] 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). 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.

[b] 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. 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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

q1m=once monthly; R=randomization.

1.3. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented Table 1 (Period 1) and Table 2 (Period 2). Detailed descriptions of each method of procedures and assessments are provided in Section 7 (efficacy assessments), Section 8 (safety assessments), and Section 9 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 1: Study Procedures and Assessments for Period 1

Study period	**Screening**[a]	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination**[b]	**End of treatment**[b]	**Follow-up**[b]	**Unscheduled visit**[c]	**Short-term leave**[d]
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**[e]	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits**[f]								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
Informed consent	X															
Inclusion and exclusion criteria	X	X														
Medical and psychiatric history (including the number of relapse episodes and years post diagnosis)	X															
SCID-5-CT	X															

Study period	**Screening**[a]	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination**[b]	**End of treatment**[b]	**Follow-up**[b]	**Unscheduled visit**[c]	**Short-term leave**[d]
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**[e]	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits**[f]								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
Prior medication and treatment history	X															
Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis)[h]	X	X	X				X				X	X	X	X	X	
Virology and thyroid tests[i]	X										X	X	X			
FSH test[j]	X															
Randomization		X									X[k]					
Administration of oral olanzapine[l]	X															
Urine drug screen	X	X					X				X	X	X			X
Physical examination,	X	X	X				X				X	X	X	X	X	X

Study period	**Screening[a]**	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination[b]**	**End of treatment[b]**	**Follow-up[b]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11[e]**	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits[f]**								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
including height and weight[m]																
12-lead ECG[n]	X	X					X				X	X	X	X		
Vital signs measurement[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum β-HCG test for women of childbearing potential	X													X		
Urine β-HCG test for women of childbearing potential[p]		X					X				X	X	X			
PANSS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
CGI-I[q]							X				X	X	X	X	X	
AIMS	X	X		X	X	X	X	X	X	X	X	X	X	X		
BARS	X	X		X	X	X	X	X	X	X	X	X	X	X		
SAS	X	X		X	X	X	X	X	X	X	X	X	X	X		

Study period	**Screening[a]**	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination[b]**	**End of treatment[b]**	**Follow-up[b]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11[e]**	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits[f]**								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
C-SSRS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
PSP	X	X					X				X	X	X	X		
SQLS	X	X					X				X	X	X	X		
[redacted]	X	X					X				X	X	X	X		
CDSS	X	X					X				X	X	X	X	X	
PGI-I					X		X				X	X	X			
[redacted][r]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Abdominal fat measurement (waist-to-hip ratio)		X					X				X	X	X	X	X	
Blood samples for plasma concentration of IMP[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood samples for plasma concentration of		X					X				X					

Study period	**Screening[a]**	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination[b]**	**End of treatment[b]**	**Follow-up[b]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11[e]**	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits[f]**								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
IMP at 2.5 to 3 hours postdose																
Blood samples for biomarker analysis[t]		X									X		X	X	X[u]	
Blood samples for pharmacogenetics[v]		X														
Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site findings and pain assessment[x]		X	X	X	X	X	X	X	X	X	X	X	X			
Inquiry regarding	X	X						X	X	X	X	X	X	X	X	X

Study period	**Screening**[a]	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination**[b]	**End of treatment**[b]	**Follow-up**[b]	**Unscheduled visit**[c]	**Short-term leave**[d]
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**[e]	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits**[f]								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
alcohol consumption/illicit drug use[y]																
Cigarette use assessment[z]	X	X					X				X					
IMP administration[aa] [bb]		X					X				X[cc]					
Site confinement[d]	X	X	X	X	X	X	X									
RDQ –discharge from site confinement[dd]							X[d]									
Outpatient period of the study[ee d]							X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study period	**Screening**[a]	**Double-blind treatment period (acute treatment phase; Period 1)**										**Early termination**[b]	**End of treatment**[b]	**Follow-up**[b]	**Unscheduled visit**[c]	**Short-term leave**[d]
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**[e]	**ET**	**EOT**	**FU**		
Day	**Day -8**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**					
Allowed time window	**Up to 8 days prior to day 1**	**N/A**	**N/A**	**±3 days for dosing visits; ±2 days for all non-dosing visits**[f]								**N/A**	**±1 week**	**–1/+2 weeks**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk -2 to -1**	**Wk 0 BL**	**Wk 0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**N/A**	**4 weeks after last dose**	**8 weeks after last dose**	**Per investigator decision**	**N/A**
Review of eligibility (stability) criteria											X[ff]					

[a] 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 (eg, extreme weather) after receiving approval from the medical monitor (MM) or sponsor. In case the site faces a delay in obtaining the central laboratory results for the clinical laboratory tests performed during screening that are needed to determine eligibility, additional screening blood samples (specifically those with delayed results) may be collected as soon as possible and analyzed in a local laboratory to allow study eligibility determination within the 8-day screening window. Refer to Section 8.4 for more details.

[b] Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) 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 (±1 week), and a FU visit for safety evaluation will be conducted at 8 weeks (-1/+2 weeks) after the last dose of IMP. 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.

[c] Other procedures may be performed according to the discretion of the investigator. However, in order to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether all unscheduled visit procedures should be performed during the unscheduled visit in the event that (i) the unscheduled visit is one of multiple in-clinic visits that are deemed necessary in close proximity (ie, 2 or more visits within 1 week) or (ii) the visit is for administrative purposes (eg, reconsenting) or technical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event) and not due to a change in the patient's medical status per clinical judgment.

[d] 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.

[e] Visit 11 (week 8) assessments are included in both Table 1 and Table 2 for completeness; however, they need to be performed only once prior to randomization to Period 2 (refer to footnote "k" for a list of procedures and assessments that must be performed prior to randomization).

[f] 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 non-dosing 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 MM or sponsor, dosing visits may take place up to 5 days before the scheduled visit date (and recorded accordingly).

[g] Days/weeks shown are nominal; visit dates should be calculated from date of previous IMP administration.

[h] Clinical laboratory tests (including serum chemistry, hematology, coagulation, and urinalysis) may also be performed at any time if clinically indicated. Coagulation laboratory tests are performed at screening only. Glomerular filtration rate will be calculated at screening only. At baseline (visit 2; week 0), visit 11 (week 8), and at the EOT visit, clinical laboratory tests will also include hemoglobin A1C. Patients must fast for at least 8 hours prior to baseline (visit 2; week 0), visit 11 (week 8), and the EOT visit (and preferably the ET visit). At screening (prior to intake of oral olanzapine, where relevant), baseline (visit 2; week 0 [prior to IMP administration]), visit 11 (week 8 [prior to IMP administration]), and at the EOT visit, clinical laboratory tests will also include prolactin. Additionally, toxicological blood test should be collected as soon as a potential PDSS event is suspected. In cases where performing toxicological blood test is not feasible due to a lack of suitable analytical facilities, a urine drug screen may be performed instead. In case visit 3 safety laboratory blood samples cannot be shipped to the central laboratory on the same day, the samples may be processed in the local clinical laboratory instead. If needed, an additional set of safety laboratory tests may be collected for that purpose. In case visit 3 occurs over the weekend and the local safety laboratory tests cannot be processed on the collection day, visit 3 safety laboratory samples will be collected up to 2 days after the visit 3 nominal date and sent to the central laboratory.

[i] Includes HIV, HBsAg, hepatitis C antibody, TSH, T_3, and T_4. Virology (HIV, HBsAg, and hepatitis C antibody) is only performed at screening.

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

[k] 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. 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, on a patient-by-patient basis. Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, CGI-I, AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, AE inquiry, injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry. Procedures and assessments that need to be performed after randomization into Period 2 at visit 11 (week 8) include IMP administration and blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose, pain 30 minutes after injection and pain and injection site findings 3 hours after injection. Remaining procedures and assessments at visit 11 (week 8) may be performed either before or after randomization. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

[l] Patients will receive 2 consecutive treatments with oral olanzapine (oral olanzapine 10 mg/day or higher [but not exceeding 20 mg/day] per investigator decision) at an interval of 24 hours apart to assess patient tolerability. The second dose should be given at least 24 hours prior to randomization. The PANSS and 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.

[m] Height will be measured at the screening visit only. Weight does not need to be measured at visit 3 (day 2), since it will be measured at visit 2 (day 1). Full physical examination will be conducted at screening visit and unscheduled visits only; the rest of the visits will include an abbreviated physical examination (including weight).

[n] At screening and baseline, measurements will be done in triplicate (approximately 5 minutes apart). Single measurements will be performed at all other in-clinic visits where ECG recordings are taken.

[o] Vital signs (blood pressure [systolic/diastolic], pulse and orthostatic changes, respiratory rate, and temperature) should be measured at each in-clinic visit pre-injection. Before blood pressure and pulse are measured, the patient must rest in a supine or semi-erect position for at least 5 minutes; measurements should be taken again after standing for approximately 2 minutes. [redacted] Vital signs should also be measured in the event of an injection site pus-containing lesion (abscess, infection, or inflammation), ulceration, or necrosis.

[p] Urine β-HCG (dipstick) test: a negative result must be obtained prior to administration of IMP, as applicable (if a borderline result is obtained on a urine test, a serum test should be performed and a negative result obtained prior to IMP administration).

[q] CGI-I during Period 1 will be relative to the CGI-S score at the baseline visit.

[r] This assessment is optional and applicable in the US only for patients who sign a dedicated ICF for participation in this assessment. This assessment will be performed only after the PANSS, CGI-S, PSP, PGI-I, CGI-I, and SQLS are complete (as applicable).

[s] When collected at dosing visits, blood samples for plasma drug concentration determination will be collected prior to TV-44749 dosing (ie, trough levels). It is recommended that at non-dosing visits, blood samples should be collected at approximately the same time of day as the IMP administration at the previous visit. [redacted] Unscheduled pharmacokinetic samples may also be collected after any serious adverse event and patient withdrawal. Every effort should be made to obtain the additional pharmacokinetic sample at the closest time possible to the occurrence of the serious adverse event.

[t] Biomarker samples (6 mL serum, 6 mL plasma, and 2.5 mL PAXgene RNA) will be collected prior to IMP administration. Additionally, patients who develop metabolic syndrome (Section 9.3) after starting IMP will have an additional biomarker sample collected at the following visit that contains a blood draw. [redacted]

[u] Additional biomarker samples will be collected (where local regulations allow, unless the patient declines to provide consent) from patients with injection site reactions that require an unscheduled visit, ie, pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy or severe injection site reaction (and for 2 consecutive visits after the event is identified).

[v] A blood sample for pharmacogenetic analysis will be collected at baseline or any visit thereafter. Participation in this sampling is optional for patients and also depends on local regulations. Patients willing to participate in pharmacogenetic sampling will sign a separate ICF for this purpose.

[w] In case an adverse event associated with an ISR is reported, pain may be assessed periodically using a numeric pain rating scale until resolution.

[x] Pain will be assessed 30 minutes after the completion of each IMP administration; pain and injection site findings will be assessed 3 hours after the completion of each IMP administration. Allowed time windows for these local tolerability assessments are ±15 minutes. In Period 1, injection site findings and pain will also be assessed weekly. The site of the preceding IMP injection will be assessed on the day of the following IMP administration prior to IMP administration

and at the EOT visit. No time windows are specified for these assessments. In addition, telephone call visits in Period 2 will include inquiries about injection site findings and pain.

[y] This inquiry is only required for outpatients (except for at the screening and baseline visits), as well as for patients who are given short-term leave during their inpatient period.

[z] Data on cigarette use will be collected using the question, "How many packs of cigarettes did you smoke over the past 7 days?" at the time points specified in the table of assessment.

[aa] At visits 2 and 7, the PANSS, C-SSRS, CGI-S, and CGI-I (visit 7 [week 4] only) scales should be completed prior to 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.

[bb] Following IMP administration, patients will remain in the clinic for at least 3 hours for observation.

[cc] First treatment in Period 2. IMP administration will be performed after all visit procedures and assessments have been completed, and after randomization into Period 2.

[dd] Please refer to the discharge criteria (Section 4.1). The RDQ should be completed by a qualified health care professional (HCP) who has a thorough knowledge of the patient's clinical condition, and has been following them throughout the duration of the hospitalization.

[ee] Patients will return to the CU on an outpatient basis for scheduled assessments.

[ff] 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, and 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.

β-HCG=beta-human chorionic gonadotropin; AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BL=baseline; CDSS=Calgary Depression Scale for Schizophrenia; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia Suicide Severity Rating Scale; CU=Clinical Unit; ECG=electrocardiogram; EOT=end-of-treatment; [redacted]; ET=early termination; FSH=follicle-stimulating hormone; FU=follow-up; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; ICF=informed consent form; IMP=investigational medicinal product; ISR=injection site reaction; LAI=long-acting injectable; MM=medical monitor; N/A=not applicable; PANSS=Positive and Negative Syndrome Scale; PDSS=Post-injection Delirium/Sedation Syndrome; PGI-I=Patient Global Impression-Improvement; PSP=Personal and Social Performance Scale; RDQ=Readiness for Discharge Questionnaire; RNA=ribonucleic acid; SAS=Simpson-Angus Scale; SCID-5-CT=Structured Clinical Interview for DSM-5, Clinical Trials Version; SQLS=Schizophrenia Quality of Life Scale; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone; US=United States; V=visit; Wk=week

Table 2: Study Procedures and Assessments for Period 2

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Review of eligibility (stability) criteria	X[j]																			
Randomization	X[k]																			
Clinical laboratory tests[l] (serum chemistry, hematology, and urinalysis)	X						X						X			X	X	X	X	
Thyroid test[m]	X															X		X		
Urine drug screen	X		X		X		X		X		X		X			X		X		X

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Concomitant medication inquiry	X		X		X		X		X		X		X			X	X	X	X	X
Physical examination, including weight[n]	X		X		X		X		X		X		X			X	X	X	X	X
Abdominal fat measurement (waist-to-hip ratio)	X		X		X		X		X		X		X			X	X	X	X	
Vital signs measurement[o]	X		X		X		X		X		X		X			X	X	X	X	
12-lead ECG[p]	X				X				X				X			X	X	X		

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Serum β-HCG test for women of childbearing potential																	X			
Urine β-HCG test for women of childbearing potential[q]	X		X		X		X		X		X		X			X		X		
Inquiry about pregnancy status (for women of childbearing potential)		X		X		X		X		X		X		X						
PANSS	X		X		X		X		X		X		X			X	X	X	X	
CGI-S	X		X		X		X		X		X		X			X	X	X	X	

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
CGI-I[r]	X						X						X			X	X	X	X	
AIMS	X						X						X			X	X	X		
BARS	X						X						X			X	X	X		
SAS	X						X						X			X	X	X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
PSP	X						X						X			X	X	X		
SQLS	X						X						X			X	X	X		
[redacted]	X						X						X			X	X	X		
CDSS	X		X		X		X		X		X		X			X	X	X	X	
PGI-I	X															X		X		
[redacted][s]	X		X		X		X		X		X		X			X	X	X	X	

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
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Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Blood samples for biomarker analysis[t]	X															X	X		X[u]	
Blood samples for plasma concentration of IMP[v]	X		X		X		X		X		X		X			X	X	X	X	
Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose	X		X		X		X		X		X		X							
IMP administration [w] [x]	X		X		X		X		X		X		X							

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Injection site findings and pain assessment[z]	X		X		X		X		X		X		X			X		X		

Study period	**Safety period (long-term safety phase; Period 2 [up to 48 weeks])[a]**															**Follow-up[b]**	**ET[a]**	**Unscheduled visit[c]**	**Short-term leave[d]**
Visit number	**The series from visit 12 to visit 17c repeats until EOT or ET (visit 22c being the last visit prior to EOT)**														**EOT[b]**	**FU**	**ET**		
	V11	**V11a 11b 11c[e]**	**V12**	**V12a 12b 12c[e]**	**V13**	**V13a 13b 13c**	**V14**	**V14a 14b 14c**	**V15**	**V15a 15b 15c**	**V16**	**V16a 16b 16c**	**V17**	**V17a 17b 17c**	**V18-22c**				
Allowed time window	**±3 days[f]**														**±1 week**	**-1/+2 weeks**	**N/A**	**N/A**	**Upon patient return to the site**
Week[g]	**Wk 8 (Day 57)**	**Wk 9-11**	**Wk 12**	**Wk 13-15**	**Wk 16**	**Wk 17-19**	**Wk 20**	**Wk 21-23**	**Wk 24**	**Wk 25-27**	**Wk 28**	**Wk 29-31**	**Wk 32**	**Wk 33-35**	**See footnote [a]**	**4 wks after last dose**	**8 wks after last dose**	**N/A**	**Per investigator decision**	**N/A**
In-clinic visit	**X**		**X**		**X**		**X**		**X**		**X**		**X**			**X**	**X**	**X**	**X**	**X**
Telephone call[h] [i]		**X**		**X**		**X**		**X**		**X**		**X**		**X**						
Inquiry regarding alcohol consumption/ illicit drug use[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Cigarette use assessment[bb]	X		X		X		X		X		X		X							
Brief set of clinical questions to detect psychotic symptoms[cc]		X		X		X		X		X		X		X						

[a] The open-label safety period in Period 2 will be up to 48 weeks, with patients continuing until the end of Period 2 or until they meet 1 or more of the study discontinuation or withdrawal criteria. Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) should be invited to perform the ET visit as soon as possible. The series from visit 12 to visit 17c repeats until EOT (visit 22c being the last visit prior to EOT) or ET (ie,

visit 18 should be identical to visit 12, visit 19 should be identical to visit 13, visit 20 should be identical to visit 14, visit 21 should be identical to visit 15, and visit 22 should be identical to visit 16).

[b] An EOT visit will be conducted at 4 weeks after the last dose of IMP (ie, 4 weeks [±1 week] after visit 22 if the patient completes the entire Period 2 or earlier if the patient early terminates or the sponsor stops the study), and a FU visit for safety evaluation will be conducted at 8 weeks (-1/+2 weeks) after the last dose of IMP. 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.

[c] Other procedures may be performed according to the discretion of the investigator. However, in order to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether all unscheduled visit procedures should be performed during the unscheduled visit in the event that (i) the unscheduled visit is one of multiple in-clinic visits that are deemed necessary in close proximity (ie, 2 or more visits within 1 week) or (ii) the visit is for administrative purposes (eg, reconsenting) or technical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event) and not due to a change in the patient's medical status per clinical judgment.

[d] For any patients who are inpatients at the beginning period 2, 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.

[e] For patients who are inpatients (for up to the first 8 weeks of Period 2), in-clinic visits will take place instead of phone visits, using the same assessments specified for the phone visits.

[f] A window of ±3 days will be allowed around the scheduled visit dates for dosing and non-dosing visits during Period 2; 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).

[g] Weeks shown are nominal; visit dates should be calculated from date of previous IMP administration.

[h] Telephone contacts (or other comparable form of remote communication) will occur weekly between clinic visits. These contacts will be referred to by the previous visit number and a letter (eg, the telephone contacts that take place 1, 2, and 3 weeks after visit 11 [week 8] will be referred to as "visit 11a," "visit 11b," and "visit 11c," respectively).

[i] Each telephone contact will include inquiries about injection site pain, suicidal ideation and behavior (C-SSRS), adverse events, alcohol consumption, and pregnancy status (for women of childbearing potential). Patients will also be asked a brief set of clinical questions in order to detect psychotic symptoms (see row and corresponding footnote for "brief set of clinical questions to detect psychotic symptoms" in the table).

[j] 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, and 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.

[k] 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. 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, on a patient-by-patient basis. Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, CGI-I, AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, AE inquiry, injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry. Procedures and assessments that need to be performed after randomization into Period 2 at visit 11 (week 8) include IMP administration and blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose. Remaining procedures and assessments at visit 11 (week 8) may be performed either before or after randomization. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

[l] Clinical laboratory tests (including serum chemistry, hematology, coagulation, and urinalysis) may also be performed at any time if clinically indicated. At visit 11 (week 8), visit 14 (week 20), visit 17 (week 32), visit 20 (week 44), and at the EOT visit, clinical laboratory tests will also include hemoglobin A1C. Patients must fast for at least 8 hours prior to visit 11 (week 8) and the EOT visit (and preferably the ET visit). At visit 11 (week 8 [prior to IMP administration]), visit 14 (week 20 [prior to IMP administration]), and at the EOT visit, clinical laboratory tests will also include prolactin. Additionally, toxicological blood test should be collected as soon as a potential PDSS event is suspected. In cases where performing toxicological blood test is not feasible due to a lack of suitable analytical facilities, a urine drug screen may be performed instead.

[m] Includes TSH, T_3, and T_4.

[n] Full physical examination will be conducted at unscheduled visits only; the rest of the visits will include an abbreviated physical examination (including weight).

[o] Vital signs (blood pressure [systolic/diastolic], pulse and orthostatic changes, respiratory rate, and temperature) should be measured at each in-clinic visit pre-injection. Before blood pressure and pulse are measured, the patient must rest in a supine or semi-erect position for at least 5 minutes; measurements should be taken again after standing for approximately 2 minutes. [redacted] Vital signs should also be measured in the event of an injection site pus-containing lesion (abscess, infection, or inflammation), ulceration, or necrosis.

[p] Single measurements will be performed at all in-clinic visits where ECG recordings are taken.

[q] Urine β-HCG (dipstick) test: a negative result must be obtained prior to administration of IMP, as applicable (if a borderline result is obtained on a urine test, a serum test should be performed and a negative result obtained prior to IMP administration).

[r] CGI-I during Period 2 will be relative to the CGI-S score at the baseline visit (visit 2 in Period 1).

[s] This assessment is optional and applicable in the US only for patients who sign a dedicated ICF for participation in this assessment. This assessment will be performed only after the PANSS, CGI-S, PSP, PGI-I, CGI-I, and SQLS are complete (as applicable).

[t] Biomarker samples (6 mL serum, 6 mL plasma, and 2.5 mL PAXgene RNA) will be collected prior to IMP administration. Additionally, patients who develop metabolic syndrome (Section 9.3) after starting IMP will have an additional biomarker sample collected at the following visit that contains a blood draw. [redacted]

[u] Additional biomarker samples will be collected (where local regulations allow, unless the patient declines to provide consent) from patients with injection site reactions that require an unscheduled visit, ie, pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy or severe injection site reaction (and for 2 consecutive visits after the event is identified).

[v] Blood samples for plasma drug concentration determination will be collected prior to TV-44749 dosing (ie, trough levels). [redacted] Unscheduled pharmacokinetic samples may also be collected after any serious adverse event and patient withdrawal. Every effort should be made to obtain the additional pharmacokinetic sample at the closest time possible to the occurrence of the serious adverse event.

[w] 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 as detailed in Section 6.9.1 and footnote "k" of Table 1 and Table 2). Any assessments performed after IMP administration must be completed on the day of IMP administration.

[x] Following IMP administration, patients will remain in the clinic for at least 3 hours for observation. 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.

[y] In case an adverse event associated with an ISR is reported, pain may be assessed periodically using a numeric pain rating scale until resolution.

[z] Pain will be assessed 30 minutes after the completion of each IMP administration; pain and injection site findings will be assessed 3 hours after the completion of each IMP administration. Allowed time windows for these local tolerability assessments are ±15 minutes. In Period 2, injection site findings and pain will also be assessed monthly. The site of the preceding IMP injection will be assessed on the day of the following IMP administration prior to IMP administration and at the EOT visit. No time windows are specified for these assessments. In addition, telephone call visits in Period 2 will include inquiries about injection site findings and pain.

[aa] This inquiry is only required for outpatients (as well as for any patients who are inpatients at the beginning of Period 2 and who are given short-term leave during their inpatient period).

[bb] Data on cigarette use will be collected using the question, "How many packs of cigarettes did you smoke over the past 7 days?" at the time points specified in the table of assessment.

[cc] The specific questions asked will be at the discretion of the investigator. A list of suggested questions will be provided to the investigator. Psychiatric adverse events or suspicion of a psychiatric deterioration as a result of the telephone contact will trigger an invitation of the patient to an unscheduled visit where psychiatric scales will be administered to rule out an impending relapse at the discretion of the investigator.

β-HCG=beta-human chorionic gonadotropin; AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; CRF=case report form; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end-of-treatment; [redacted]; ET=early termination; FU=follow-up; ICF=informed consent form; IMP=investigational medicinal product; ISR=injection site reaction; LAI=long-acting injectable; MM=medical monitor; N/A=not applicable; PANSS=Positive and Negative Syndrome Scale; PDSS=Post-injection Delirium/Sedation Syndrome; PGI-I=Patient Global Impression-Improvement; PSP=Personal and Social Performance Scale; RDQ=Readiness for Discharge Questionnaire; RNA=ribonucleic acid; SAS=Simpson-Angus Scale; SQLS=Schizophrenia Quality of Life Scale; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone; US=United States; V=visit; Wk=week

Table 3: Study Procedures and Assessments for a Potential Post-injection Delirium/Sedation Syndrome Event

[redacted]	[redacted]	[redacted]				

2. INTRODUCTION AND BACKGROUND INFORMATION

2.1. Introduction

2.1.1. Schizophrenia

Schizophrenia is a severely debilitating psychotic disorder characterized by positive symptoms (eg, delusions, hallucinations, and grossly disorganized behavior) and negative symptoms (eg, affective flattening, alogia, and avolition) (Kahn et al 2015, New York State Office of Mental Health 2018, Stefan et al 2002).

The worldwide lifetime morbidity risk of the disorder is approximately 1% across diverse geographic, cultural, and socioeconomic regions. Since, in most patients, the disease follows a chronic course with long-lasting impairment, long-term treatment with antipsychotic agents is usually required.

Noncompliance and high discontinuation rates are particularly problematic in patients with schizophrenia. Premature discontinuation of antipsychotic drug therapy is a common phenomenon; in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 74% of patients discontinued their drug within 18 months either due to poor tolerability, lack of efficacy, patient choice (ie, nonadherence/study withdrawal), or for investigator reasons (Lieberman et al 2005). Even among those who do not explicitly discontinue drug therapy, nonadherence to long-term oral medication regimens is one of the most significant therapeutic issues in the therapy of schizophrenia and related disorders (Kane et al 2013). As a result, many of these patients do not experience the full benefit of antipsychotic drug therapy and suffer frequent relapses or exacerbations that require rehospitalization (Carbon and Correll 2014), often in the context of psychiatric emergency (Rainer 2008).

Thus, long-acting injectable (LAI) antipsychotic agents may increase adherence in patients with schizophrenia (Barnes and Curson 1994, Hughes 2008, Keith and Kane 2003, Walburn et al 2001) and have been shown to significantly reduce relapse and rehospitalization as well as improve many clinically relevant outcomes significantly more than oral antipsychotics in randomized trials, cohort studies, and mirror-image studies (Kishimoto et al 2021).

The critical importance of optimal adherence with prescribed antipsychotic regimens has been repeatedly and convincingly demonstrated in patients with schizophrenia (Kane et al 2013). Adherence increases the likelihood of positive outcomes in all aspects of a patient's life including better symptom control, reduced risk of relapse and rehospitalization, and improved quality of life as well as social and occupational functioning. Despite their proven effectiveness, poor adherence to prescribed antipsychotic regimens remains the most important driver of suboptimal clinical outcomes in patients with schizophrenia (Birnbaum and Sharif 2008).

Note: the terms "long-acting" and "extended-release" are used interchangeably within this document.

2.1.2. Olanzapine for Oral and Intramuscular Use

Olanzapine is a well characterized and commonly prescribed second-generation antipsychotic drug available as oral and intramuscular (im) formulations and has not yet been approved for use as a subcutaneous (sc) injection.

Oral formulations (Section 2.1.2.1) are approved for the treatment of adults and adolescents affected by schizophrenia. The long-acting im depot preparation containing olanzapine pamoate (Section 2.1.2.2) is approved for the treatment of adults affected by schizophrenia, while a rapid-acting im formulation of olanzapine (Section 2.1.2.1) is approved for the treatment of adults with acute agitation associated with schizophrenia.

2.1.2.1. Immediate-Release Olanzapine Formulations

Olanzapine is currently marketed in the United States (US) as ZYPREXA® tablets (2.5, 5, 7.5, 10, 15, and 20 mg); ZYPREXA® INTRAMUSCULAR for rapid-acting injection (10 mg/mL) and as ZYPREXA® ZYDIS® orally disintegrating tablets (5, 10, 15, and 20 mg) (ZYPREXA United States Prescribing Information [USPI] 2021).

2.1.2.2. Extended-Release Olanzapine Formulations

ZYPREXA® RELPREVV™, an extended-release olanzapine pamoate powder and diluent for suspension, is administered by deep im gluteal injection. Before use, the powder for injection is suspended in a viscous, aqueous vehicle containing croscarmellose sodium, mannitol, polysorbate 80, water, as well as hydrochloric acid and sodium hydroxide for pH adjustment (ZYPREXA RELPREVV USPI 2021). ZYPREXA RELPREVV should be administered im either every 2 weeks (150, 210, and 300 mg) or every 4 weeks (300 and 405 mg), depending on the target oral olanzapine dose (10, 15, or 20 mg/day). ZYPREXA RELPREVV is currently approved and marketed in the US for the treatment of schizophrenia; however, it is only available through a restricted distribution program.

ZYPREXA RELPREVV must be administered in a registered healthcare facility (such as a hospital, clinic, residential treatment center, or community healthcare center) with ready access to emergency response services. After each ZYPREXA RELPREVV injection, a healthcare professional must continuously observe the patient at the healthcare facility for at least 3 hours and must confirm that the patient is alert, oriented, and absent of any signs and symptoms of Post-injection Delirium/Sedation Syndrome (PDSS), as a consequence of the route of administration, prior to being released. All patients must be accompanied to their destination upon leaving the facility. For the remainder of the day, patients should not drive or operate heavy machinery and should be advised to be vigilant for symptoms of PDSS and be able to obtain medical assistance if needed. If PDSS is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation. If parenteral benzodiazepines are required for patient management during an event of PDSS, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Because of the precautions required for safe use of ZYPREXA RELPREVV, the product is rarely used in routine clinical practice. As a consequence, the options available to psychiatrists for clinical management of schizophrenia are curtailed.

2.1.3. Olanzapine for Subcutaneous Use (TV-44749)

The sponsor is developing a new formulation of olanzapine as an extended-release injectable suspension for sc use that will deliver therapeutic levels of olanzapine over a 1-month interval to patients with schizophrenia.

[redacted]

The purpose of this study is to evaluate the efficacy, safety, and tolerability of olanzapine for extended-release injectable suspension (TV-44749) for sc use in adult patients with schizophrenia.

2.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

The systemic and local safety of olanzapine has been well characterized in nonclinical and clinical studies, both for oral and im routes of administration (ZYPREXA USPI 2021). ZYPADHERA® (European Union [EU]; Summary of Product Characteristics [SmPC] 2022), which is identical to ZYPREXA RELPREVV, was also used to support the nonclinical development of TV-44749.

2.2.1. Nonclinical Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.2. Clinical Studies

2.2.2.1. Clinical Pharmacology Studies

[redacted]

[redacted]

2.2.2.1.1. Pharmacokinetics of TV-44749 Single-Dose Cohorts

[redacted]

[redacted]

2.2.2.1.2. Pharmacokinetics of TV-44749 Multiple-Dose Cohorts

[redacted]

2.2.2.1.3. TV-44749 Comparability to Oral Olanzapine

[redacted]

2.2.2.1.4. Olanzapine Pharmacokinetics After Oral Administration

ZYPREXA olanzapine tablets and ZYPREXA ZYDIS olanzapine orally disintegrating tablets are intended for oral use only. A ZYPREXA tablet contains olanzapine equivalent to 2.5, 5, 7.5, 10, 15, or 20 mg. A ZYPREXA ZYDIS orally disintegrating tablet contains olanzapine equivalent to 5, 10, 15, or 20 mg.

2.2.2.1.4.1. Single Oral Dose

The pharmacokinetics of olanzapine are linear and dose proportional within the approved dosage range (Callaghan et al 1999). In clinical studies in healthy subjects, olanzapine peak concentrations were reached in approximately 6 hours following an oral dose. Its mean half-life in healthy individuals was 30 hours, ranging from 21 to 54 hours (5^{th} to 95^{th} percentile). The mean apparent plasma clearance was 25 L/h, ranging from 12 to 47 L/h (5^{th} to 95^{th} percentile). Smokers and men had a higher clearance of olanzapine than women and nonsmokers.

2.2.2.1.4.2. Multiple Oral Doses

The pharmacokinetic profile of olanzapine after multiple doses follows linear principles (ie, plasma concentrations after multiple doses can be linearly related to dose and can be predicted from single dose C_{max} and AUC parameters) (Callaghan et al 1999). Once-daily administration of olanzapine leads to steady-state concentrations in approximately 1 week. The steady-state C_{max} of olanzapine was approximately 2-fold higher than after single doses. The pharmacokinetics of olanzapine at steady state were consistent with those generated in single dose studies.

A population pharmacokinetic model involving data from 1711 patients with schizophrenia receiving olanzapine daily for up to 6 weeks in Phase 2 and 3 studies characterized 655 patients in a low-clearance group (38%) and 1056 patients in a high-clearance group (Callaghan et al 1999). In both populations, olanzapine clearance was lower in women than in men (by about 25%). The typical apparent clearance values in these groups differed by approximately 2-fold. Smoking and gender were identified as important factors contributing to clearance only in the high-clearance group. In the high-clearance group, nonsmokers had a lower clearance. Smoking and gender were also important factors for the volume of distribution across the entire population.

2.2.2.1.5. Olanzapine Pharmacokinetics Following Intramuscular Injection of Long-Acting Preparation of Olanzapine

ZYPREXA RELPREVV (olanzapine [pamoate] long-acting injection; OLAI) is provided as powder for suspension for im use only in vials containing 210, 300, and 405 mg. Dose linear exposure for ZYPREXA RELPREVV aligns with the corresponding exposure for an oral dose of olanzapine. Olanzapine presents a linear pharmacokinetic profile over the clinical dosing range (an overview is provided in Heres et al 2014). In clinical studies, olanzapine concentrations were observed immediately upon injection. Peak concentrations most often occurred at 2 to 4 days after injection. Upon multiple dosing, olanzapine concentrations increase gradually, taking approximately 3 months to reach steady-state conditions. Despite this slower time to reach steady-state conditions (compared to oral), data indicated that therapeutic concentrations were available within hours of the first OLAI. Half-life was approximately 30 days, controlled by the

slow rate of im absorption, while the 30-hour half-life of oral olanzapine is elimination rate based.

OLAI dosages of 150 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks in patients with schizophrenia stabilized on daily oral olanzapine (10, 15, or 20 mg/day), produced average (10^{th} to 90^{th} percentile) steady-state plasma olanzapine concentrations (5 to 41, 8 to 51, and 7 to 73 ng/mL, respectively) that were similar to those for oral olanzapine at dosages of 10, 15, and 20 mg/day (13 to 48, 21 to 63, and 21 to 85 ng/mL, respectively) (Kane et al 2010).

2.2.2.2. Clinical Efficacy and Safety Studies

Several safety concerns have been identified in the adult clinical studies programs for olanzapine. The most commonly observed adverse reactions associated with the use of oral olanzapine in patients with schizophrenia (incidence of 5% or greater, rounded to the nearest percent) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) in 6-week, placebo-controlled trials were dizziness (11%), constipation (9%), personality disorder (8%), weight gain (6%), and postural hypotension and akathisia (5% each) (ZYPREXA USPI 2021). In 3- and 4-week placebo-controlled trials in patients with bipolar I disorder (manic or mixed episodes), the most commonly observed adverse reactions associated with the use of oral olanzapine (adverse event incidence of 5% or greater, rounded to the nearest percent) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were somnolence (35%), dry mouth (22%), dizziness (18%), asthenia (15%), constipation and dyspepsia (11% each), and increased appetite and tremor (6% each).

There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among im olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24-hour im treatment period in clinical studies in agitated patients with schizophrenia or bipolar I mania was 6% for im olanzapine for injection and 3% for placebo (ZYPREXA USPI 2021).

A dose group difference has been observed for fatigue, dizziness, weight gain, and prolactin elevation. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200), and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) was observed with significant differences between 10 versus 40 mg/day and 20 versus 40 mg/day. The incidence of dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) was observed with significant differences between 20 versus 40 mg. Dose group differences were also noted for weight gain and prolactin elevation.

Eleven ZYPREXA RELPREVV-treated patients (3.6%) and 0 placebo-treated patients experienced treatment-emergent injection-related adverse reactions (injection site pain, buttock pain, injection site mass, induration, injection site induration) in the placebo-controlled database. The most frequently occurring treatment-emergent adverse reaction was injection site pain (2.3% ZYPREXA RELPREVV-treated; 0% placebo-treated) (ZYPREXA RELPREVV USPI 2021).

PDSS has been characterized by signs of delirium and/or excessive sedation following deep im injection with OLAI (Detke et al 2010). The symptomatology is consistent with olanzapine overdose (eg, sedation, confusion, slurred speech, altered gait, or unconsciousness), although no clinically significant decreases in vital signs are observed.

In the clinical development of im OLAI, 30 cases (in 29 patients) of PDSS were identified (Detke et al 2010). Symptom onset ranged from immediate to 3 to 5 hours post-injection, with a median onset time of 25 minutes post-injection. All patients recovered within 1.5 to 72 hours after onset. PDSS could be readily identified based on symptom presentation, progression, and temporal relationship to the injection. Olanzapine overdose resulted in excessive sedation (which can include coma) and/or delirium.

All 30 cases described by (Detke et al 2010) presented with at least 1 symptom related to either delirium or sedation, with 83% of cases resulting in both delirium- and sedation-related symptoms. Delirium-related adverse events, such as disorientation, confusion, ataxia, and dysarthria, were reported in 97% of events. Sedation-related adverse events, defined as somnolence, sedation, or other change in level of consciousness, were reported in 87% of the events. Initial symptoms (ie, symptoms first noted by the patient, investigator, or other witness at the onset of the event) included delirium-related symptoms (47% of cases) and sedation-related symptoms (40% of cases). However, in another 40% of cases, the first symptoms noted did not include signs of sedation or delirium but were instead related to general malaise or other symptoms such as extrapyramidal symptoms, agitation, anxiety, or irritability. In those cases, the delirium or sedation developed subsequent to the initial symptoms.

Incapacitation was found in 21 cases, defined as the presence of clinically significant disorientation, ataxia, or sedation such that the patient would not have been able to seek assistance on his own (Detke et al 2010).

Plasma drug levels after im olanzapine pamoate injection typically result in a slowly increasing plasma concentration profile that does not show any initial rapid release or “dose dumping” effect (McDonnell et al 2010). Instead, the slow depot release of ZYPREXA RELPREVV maintains the olanzapine concentration within the expected therapeutic range. Injections that result in a PDSS event demonstrated higher olanzapine concentrations in the plasma exceeding 100 ng/mL and in some cases reaching >600 ng/mL at the first hours post-injection. These plasma levels are significantly higher than the expected therapeutic range of olanzapine of 5 to 73 ng/mL. Olanzapine concentrations gradually return to the therapeutic range over the following 24 to 72 hours (McDonnell et al 2010). Resolution of the clinical symptoms of an event is concordant with the return of plasma olanzapine concentrations to therapeutic levels.

2.3. Known and Potential Benefits and Risks to Patients

2.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

Olanzapine is a well characterized and commonly prescribed second-generation antipsychotic drug available as oral and im formulations. Oral formulations (Section 2.1.2.1) are approved for the treatment of adults and adolescents affected by schizophrenia. The long-acting im depot preparation containing olanzapine pamoate (Section 2.1.2.2) is approved for the treatment of adults affected by schizophrenia, while a rapid-acting im formulation of olanzapine

(Section 2.1.2.1) is approved for the treatment of adults with acute agitation associated with schizophrenia.

Data from Study TV44749-SAD-10154, including pharmacokinetics, safety, and tolerability associated with TV-44749, ie, olanzapine for extended-release injectable suspension (for sc use), are available. To date, the sponsor has evaluated TV-44749 safety data from 71 patients and 30 healthy subjects at doses of 70 to 566 mg and 6 healthy subjects treated with TV-44749 vehicle. The safety profile emerging from these data is consistent with that seen with other olanzapine formulations (Section 2.2.2.2), with the exception of the identification of ISRs. None of these were identified as serious events, and they have not significantly impacted TV-44749's benefit-risk profile. [redacted] The current ZYPREXA label contains warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations. The label also contains the standard boxed warning regarding increased risk of mortality in elderly patients with dementia-related psychosis.

Furthermore, it has been proposed that the rapid and significant increases in plasma concentration leading to an olanzapine overdose and PDSS with ZYPREXA RELPREVV arise from vessel injury during the im injection process. Vessel injury could result in blood contact, causing rapid dissolution due to the marked increase in solubility of olanzapine pamoate in plasma compared to the intended im environment, and ultimately lead to an olanzapine overdose (Heres et al 2014). [redacted] No suspected PDSS event occurred in Study TV44749-SAD-10154.

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

In summary, the benefit and risk assessment for TV-44749 is favorable following review of the outlined data.

2.3.2. Known and Potential Benefits and Risks of Other Treatment

Information regarding benefits and risks to patients of oral olanzapine used in this study during the screening period may be found in the prescribing information for oral olanzapine (ZYPREXA USPI 2021).

2.3.3. Overall Benefit and Risk Assessment for This Study

[redacted]

[redacted]

The study design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect patient safety. Management of study activities during coronavirus disease 2019 (COVID-19) outbreaks is detailed in Appendix L.

3. STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. 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 key 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 endpoints in Period 1 in adult patients with schizophrenia.	• Change in total PANSS score from baseline to weeks 1, 2, and 4 • Change in Clinical Global Impression-Improvement (CGI-I) scale score from baseline to weeks 4 and 8 • Change in CGI-S scale score from baseline to weeks 1, 2, and 4 • Change in Patient Global Impression-Improvement (PGI-I) scale score from baseline to week 8 • Change in PGI-I scale score from baseline to weeks 2 and 4 • Change in Schizophrenia Quality of Life Scale (SQLS) score from baseline to weeks 4 and 8 • Change in PSP score from baseline to week 4

3.1.1. 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 technique 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 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. PANSS has high internal validity and reliability and excellent sensitivity to change in both short- and long-term trials (Gopalakrishnan et al 2021, Curson et al 1986, Wyatt et al 1999).

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

3.2. Estimand

3.2.1. Primary Estimand

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

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 from baseline to week 8 in the PANSS total score while (as if) patients did not withdraw from randomized treatment or use prohibited antipsychotic medications.

d. **Population-level summary**: Rubin's rule-derived least squares means of the difference in the change from baseline to week 8 between treatment groups according to the randomization assignment, regardless of the treatment actually received.

Any data collected after the intercurrent event (ICE) of taking prohibited antipsychotic medications or early termination (ET) due to insufficient clinical response (lack of efficacy) will be regarded as patients not reaching the optimal treatment effect (ie, missing not at random [MNAR]). ICE of early discontinuation for other reasons will be regarded as if the patient fully complied and completed the study (assuming missing at random [MAR]); see Table 4 for further details on the classification and handling of ICEs. This complies with the hypothetical approach.

Table 4: Classification of Intercurrent Events

Intercurrent Event	Strategy	Analysis
Early discontinuation due to: Lack of efficacy Prohibited antipsychotic Disease progression	Hypothetical	Measurements after ICE will be imputed using reference-based imputation (assuming MNAR)
Self-administered prohibited antipsychotics Suicide	Hypothetical	Measurements after ICE will be imputed using reference-based imputation (assuming MNAR)

Table 4: Classification of Intercurrent Events (Continued)

Intercurrent Event	Strategy	Analysis
Early discontinuation due to other reasons (including due to adverse event)	Hypothetical	Measurements after ICE will be imputed based on randomized treatment group (assuming MAR)
Allowed concomitant medications Adverse event that did not lead to discontinuation Use of prohibited medications that are not antipsychotic Injection site reaction Out of window safety assessments	Treatment policy	Measurements after ICE will be included in analysis

ICE=intercurrent event; MAR=missing at random; MNAR=missing not at random.

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 will be done in a blinded manner on a case-by-case basis prior to database lock for efficacy and will be documented in a dedicated document. Also, the classification above will be revisited in a blinded manner before database lock for efficacy and will be documented in the same document.

The purpose of this estimand is to evaluate the efficacy of TV-44749 when patients adhere to treatment, while patients who used any prohibited antipsychotic medications or withdrew from the study due to disease progression or lack of efficacy are regarded from that withdrawal time point as behaving like patients randomized to the placebo arm. This also applies to the "other efficacy estimand" (Section 3.2.2).

3.2.2. Other Efficacy Estimand

This efficacy estimand will be used for the key secondary endpoints based on the CGI-S and PSP scores. Attributes "a" and "b" will be implemented in the same manner as planned for the primary efficacy 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 from baseline to week 8 in the CGI-S and PSP scores as if patients did not withdraw from randomized treatment or use prohibited antipsychotic medications.

d. **Population-level summary**: details are described in the statistics section.

See "Primary and Secondary Objectives and Endpoints" table above; the endpoint will be evaluated while (as if) patients are on treatment and did not use prohibited antipsychotic medications. Any data collected after the ICE of taking prohibited antipsychotic medications or ET due to insufficient clinical response (lack of efficacy) will be regarded as patients not

reaching the optimal treatment effect (ie, MNAR). ICE of early discontinuation for other reasons will be regarded as if the patient fully complied and completed the study (assuming MAR); see Table 4 for further details on the classification and handling of ICEs. This complies with the hypothetical approach.

3.2.3. Safety and Tolerability Estimand

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 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 study drug (as per Safety Analysis Set; see Section 10.2.3).

c. **Endpoint**: see table of "Primary and Secondary Objectives and Endpoints" above; the endpoints will be evaluated without regard to any ICE.

d. **Population-level summary**: details are described in the statistics section.

3.3. Exploratory Objectives and Endpoints

Exploratory objectives are:

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

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

[redacted]

4. STUDY DESIGN

4.1. General Study Design and Study Schematic Diagram

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 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 [318 mg q1m], medium [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 to the Sponsor, the site staff, and the study participants 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 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 (Section 6.9.1), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

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.

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

Refer to Section 6.7.1 for a description of allowed concomitant medications (including rescue medications [Section 6.7.1.1] and antidepressants and/or mood stabilizers [Section 6.7.1.2]).

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 subscale: 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 site personnel must identify the caregiver at the screening visit and consider the caregiver a reliable contact person. The caregiver must have regular contact with the patient (defined as direct contact not fewer than 3 times per week), with the expectation that this frequency of contact would continue throughout the outpatient portion of Period 1 (it is also advised during the rest of the study, including Period 2 and the FU period). 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 (eg, 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 by a qualified health care professional (HCP) who has a thorough knowledge of the patient's clinical condition, and has been following them throughout the duration of the hospitalization. The RDQ consists of 6 items, as presented below.

Discharge Criteria (RDQ):

1. The patient is not actively suicidal or homicidal.
2. The patient has adequate control over aggression and impulsivity.
3. The patient has the ability to carry out basic activities of daily living such as bathing, dressing, climbing stairs, eating, etc.
4. The patient has the ability to take medicine independently (from the hospital/medical staff).
5. The patient's delusions and hallucinations do not significantly interfere with functioning.
6. The patient has a CGI-S score of ≤4.

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 no longer has a caregiver or lacks a supervised environment, the patient can also be discharged if the patient has stable housing (ie, a permanent address or a tenancy agreement) and the site can provide frequent monitoring via telephone contact. 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 (including if the caregiver has resigned or excluded himself/herself from the responsibility), 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.

An unscheduled visit may be performed at any time per investigator decision. Each unscheduled visit should include clinical laboratory tests, a full physical examination (including weight), abdominal fat measurement (waist-to-hip ratio), inquiry regarding alcohol consumption/illicit drug use, vital signs measurements, PANSS, CGI-S, CGI-I, C-SSRS, Calgary Depression Scale for Schizophrenia (CDSS), blood samples for plasma concentration of IMP, adverse event and concomitant medication inquiries (Table 1), and any other procedures according to the discretion of the investigator. However, in order to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether all unscheduled visit procedures (Table 1) should be performed during the unscheduled visit in the event that (i) the unscheduled visit is one of multiple in-clinic visits that are deemed necessary in close proximity (ie, 2 or more visits within 1 week) or (ii) the visit is for administrative purposes (eg, reconsenting) or technical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event) and not due to a change in the patient's medical status per clinical judgment.

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 non-dosing 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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

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 (as described

under "Period 1" above, per assessments specified in Table 2) 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 as detailed in Section 6.9.1 and footnote "k" of Table 1 and Table 2). 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 and for non-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.

Section 6.9.4 provides details for dose adjustment following outcome of primary endpoint analysis.

Procedures for Potential Post-injection Delirium/Sedation Syndrome

[redacted]

Early Termination and Follow-up Period

Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) 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] 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 time window for the EOT visit is ±1 week, and the time window for the FU visit is -1/+2 weeks.

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 Q4 2022 (first patient screened) to Q2 2025 (last patient last visit).

The study schematic diagram is presented in Figure 1.

4.2. Planned Number of Patients and Countries

Approximately [redacted] patients will be screened to achieve approximately 640 randomized patients.

Following the primary efficacy estimand, all randomized patients will be evaluable for efficacy analysis in this study. Details on definition of evaluable patients and sample size are given in Section 10.

The study is planned to be conducted in the US, Bulgaria, [redacted], Romania, [redacted], Turkey, and possibly other countries, in approximately 100 investigational centers. The study is expected to start in Q4 2022 and last until approximately Q2 2025.

4.3. Justification for Study Design and Selection of Population

Schizophrenia is a lifelong illness with evolving symptoms that can fluctuate in severity over time. A major goal in designing treatments for schizophrenia is to effectively stabilize symptoms, keep them stable over the long term, and maintain an acceptable safety profile. The

present study is designed to assess the ability of TV-44749 to stabilize symptoms in a patient population with unstable symptomology experiencing an acute exacerbation of schizophrenia. The study will evaluate the efficacy of TV-44749 on psychiatric symptoms, relative to placebo. It will also assess the safety and tolerability of TV-44749 in patients with schizophrenia over a treatment period of 56 weeks.

Refer to Section 6.3 for the justification of the IMP dose and the use of placebo IMP and to Section 3.1.1 for the justification of the primary endpoint.

4.3.1. Study Duration

Registration trials for drugs indicated for schizophrenia, in patients experiencing an acute symptom exacerbation, are typically randomized, double-blind, placebo-controlled studies, 6 to 8 weeks in duration. This is because thus far, for second-generation antipsychotics, a reasonable stability of effect is often observed (as well as some effect on negative symptoms) only after 6 weeks of treatment (Gopalakrishnan et al 2021).

In case of LAIs, the selection of the timing for the primary endpoint should take into consideration the dosing interval of the LAI under investigation as well as the anticipated onset of therapeutic effect. For instance, the confirmatory efficacy trial for the recently approved LAI risperidone product PERSERIS® (Indivior Inc.) used mean change from baseline to week 8 in the PANSS total score as the primary efficacy endpoint, aligned with the q1m administration regimen of the investigational product (Nasser et al 2016).

Similarly, as TV-44749 is an LAI intended for q1m administration, this study is designed as a randomized, double-blind, placebo-controlled study in patients with acute exacerbation of schizophrenia, comparing 3 dose strengths of TV-44749 q1m with placebo q1m with a primary endpoint of change from baseline to week 8 in the PANSS total score, with a long-term safety period.

Shorter study duration (eg, 4 weeks) could also be considered, especially given the fact that TV-44749 has a similar profile to existing antipsychotic drugs. However, this carries the risk of negative results if maximal therapeutic effect is not obtained at 4 weeks, and the shorter duration is disadvantageous in terms of the ability to demonstrate stability of effect.

4.3.2. Patient Selection

This study will enroll patients diagnosed with schizophrenia according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The diagnosis will be confirmed using a structured assessment tool (Structured Clinical Interview for DSM-5, Clinical Trials Version [SCID-5-CT]).

The acute status will be confirmed by the total PANSS score between 80 and 120, inclusive, at screening and 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, and a CGI-S score of ≥4 (moderately ill) at screening and baseline (prior to randomization).

Further descriptive parameters, demographic characteristics, and a detailed disease history, such as age, sex, ethnicity, age at onset of illness, duration of current episode, baseline psychopathology, comorbid conditions, substance abuse, etc will be documented.

Exclusion of patient groups that may introduce confounding factors (eg, comorbidities or concomitant medication as detailed in study exclusion criteria) will maximize external validity and broad applicability to the intended patient population without unduly compromising internal validity.

4.4. Stopping Rules for the Study

A conditional power approach will be used in case the IDMC considers an ET of the study due to poor efficacy, as applicable. Full details of this approach will be depicted in the IDMC charter and the statistical analysis plan. 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

If the whole study or arms of the study will be stopped, the patients who are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 5.4).

4.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1 (Period 1) and Table 2 (Period 2). Detailed descriptions of each method of procedures and assessments are provided in Section 7 (efficacy assessments), Section 8 (safety assessments), and Section 9 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B.

5. SELECTION AND WITHDRAWAL OF PATIENTS

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

5.1. Patient Inclusion Criteria

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

a. [Revision 1] The patient is a male or female of any ethnic origin, 18 to 64 years of age, inclusive, at the time of screening.

b. [Revision 1] The patient is capable of providing signed informed consent. 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]

c. The patient has a current confirmed diagnosis of schizophrenia according to the DSM-5, for >1 year. Diagnosis must be reconfirmed by the SCID-5-CT.

d. The patient has a total PANSS score between 80 and 120, inclusive, at screening and 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.

e. The patient has exacerbation of schizophrenia that started ≤8 weeks prior to screening and would benefit from psychiatric hospitalization or continued hospitalization for symptoms of schizophrenia.

f. The patient has a CGI-S score of ≥4 (moderately ill) at screening and baseline (prior to randomization).

g. Patients who have received an antipsychotic treatment (other than clozapine) in the past year must have been responsive based on the investigator's judgment (and based on discussions with family members, caregivers, or healthcare professionals, as applicable).

h. [Revision 1] The patient has 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 site personnel must identify the caregiver at the screening visit and consider the caregiver a reliable contact person. The caregiver must have regular contact with the patient (defined as direct contact not fewer than 3 times per week), with the expectation that this frequency of contact would continue throughout the outpatient portion of Period 1 (it is also advised during the rest of the study, including Period 2 and the FU period). This regular contact with the patient is not mandatory during the

hospitalization period of Period 1. The patient's caregiver will be asked to sign a caregiver ICF during the screening period.

i. Body mass index between 18.0 and 40.0 kg/m^2, inclusive, at the time of screening.

j. Women may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at screening and baseline (if a borderline result is obtained on a urine test, a serum test should be performed and a negative result obtained) or are sterile (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or congenitally sterile) or postmenopausal (Appendix E).

k. Women of childbearing potential must agree not to try to become pregnant, and, unless they have exclusively same-sex partners, must agree to use a highly effective method of contraception prior to the first administration of IMP, and agree to continue the use of this method for the duration of the study, and for 70 days after the last dose of IMP. Highly effective methods of contraception include the following:

   – Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at the screening visit before the first dose of IMP.

   – Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at the screening visit before the first dose of IMP.

   – Intrauterine device and intrauterine hormone-releasing system; these need to be in place at least 2 months before screening.

   – Bilateral tubal occlusion.

   – Vasectomized partner, provided that he is the sole sexual partner and has received medical assessment of the surgical process.

   – Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

l. The patient, if an adult male, is surgically sterile, or, if capable of producing offspring, has exclusively same-sex partners or is currently using an approved method of birth control and agrees to the continued use of this method for the duration of the study (and for 70 days after the last dose of IMP). Male patients with sex partners who are women of childbearing potential must use condoms even if surgically sterile. In addition, male patients may not donate sperm for the duration of the study and for 70 days after the last dose of IMP.

m. The patient is able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens (oral and sc administration), non-use of prohibited concomitant medications, and hospitalization for at least 4 weeks at the clinical site; can read and understand the written word in order to complete patient-reported outcomes measures by themselves; and can be reliably rated on assessment scales.

n. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period (including hospitalization for at least 4 weeks at the clinical site) and must be willing to return to the investigational center for further visits, as applicable, and for the FU procedures and assessments as specified in this protocol.

o. The patient has a stable place of residence for approximately 3 months before screening, and changes in residence are not anticipated over the course of study participation.

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

5.2. Patient Exclusion Criteria

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

a. The patient has a current clinically significant DSM-5 diagnosis other than schizophrenia (has a primary current diagnosis other than schizophrenia or a comorbid diagnosis that is primarily responsible for the current symptoms and functional impairment).

b. The patient has a known history of the following: (a) borderline personality disorder, antisocial personality disorder, or bipolar disorder; (b) traumatic brain injury causing ongoing cognitive difficulties, Alzheimer's disease, or another form of dementia, or any chronic organic disease of the central nervous system; and (c) intellectual disability of a severity that would impact ability to participate in the study.

c. The patient has an improvement (reduction) in the total PANSS score of ≥20% between screening and day 1 (baseline [randomization] visit).

d. The patient was hospitalized for >14 days (with the exception of social or administrative hospitalization) in the current exacerbation episode prior to screening.

e. The patient has a significant risk of violent behavior based on the patient's medical history or investigator's judgment.

f. The patient has a significant risk of committing suicide based on the patient's medical history or C-SSRS, and the investigator's judgment.

   Patients with a C-SSRS positive response to suicidal ideation items 3, 4, or 5 and/or positive suicidal behavior response in the past 6 months are not eligible.

g. The patient meets criteria for moderate to severe substance use disorder (based on DSM-5 criteria) within the past 6 months, such as chronic alcohol abuse or drug abuse (excluding those related to caffeine or nicotine). If, per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a positive result on the urine drug test is not exclusionary. Patients' eligibility in such case of positive result, without medical explanation, will be determined by the investigator based on the patient's background, history of substance use, and the investigator's

discussions with family members, caregivers, or healthcare professionals, as applicable.

h. The patient is currently using an LAI antipsychotic or is still under the coverage period of the specific LAI at time of screening.

i. The patient has taken clozapine or has received electroconvulsive therapy within the last 12 months prior to screening.

j. The patient is currently receiving daily oral olanzapine at a dose >20 mg/day.

k. The patient has current or a history of known hypersensitivity to olanzapine or any of the excipients of TV-44749 or the oral formulation of olanzapine.

l. The patient has treatment-resistant schizophrenia according to medical and psychiatric history, as judged by the investigator or documented failure of 2 or more antipsychotic medications (administered at the maximum tolerated dose for at least 6 weeks each). Participants who have responded to antipsychotics only when paired with clozapine are considered treatment resistant.

m. The patient has had a significant sedation or delirium after antipsychotic treatment according to medical and psychiatric history and as judged by the investigator or suffered from delirium due to a medical condition.

n. [Revision 1] The patient has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize study participant's safety (including in the context of local oral olanzapine label) or would compromise the patient’s ability to participate in this study.

o. The patient has known risk factors for undiagnosed/instable arrhythmia, congenital long QT, hypokalemia, hypomagnesemia, or autonomic failure (mostly with clinically significant orthostatic hypotension).

p. The patient has any clinically significant uncontrolled medical condition (treated or untreated).

q. Any disorder that may interfere with absorption, metabolism, or elimination of olanzapine

r. The patient has a non-fasting glucose level of ≥200 mg/dL at screening.

s. The patient had a change in their diabetes treatment within 4 weeks before the first injection of the IMP.

t. The patient has serum triglycerides levels of ≥500 mg/dL.

u. The patient has low-density lipoprotein levels of ≥190 mg/dL.

v. The patient has a history of ketoacidosis or hyperosmolar coma.

w. [Revision 1] The patient has alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase values ≥2 × the upper limit of normal (ULN) of the performing laboratory, and aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase values ≥2 × ULN, and total bilirubin values ≥1.5 × ULN at screening.

Isolated parameters for exclusion are as follows:

- ALT or AST >5 × ULN
- ALT or AST >3 × ULN, and in addition either total bilirubin level >2 × ULN or international normalized ratio >1.5 (if elevation of international normalized ratio is not caused by anticoagulants)
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

x. The patient has a neutrophil count of <1200/mm^3.

y. The patient has platelet count ≤75 × 10^3 μL.

z. The patient has serum creatinine >2.5 mg/dL.

aa. The patient has a positive serology for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen, and/or hepatitis C. If serology is positive for hepatitis C but the ribonucleic acid (RNA) test is negative, and the patient has no history of liver disease or symptoms of active liver disease, enrollment will be allowed based on clinical judgment.

bb. The patient is a pregnant or lactating woman or plans to become pregnant during the study.

cc. The patient has previously participated in this study (except for rescreening).

dd. The patient is or has been using or consuming the medications prohibited in this protocol.

ee. The patient used an investigational drug (new chemical entity) or a medical device in a clinical study within 30 days or 5 half-lives (whichever is longer), or, in case of a biologic investigational drug, within 3 months or 5 half-lives (whichever is longer) prior to the first TV-44749 administration.

ff. The patient has donated or received any blood, plasma, or platelet transfusions within 30 days prior to the study or have planned donations during the study period or 6 months following the last dose of IMP administration.

gg. The patient has a pending court appearance that may result in incarceration.

5.3. Eligibility Criteria for Period 2

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.

5.4. Withdrawal Criteria and Assessments/Procedures for the Patient

Patients are expected to participate in the study for its entire duration and perform the scheduled visits and procedures. Each patient is free to withdraw from the study or discontinue treatment with IMP at any time, without prejudice to their continued care, but every effort should be undertaken to determine the reason for discontinuation.

Patients must discontinue treatment with IMP and/or withdraw from the study if any of the following events occur:

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

Additionally, patients who meet the following study-specific criteria will be early terminated (ie, discontinued from further treatment with IMP and encouraged to complete the EOT and FU visits):

1. Patient is diagnosed with a clinically significant DSM-5 disorder other than schizophrenia.
2. A patient demonstrates a significant clinical deterioration that cannot be managed with permitted rescue medication as judged by the investigator based on any relevant history or observation made by the investigative site, and/ or requires other antipsychotic treatment apart from TV-44749. Hospitalization due to deterioration of schizophrenia that does not require other antipsychotic treatment will not be a withdrawal criterion unless determined as such by the investigator.
3. A patient experiences 3 events of pus-containing lesions (abscess, infection, or inflammation) at the site of injection requiring intervention/systemic treatment following 3 separate IMP injections.

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

Investigators should attempt to obtain information on patients in case of withdrawal from the study or discontinuation from the IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from the IMP, must be recorded in the source documents. The CRF must document the primary reason for withdrawal from the study or discontinuation from the IMP.

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

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

The patient will be monitored as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the test IMP or study procedure is made). The investigator must inform the MM or other applicable study contact person as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

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

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

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. 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] 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).

5.5. Replacement of Patients

Randomized patients will not be replaced.

5.6. Rescreening

A patient who is screened but not randomized (eg, because the inclusion and exclusion criteria were not met or randomization did not occur within the specified time) may be considered for screening again if, for example, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.

Patients may be rescreened only once and at the same investigational center. In case rescreening is considered, the investigator should contact the MM or the sponsor, in order to determine which parameters need to be retested for the rescreening (eg, some parameters may not need to be retested if the repeated values for the laboratory, vital sign, or ECG screening criteria are within acceptable limits as judged by the investigator and the sponsor/MM or if repeated values show normalization of the out-of-range values, but their initial screening period has expired).

If the patient is rescreened, informed consent will need to be provided again according to the different requirements described in this protocol.

5.7. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. Minimal information should be collected that includes but is not limited to demography, screening failure details, eligibility criteria, and any serious adverse events.

6. TREATMENTS

6.1. Investigational Medicinal Products Used in the Study

IMP is defined as the test IMP and matching placebo IMP to the test IMP.

Refer to Table 6 for a description of the test IMP (TV-44749) and placebo IMP.

The test IMP and placebo IMP are not authorized products.

6.1.1. Test Investigational Medicinal Product

[redacted]

Detailed preparation and administration instructions are provided in the pharmacy manual.

Additional details may be found in the IB for TV-44749.

6.1.1.1. Dosing Groups

TV-44749 is administered at 3 doses in this study: low (318 mg q1m), medium (425 mg q1m), and high (531 mg q1m).

Table 5: Conversion Between Oral Olanzapine and TV-44749 Doses

Oral dose of olanzapine	TV-44749 dose	TV-44749 volume to be dosed
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6.1.1.2. Dose Adjustment

Refer to Section 4.1 for a description of the dose adjustments that are permitted during Period 2.

6.1.2. Placebo Investigational Medicinal Product

[redacted]

[redacted]

Detailed preparation and administration instructions are provided in the pharmacy manual.

6.1.3. Other Components

The kit for IMP and placebo IMP contains the following:

- [redacted]
- [redacted]
- [redacted]

Table 6: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	TV-44749	TV-44749 placebo
Formulation	[redacted]	[redacted]
Unit dose strength(s)/Dosage level(s)	[redacted]	[redacted]
Route of administration	sc injection (abdomen)	sc injection (abdomen)
Dosing instructions	q1m injections per the patient's assigned treatment group	q1m injections per the patient's assigned treatment group
Packaging	IMP will be provided in a blister tray in a carton box.	IMP will be provided in a blister tray in a carton box.
Manufacturer	[redacted]	[redacted]

IMP=investigational medicinal product; INN=international nonproprietary name; q1m=once monthly; sc=subcutaneous.

6.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

The test IMP is TV-44749 (olanzapine for extended-release injectable suspension) for sc use.

[redacted]

Details of the preparation of the drug product will be fully described in the pharmacy manual.

6.2.1. Storage and Security

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMPs received, and any discrepancies are reported and resolved before use of the IMPs.

The IMPs (TV-44749 [olanzapine] powder and empty 10-mL clear glass vial [for placebo]) must be stored at a controlled temperature in a secure area. The site should have a process for monitoring the storage temperature for unused IMP.

6.2.2. Labeling

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

6.2.3. Accountability

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

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

Only patients randomized in the study may receive IMPs, and only authorized unblinded staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored area (automated monitoring, including alerts in case of deviations, is highly recommended) in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies.

Further guidance and information are provided in the pharmacy manual.

6.3. Justification for Investigational Medicinal Products

6.3.1. Justification for Dose of Test Investigational Medicinal Product

[redacted]

6.3.2. Justification for Use of Placebo Investigational Medicinal Product

Based on the pre-Investigational New Drug meeting with the Food and Drug Administration (FDA) in 2019, the Agency recommended that the sponsor conduct a prospective, randomized, placebo-controlled study to assess the safety and efficacy of TV-44749, with a primary endpoint of symptom severity, as measured by PANSS, at 8 weeks.

The use of a placebo control treatment group for comparison is acceptable and commonly used in clinical studies assessing efficacy in patients with schizophrenia (Nasser et al 2016, Potkin et al 2020).

Several measures to ensure adequate treatment of patients assigned to the placebo group are included in the study protocol. Patients will be treated with placebo for a limited period (8 weeks). All patients will be hospitalized and closely monitored for at least 4 weeks following the first IMP administration (Table 1). Patients who fail to meet discharge criteria (RDQ) at this point may continue as inpatients until the end of Period 1 (week 8), at which point active treatment will be administered to all patients who meet Period 2 entry criteria. Throughout Period 1 (placebo-controlled period), rescue medications use will be allowed per investigator clinical judgment (Section 6.7.1.1). At all times, patients may be withdrawn from the study per investigator discretion if participation in the study no longer provides a potential clinical benefit to the patient or per patient's request for any reason (Section 5.4). If a patient is withdrawn from the study at investigator discretion, patients will be advised to return to their primary physician for treatment continuation consideration.

6.4. Other Medicinal Products/Auxiliary Medicinal Products

Oral olanzapine is an authorized auxiliary medicinal product and will be used in accordance with the terms of its marketing authorizations.

Note that oral olanzapine (Table 7) is provided during the screening period (only to patients who have not previously received oral olanzapine) in order to assess tolerability; however, for the purposes of this study, it is not considered an IMP.

Table 7: Other Medicinal Products Used in the Study

Medicinal product name	**Olanzapine**
Pharmaceutical form	Tablets
Unit dose strength(s)/Dosage level(s)	2.5, 5, 7.5, and 10 mg
Route of administration	Oral use
Dosing instructions	2 consecutive doses (10 mg/day or higher [but not exceeding 20 mg/day] per investigator decision) at an interval of 24 hours apart

6.5. Treatment after the End of the Study

No further treatment is planned by the sponsor after the patient completes his or her participation in this study. Patients will be advised to return to their primary physician for treatment continuation consideration. During the FU period (4 to 8 weeks after the last dose of IMP), patients may be treated for schizophrenia per the investigator's judgment.

6.6. Restrictions

Patients will be required to comply with the following restrictions:

6.6.1. Activity

[redacted]

6.6.2. Fasting

Patients must fast for at least 8 hours prior to baseline (visit 2; week 0), visit 11 (week 8), and the EOT visit (and preferably the ET visit).

6.6.3. Specific Food and Beverages

Meals will be provided throughout the hospitalization period. Patients will be required to comply with the following additional restrictions:

- It is recommended that patients do not consume alcohol and cannabis-derived products (such as marijuana) throughout the study, including the FU period.
- It is recommended that patients avoid excessive consumption of coffee, tea, and/or caffeine-containing beverages or food (ie, 600 mg or more of caffeine per day or 5 or more cups of coffee per day) from before the first dose of IMP and throughout this study, including the FU period.

6.6.4. Blood Donation

Patients may not have donated or received any blood, plasma, or platelet transfusions within 30 days prior to the study or have planned donations during the study period or 6 months following the last dose of IMP administration.

6.6.5. Cigarette/Tobacco Use

Patients who smoke cigarettes or use other tobacco-containing products should not change their smoking habits during the study. In case there is any change in smoking habits, the patient should inform the investigator.

Patients' smoking habits will be recorded in the CRF. Data on cigarette use will be collected using the question, "How many packs of cigarettes did you smoke over the past 7 days?" at the time points specified in Table 1 and Table 2.

6.7. Prior and Concomitant Medication or Therapy

Any prior or concomitant medication 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. Trade name and international nonproprietary name (if available), indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary.

The following medications will be prohibited during this study:

- antipsychotics other than the study treatment
- strong or moderate inhibitors of CYP1A2 within 14 days or 5 half-lives (whichever occurs last) prior to randomization
- strong inducers of CYP1A2 within 30 days prior to randomization
- dopamine reuptake inhibitors or prescription psychostimulants
- opiates or opiate-containing analgesics within 14 days prior to randomization
- In addition to those listed above, medications that may be expected to significantly interfere with the metabolism or excretion of olanzapine, may be associated with a significant drug interaction with olanzapine, or may pose a significant risk to patients' participation in the study.

- Olanzapine (except when given according to the study protocol)

Allowed medications in this study include rescue medications (Section 6.7.1.1), protocol-approved antidepressants (including selective serotonin reuptake inhibitors [other than fluvoxamine], serotonin and norepinephrine reuptake inhibitors, and trazodone), and mood stabilizers (except carbamazepine) (Section 6.7.1.2), medications required for the treatment of any adverse events, and contraceptives as per Appendix E.

Medications prescribed for the treatment of chronic medical conditions, other than antipsychotic medications, or for the treatment of acute medical conditions (such as antibiotics) may be permitted per investigator judgment.

COVID-19 and seasonal flu vaccines will be allowed during the study. Other vaccinations may be allowed after consultation with the MM or sponsor.

A partial list of additional disallowed medications is provided in Appendix G. In the event that a new concomitant medication not specified in this protocol is initiated by the patient, the investigator is encouraged to approach the MM or the sponsor to discuss.

It is advised not to allow benzodiazepines and anticholinergics within 8 hours or 12 hours, respectively, of rating scales' assessments.

At each visit at the investigational center after the screening visit, the investigator will ask patients whether they have taken any medications (other than IMP[s]), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit, and whether any of the allowed concomitant medications have been used.

Concomitant medication and non-pharmacological treatment will be recorded from screening through the final visit.

6.7.1. Allowed Concomitant Medications

6.7.1.1. Rescue Medications

Allowed rescue medications will include zolpidem, zopiclone, zaleplon, or diphenhydramine for insomnia; benztropine, trihexyphenidyl, or diphenhydramine for parkinsonian symptoms; and propranolol and benzodiazepines for akathisia.

In addition, during the screening period and in Period 1, use of lorazepam (up to 6 mg/day or up to the maximal daily dose allowed locally [the lower of the two]) is permitted on an as-needed basis for indications other than akathisia (eg, anxiety). Use in this context must be limited to no more than 72 consecutive hours, and lorazepam should not be taken within 8 hours prior to rating scale assessments.

In Period 2, use of lorazepam (per local label approved dose) is permitted on an as-needed basis for indications other than akathisia (eg, anxiety).

Antihistamine and anticholinergic drugs will be permitted during the study for agitation and insomnia.

6.7.1.2. Antidepressants and Mood Stabilizers

Screening Period and Period 1: Patients who are currently treated with antidepressants and/or mood stabilizers for at least 3 months prior to screening and with no change in dose for at least 4 weeks prior to screening (except for indications excluding the patient from entering the study, such as schizoaffective disorder) may continue their treatment during the screening period/Period 1. No change of dose or new treatment initiation with such medications will be permitted in the screening period/Period 1.

Period 2: During Period 2, patients who received mood stabilizers and protocol-approved antidepressants prior to study entrance for at least 3 months prior to screening and with no change in dose for at least 4 weeks prior to screening and continued their treatment during Period 1 will be allowed to continue their treatment. New administrations of mood stabilizers will be not permitted; dose adjustments of mood stabilizers may be allowed on a case-by-case basis after discussion with the MM.

Dose adjustment of protocol-approved antidepressants will be allowed in Period 2 according to the investigator's clinical judgment. Patients who did not receive antidepressants previously will be allowed to initiate treatment with protocol-approved antidepressants (including selective serotonin reuptake inhibitors [other than fluvoxamine], serotonin and norepinephrine reuptake inhibitors, and trazodone) during Period 2 based on the investigator's clinical judgment.

The use of other antidepressants (such as tricyclic and tetracyclic antidepressants and bupropion) will be prohibited for the entire duration of the study. Investigators are encouraged to approach the MM or the sponsor prior to initiating any new antidepressant treatment.

6.8. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance until completion of the IMP administration according to the protocol or discontinuation from the IMP. A check of compliance with IMP intake and completion of protocol-specified assessments and procedures will be performed during each visit after the IMP has been administered; IMP accountability records will be completed.

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

6.9. 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; Far East; 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 and delegates involved in the study as well as the blinded site staff and the study participants will be blinded to the identity of the IMPs until the Period 1 database is locked for final efficacy analysis. Site staff and study participants unblinding may be done only after authorization is given by the sponsor. 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.

The randomization list 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.

Period 2: Period 2 will be open-label and will not include a placebo group. Period 1 will remain blinded to the Sponsor, the site staff, and the study participants 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 a 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 (Section 6.9.1), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed after week 8 (visit 11) by the 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).

6.9.1. Procedures and Assessments to be Performed Before and After Randomization into Period 2 at Visit 11 (Week 8)

Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) are as follows:

- Clinical laboratory tests

- Thyroid tests
- Physical examination
- ECG
- Vital signs
- Urine β-HCG
- PANSS
- CGI-S
- CGI-I
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- C-SSRS
- Personal and Social Performance Scale (PSP)
- CDSS
- Patient Global Impression-Improvement (PGI-I)
- Blood samples for plasma concentration of IMP
- Adverse event inquiry
- Injection site findings and pain assessment of last injection
- Inquiry regarding alcohol consumption/illicit drug use
- Concomitant medication inquiry

Procedures and assessments that need to be performed after randomization into Period 2 at visit 11 (week 8) are as follows:

- IMP administration
- Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose

Remaining procedures and assessments at visit 11 (week 8) may be performed either before or after randomization.

6.9.2. 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.

6.9.3. 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 will be discontinued and additional patients may be randomized to the study (ie, to Period 1) to the TV-44749 treatment groups only. The 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 to the Sponsor, the site staff, and the study participants 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 the purpose of the Period 1 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.

6.9.4. Treatment of Study Participants Following the Outcome of Primary Efficacy Analysis Availability

Following the completion of the efficacy analysis for Period 1, the Sponsor will communicate the topline results regarding TV-44749 efficacy to the Investigators. Subsequently, based on these results and guided by clinical judgment, Investigators will determine the course of action for Period 2 participants under their care. This may involve deciding whether participants will continue their current TV-44749 dose, adjusting their dose, or terminating their study participation. This also includes the option that a patient may remain on their current dose even if the population-level results indicate that the treatment arm for that dose was found futile, provided that the patient is stable on this dose and would benefit from continuing on it according to the investigator’s assessment. The rationale for this approach is rooted in olanzapine's high variability, where an exposure deemed inadequate on a population level may still offer a positive risk-benefit ratio for individual patients with specific intrinsic and extrinsic characteristics affecting Olanzapine PK and patient's psychiatric stabilization and safety profile. Therefore, PI

discretion is advised when deciding on continued participation and potential dose adjustments. The possibility that one or more treatment arms may show initial failure in the topline efficacy analysis does not necessarily preclude its submission for regulatory approval. The totality of data, including secondary endpoints and sensitivity analyses, will be considered, taking into account the established efficacy of olanzapine.

It is the responsibility of the Investigator to convey the study top-line efficacy results to study participants once these become available, including the Investigator's recommendation regarding a change in TV-44749 dose or continuation of existing dose, or Investigator's decision regarding early termination. The investigator is responsible to obtain informed consent to continue participation in the study in case the participants were assigned to the dose level found to be futile. Notification of positive results to study participants, as relevant, will not require re-consent.

6.10. Maintenance of Randomization and Blinding

6.10.1. Maintenance of Randomization

Patient randomization codes will be maintained in a secure location at the service provider contracted to generate the codes. At the time of analysis (ie, after the efficacy portion of the study is completed), after receiving unblinding request from a Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

6.10.2. Blinding and Unblinding

Pharmacokinetic sample analysis by the bioanalytical laboratory may be performed during the course of the study. The population pharmacokinetic model for TV-44749 may be updated with new pharmacokinetic data emerging from the ongoing study. Population pharmacokinetic and pharmacokinetic analyses are required for the monitoring of the patients and enable IDMC evaluation of patient's safety-related issues. The process to ensure study integrity, maintenance of the double blind during Period 1, and the responsibilities of the relevant study personnel will be described in a pharmacokinetic analysis plan that will be approved prior to any data transfer, per the unblinded analyses group's interim analysis SOP and other relevant SOPs.

In addition, if a prioritized sample analysis is needed (ie, assessment of a pharmacokinetic sample for a potential PDSS event), relevant sponsor personnel may be unblinded during Period 1. Additional information will be provided in the separate predefined unblinded pharmacokinetic analyses plan.

As prolactin levels are highly affected by olanzapine and reach steady state approximately 8 weeks after treatment initiation (Yang et al 2018), in order to maintain the blind, prolactin level results obtained after first IMP administration and before visit 13 (8 weeks into Period 2) will not be available for review by the sponsor or the sites until Period 1 database lock. The IDMC will review the unblinded data periodically.

For information about personnel who may be aware of IMP assignments, see Section 6.9. These individuals will not be involved in the conduct of any study procedures or assessment of any adverse events.

In cases when knowledge of the IMP assignment is needed to make treatment decisions during Period 1, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes indicating the IMP assignment for each randomized patient will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, via internet. A back-up process will be available to the investigator in case of internet connection issues. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code during Period 1. The patient's IMP assignment should not be revealed to the sponsor (during Period 1).

If a blind is broken during Period 1, the patient will be withdrawn from the study, and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP during Period 1 should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 8.1.4), the Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs during Period 1, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study and in the analysis and reporting of the data.

6.10.3. Independent Data Monitoring Committee

There will be an IDMC in this study. Details are given in Appendix A.

6.11. Total Blood Volume

The total blood volume for routine sampling to be collected for each patient in this study is approximately 257 mL (at maximum), not including the optional samples for pharmacogenetics and biomarkers.

[redacted]

7. ASSESSMENT OF EFFICACY

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

7.1. Assessments of Efficacy

7.1.1. Positive and Negative Syndrome Scale

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

[redacted]

The PANSS will be administered by the investigator/trained rater at screening and all the time points specified in Table 1 and Table 2.

In addition to the patient and the rater, the information used for PANSS assessment may be obtained from 3rd party sources, such as the caregiver and an informant. In such cases, the name of the person/s who had provided the information and their relation to the patient (ie, caregiver or informant) should be recorded in the source documents.

7.1.2. Clinical Global Impression–Improvement

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

The CGI-I will be administered by the investigator/trained rater at time points specified in Table 1 and Table 2. The CGI-I during Periods 1 and 2 will be relative to the CGI-S score at the baseline visit (visit 2 in Period 1).

7.1.3. Clinical Global Impression–Severity of Illness Scale

The investigator/trained rater will complete the CGI-S at the time points specified in Table 1 and Table 2. 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 (Guy 1976b).

7.1.4. Patient Global Impression-Improvement

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 Table 1 and Table 2).

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 (Steinert et al 2010).

7.1.5. Personal and Social Performance Scale

The PSP will be administered to patients at the time points specified in Table 1 and Table 2 and is a clinician-rated instrument that measures personal and social functioning in patients with schizophrenia (Morosini et al 2000). The PSP is a 100-point single-item rating scale, divided into 10 equal intervals. 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.

7.2. Other Assessment

7.2.1. Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)

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

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

7.2.2. Quality of Life Scales

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

7.2.2.1. Schizophrenia Quality of Life Scale

The Schizophrenia Quality of Life Scale (SQLS) Revision 4 (Martin and Allan 2007) will be administered at the time points specified in Table 1 and Table 2 and will be used to capture quality of life. The 33-item measure yields 3 subscale scores: psychosocial, motivation/energy, and symptoms/side effects (Wilkinson et al 2000). Higher scores on the scales indicate worse quality of life.

7.2.2.2. [redacted]

[redacted]

[redacted]

8. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events (including serious adverse events, extrapyramidal symptoms, injection pain and other injection site findings [local tolerability]), vital signs (blood pressure, pulse and orthostatic changes, and temperature), body weight, laboratory tests, ECG, concomitant medication use, time to all-cause discontinuation, all-cause discontinuation rates and discontinuation rates due to adverse events (tolerability), and rating scales (including AIMS, BARS, SAS, C-SSRS, and CDSS).

Adverse events are categorized by ICH guidelines.

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

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

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the IMP.

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

- a new condition or the worsening of a pre-existing condition
- intercurrent illnesses
- physical injuries and the mechanism that caused the injury
- events possibly related to concomitant medication
- drug/drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities

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

In Period 2, worsening of the schizophrenia will be assessed using PANSS, CGI-I, and CGI-S and should be recorded as an adverse event per investigator judgment.

A relapse event will be classified as an adverse event if specifically assessed as such by the investigator.

An adverse device effect is an adverse event related to the use of a medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the

medical device, including any event resulting from user error or from intentional misuse of the medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to medical devices.

8.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of the FU period. Treatment-emergent adverse events are defined as adverse events that occurred after the first dose of IMP was administered through the end of the study.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events and protocol-defined adverse events of special interest (PDAESIs) for expedited reporting to GPSP, the serious adverse event and PDAESI form must be completed, and the serious adverse event and the PDAESI must be reported immediately (Section 8.1.6.1). The investigator does not need to actively monitor patients for new adverse events after the end of the study.

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

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

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

The relationship of each adverse event to the IMP and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described in Section 8.1.3, Section 8.1.4, and Section 8.1.5.

The investigator should make an initial determination whether the adverse event may be related to a device deficiency. If the AE/SAE could be related to the device, per Appendix I, the details of the AE/SAE related to the device will be forwarded to the manufacturer/wholesaler of the device. Adverse device effects must be recorded on the source documentation and the CRF.

Further details are given in the Safety Monitoring Plan.

8.1.3. Severity of an Adverse Event

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

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product

The relationship of an adverse event to the IMP and/or device is characterized as follows (Table 8):

Table 8: The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP and/or device.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least two of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP and/or device. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP and/or device. • It does not reappear or worsen when the IMP and/or device is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP and/or device cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least two of the following apply: • It follows a reasonable temporal sequence from administration of the IMP and/or device. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP and/or device, yet an IMP and/or device relationship clearly exists. • It follows a known pattern of response to the IMP and/or device.

IMP=investigational medicinal product.

8.1.5. Serious Adverse Events

For recording of a serious adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of the FU period. Serious adverse events occurring in a patient after the end of study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 8.1.6.1.

8.1.5.1. Definition of a Serious Adverse Event

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

- results in death
- is a life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay was required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, liver injury that meets the criteria for Hy's law, or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

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

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

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

A serious adverse device effect is an adverse device effect that results in any of the consequences characteristic of a serious adverse event and is reported per Section 8.1.6.

8.1.5.2. Expectedness

A serious adverse event that is not included in the adverse reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The RSI for this study is the RSI section of the IB for TV-44749 and the ZYPREXA SmPC 2022 or ZYPREXA USPI 2021 for the oral olanzapine treatment (where applicable) during the screening period.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

The sponsor's GPSP will determine the expectedness for all serious adverse events.

8.1.6. Reporting a Serious Adverse Event

8.1.6.1. Investigator Responsibility

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

Serious adverse events occurring after the patient has ended the study should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (as applicable, for example, a contract research organization [CRO] in a country without a sponsor LSO); the LSO will forward the report to the sponsor's GPSP.

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

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

Additional information includes the following:

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

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

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

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

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

For double-blind studies, blinding will be maintained for all study personnel. Therefore, in case of a SUSAR during Period 1, only the LSO/CRO unblinded personnel will receive the unblinded report for regulatory submission; the others will receive a blinded report.

8.1.6.2. Sponsor Responsibility

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

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

- modifying the protocol and/or ICF
- discontinuing or suspending the study
- modifying listings of expected toxicities to include adverse events newly identified as related to the IMP

8.1.7. Protocol-Defined Adverse Events of Special Interest

8.1.7.1. Protocol-Defined Adverse Events of Special Interest that Require Reporting to the Sponsor's Global Patient Safety and Pharmacovigilance

[redacted]

8.1.7.2. Protocol-Defined Adverse Events of Special Interest that Do Not Require Reporting to the Sponsor's Global Patient Safety and Pharmacovigilance

[redacted]

8.1.8. Protocol Deviations Because of an Adverse Event

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

8.2. Pregnancy

Any female patient becoming pregnant during the study will discontinue IMP and will be discontinued from the study.

All pregnancies of women participating in the study and female partners of men participating in the study that occur during the study or within 6 months after the last dose administration are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form (note that the pregnancy itself is not considered an adverse event). The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 8.1.6).

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

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

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

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

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

8.3. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported in the patients' source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria (Appendix C), all instances of incorrect IMP administration should be categorized as "Noncompliance to IMP."

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor (in a blinded manner during Period 1).

3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk.

8.4. Clinical Laboratory Tests

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

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is assessed by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 8.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Clinical Laboratory Tests During Screening

During screening, the site should collect and ship the screening blood samples as soon as possible (preferably on the first day of the screening period). In case the site faces a delay in obtaining the central laboratory results for the clinical laboratory tests performed during screening that are needed to determine eligibility, additional screening blood samples (specifically those with delayed results) may be collected as soon as possible and analyzed in a local laboratory to allow study eligibility determination within the 8-day screening window. For sites that are at high risk of encountering such delays (eg, a country or a region with long shipment durations and/or long turnaround time for receiving the central laboratory results, or sites that already experienced several incidents of delayed results during the study), additional screening blood samples for local laboratory analysis may be collected in advance at the same time when collecting the samples for the central laboratory analysis, provided that the site has the required capabilities for local analysis (consideration should be made to the specific samples that tend to have delayed results, and efforts should be made to only collect those samples twice). The sites' level of risk should be determined by the sponsor or the CRO and will be communicated to the site.

In case of a discrepancy between local and central laboratory results, the central laboratory results will determine the patient's study eligibility. Specifically:

- In case both central and local laboratory results are available within the screening window, the central laboratory results will be used to determine eligibility.
- In case only local laboratory results are available within the screening window and they indicate that the patient is eligible for randomization, the patient may be randomized (provided all other study criteria are met). When central laboratory results become available (after randomization), the patient's eligibility should be confirmed. In case the central laboratory results indicate that the patients does not meet study eligibility criteria, the patient will be early terminated.
- If only local laboratory results are available within the screening window and they exclude the patient from randomization (ie, the patient is a screening failure), but the central laboratory results later become available and confirm that the patient is eligible, the patient may be rescreened if all other study criteria are met.
- In the less likely event that the central laboratory results are available during the screening window and the patient is randomized based on these results, but the local laboratory results become available after randomization and indicate that the patient does not meet eligibility criteria, the central laboratory results will determine the patient's eligibility, and the patient may continue in the study per the investigator's discretion.

Any local laboratory results of blood samples collected for screening purposes, including any of the above scenarios, should be reported in the CRF.

Clinical Laboratory Tests During Visit 3

In cases where performing toxicological blood test is not feasible due to a lack of suitable analytical facilities, a urine drug screen may be performed instead. In case visit 3 safety laboratory blood samples cannot be shipped to the central laboratory on the same day, the samples may be processed in the local clinical laboratory instead. If needed, an additional set of safety laboratory tests may be collected for that purpose. In case visit 3 occurs over the weekend and the local safety laboratory tests cannot be processed on the collection day, visit 3 safety laboratory samples will be collected up to 2 days after the visit 3 nominal date and sent to the central laboratory.

Table 9: Clinical Laboratory Tests

Serum chemistry	Hematology and coagulation	Urinalysis
Calcium	**Hematology**	Protein
Phosphate	Hemoglobin	Glucose
Sodium	Hemoglobin A1C[c]	Ketones
Potassium	Hematocrit	Hemoglobin
Chloride	Erythrocytes	pH
Creatinine[a]	Platelets	Specific gravity
Glucose	Leucocytes	Microscopic tests
BUN	Neutrophils	Bacteria
Total cholesterol	Lymphocytes	Erythrocytes
LDL	Eosinophils	Leucocytes
HDL	Monocytes	Crystals
Triglycerides	Basophils	Casts
Urate	**Coagulation**[d]	
ALT	PT	
AST	INR	
LDH		
GGT		
Alkaline phosphatase		
Creatine kinase		
Bicarbonate		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		
Prolactin[b]		

[a] Glomerular filtration rate (to be calculated at screening only) will be calculated based on serum creatinine levels, weight, gender, and age using the Cockcroft-Gault equation.

[b] At screening (prior to intake of oral olanzapine, where relevant), baseline (visit 2; week 0 [prior to IMP administration]), visit 11 (week 8 [prior to IMP administration]), visit 14 (week 20 [prior to IMP administration]), and at the EOT visit, clinical laboratory tests will also include prolactin.

[c] At baseline (visit 2; week 0), visit 11 (week 8), visit 14 (week 20), visit 17 (week 32), visit 20 (week 44), and at the EOT visit, clinical laboratory tests will also include hemoglobin A1C.

[d] At screening only.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; EOT=end-of-treatment; ET=early termination; GGT=gamma-glutamyl transpeptidase; HDL=high-density lipoprotein; IMP=investigational medicinal product; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; PT=prothrombin time.

8.4.1. Serum Chemistry, Hematology, Coagulation, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 1 and Table 2. They may also be performed at any other time if clinically indicated. Clinical laboratory tests will be performed using the central

laboratory (refer to Section 8.4 for exceptions during the screening period). Specific laboratory tests to be performed are provided in Table 9.

8.4.2. Other Clinical Laboratory Tests

At screening, patients will be tested for HIV, hepatitis B surface antigen, and hepatitis C antibody. At screening, visit 11, and ET and EOT visits, patients will be test for thyroid stimulating hormone, triiodothyronine, and thyroxine.

8.4.2.1. Human Chorionic Gonadotropin and Follicle-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). 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 negative result must be obtained prior to study drug administration (if a borderline result is obtained on a urine test, a serum test should be performed and a negative result obtained prior to IMP administration).

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) may be allowed not to use contraceptives during the study. An FSH test will be performed at the screening visit for any female who has been without menses for at least 12 months prior to screening to confirm postmenopausal status.

8.4.2.2. Urine Drug Screen

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

Substance use disorder is exclusionary and will preclude the patient from randomization. However, if per the investigator's judgment, a patient does not meet the criteria for substance use disorder, a positive result for any of the above drugs or their metabolites is not exclusionary. Patients' eligibility in such case of positive result, without medical explanation, will be determined by the investigator based on the patient's background, history of substance use, and the investigator's discussions with family members, caregivers, or healthcare professionals, as applicable. The patients should be advised that use of these substances should be avoided during the study.

8.4.2.3. Prolactin

Blood samples will be obtained for prolactin test at the time points specified in Table 1 and Table 2 (at screening [prior to intake of oral olanzapine, where relevant], baseline [visit 2; week 0 (prior to IMP administration)], visit 11 [week 8 (prior to IMP administration)], visit 14 [week 20 (prior to IMP administration)], and at the EOT visit). As prolactin levels are highly affected by olanzapine and reach steady state approximately 8 weeks after treatment initiation (Yang et al 2018), in order to maintain the blind, prolactin level results obtained after first IMP administration and before visit 13 (8 weeks into Period 2) will not be available for review by the sponsor or the sites until Period 1 database lock. The IDMC will review the unblinded data periodically.

8.5. 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. 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 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 8.1.2.

8.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], pulse and orthostatic changes, respiratory rate, and temperature) should be measured at each in-clinic visit pre-injection.

[redacted] Vital signs should 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). All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a supine or semi-erect position for at least 5 minutes; measurements should be taken again after standing for approximately 2 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is assessed by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 8.1.2.

8.7. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1 and Table 2. At screening and baseline, measurements will be done in triplicate (approximately 5 minutes apart). Single measurements will be performed at all other in-clinic visits where ECG recordings are taken. All ECG recordings should be sent to the central diagnostic center at screening, baseline, and throughout the study. A qualified physician at a central diagnostic center will interpret the ECG.

Patients' eligibility at screening may be determined based on the investigator or designee ECG interpretation.

In case only local ECGs interpretations are available within the screening period and they indicate that the patient is eligible for randomization, the patient may be randomized (provided all other study eligibility criteria are met). When central diagnostic ECG interpretation becomes available (after randomization), the patient's eligibility should be re-confirmed. In case the central diagnostic interpretation suggest that the patient does not meet study eligibility criteria, it is recommended to repeat the ECG and consult the MM.

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

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is assessed by the investigator as clinically significant (except at the screening visit) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 8.1.2.

8.8. Assessment of Local Tolerability and Pain

[redacted]

[redacted]

Table 10: Assessment of Local Tolerability (Injection Site Findings and Pain)

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

[redacted]

8.8.1. Procedures for Injection Site Pus-Containing Lesion (Abscess, Infection, or Inflammation), Ulceration, Necrosis, or Atrophy

[redacted]

[redacted]

8.9. 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 Baseline/Screening version will be administered by a qualified HCP (ie, the investigator or a qualified person designated by the investigator) at screening, and the C-SSRS Since Last Visit version will be completed at all other time points, as described in Table 1 and Table 2. Following any positive finding on the C-SSRS Since Last Visit version, the patient must be evaluated by the Principal Investigator or a patient's mental health practitioner designated by the investigator, which may result in the patient's withdrawal from the study. Recording of positive findings as adverse events will be per investigator decision.

8.10. Post-injection Delirium/Sedation Syndrome Monitoring

[redacted]

[redacted]

8.11. Other Safety Assessments

8.11.1. Abnormal Involuntary Movement Scale

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

8.11.2. Barnes Akathisia Rating Scale

The BARS will be performed at the time points specified in Table 1 and Table 2. The BARS is an instrument that assesses the severity of drug-induced akathisia (Barnes 1989). The BARS includes 3 items for rating objective restless movements, subjective restlessness, and any subjective distress associated with akathisia that are scored on a 4-point scale of 0 to 3 and summed, yielding a total score ranging from 0 to 9. The BARS also includes a global clinical assessment of severity scored on a scale of 0 to 5. Higher scores are indicative of greater severity of akathisia.

8.11.3. Simpson-Angus Scale

The SAS will be performed at the time points specified in Table 1 and Table 2. The SAS is a 10-item instrument for the assessment of neuroleptic-induced parkinsonism (Simpson and Angus 1970). The items on the scale include measurements of hypokinesia, rigidity, glabellar reflex, tremor, and salivation. Each item is rated on a 5-point scale (0 to 4), with a higher score indicating greater severity of symptoms. The mean score is calculated by adding the individual item scores and dividing by 10.

8.11.4. Calgary Depression Scale for Schizophrenia

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

9. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/BIOMARKERS/ PHARMACOGENETICS

9.1. Pharmacokinetic Assessment

[redacted]

Blood volumes are provided in the ICF and laboratory manual. Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

9.2. Pharmacodynamic Assessment

[redacted]

9.3. Assessment of Exploratory Biomarkers

[redacted]

[redacted]

[redacted]

9.4. Pharmacogenetics

[redacted]

For information regarding pharmacogenetic assessments, see Appendix H.

9.5. [redacted]

[redacted]

10. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan and 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.

The primary endpoint is change from baseline to week 8 in the PANSS total score. The sample size is designed to detect with [redacted] probability a standardized mean difference of [redacted] (eg, an improvement of at least [redacted] points in the PANSS total score, assuming a standard deviation of [redacted] points). The 3 primary efficacy hypotheses will be tested with an overall type I error of 0.05, controlled using truncated Hochberg adjustment for multiplicity.

10.1. 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, which yielded a conservative sample size. 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 a 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 6.9.3). 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.

10.2. Analysis Sets

10.2.1. Full Analysis Set

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

[redacted]

10.2.2. Efficacy Analysis Set

The efficacy analysis set will include all patients randomized to Period 1 while patients are randomized to 1 of the 3 TV-44749 doses or placebo, regardless of the actual treatment the patients received.

Patients randomized after randomization to the placebo group is stopped (Section 10.1) will not be included in the efficacy analysis set.

This analysis set will be used for the primary efficacy estimand.

10.2.3. Safety Analysis Set

To address the safety objective by the safety estimand, the safety analysis set will include all randomized patients who received at least 1 dose of TV-44749 olanzapine or placebo.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

In cases of dosing error, treatment assignment of these patients will be decided in a blinded manner prior to unblinding of Period 1 and will be documented in the study data review document.

10.2.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include those patients from the safety analysis set who have ≥1 plasma concentration measured.

10.3. Data Handling Conventions

Detailed data imputation rules will be described in the statistical analysis plan.

10.3.1. Handling Withdrawals and Missing Data

[redacted]

10.4. Study Population

The full analysis set (Section 10.2.1) will be used for all study population summaries, unless otherwise specified. Summaries will be presented by treatment group and study period for all patients.

10.4.1. Patient Disposition

Data from patients screened, patients screened but not randomized and reason for not randomized, patients who are randomized (full analysis set), patients randomized but not treated and reason, randomized and dosed (safety analysis set), and all other analysis sets, patients who complete the study, and patients who either discontinue IMP or withdraw from the study, will be summarized using descriptive statistics. Data from patients who discontinue IMP or withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

10.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics by full analysis set and safety analysis set. 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.

10.5. Efficacy Analysis

10.5.1. Primary Estimand

Refer to Section 3.2.1 for a description of the primary estimand.

10.5.2. Primary Endpoint

The primary efficacy endpoint is the change from baseline to week 8 in the PANSS total score.

10.5.3. Other Estimands

Refer to Section 3.2.2 for a description of the other efficacy estimand.

Refer to Section 3.2.3 for a description of the safety and tolerability estimand.

10.5.4. Secondary Endpoints

Secondary endpoints are listed in Section 3.1.

10.5.5. Exploratory Endpoints

Exploratory endpoints are listed in Section 3.3.

10.5.6. Planned Method of Analysis

The efficacy analysis set (Section 10.2.1) will be used for all efficacy analyses. Summaries will be presented by treatment group and study period, but only data from Period 1 will be considered for efficacy purposes.

10.5.6.1. Primary Efficacy Analysis

The efficacy analysis will employ multiple imputation, MMRM, and Rubin's rule.

1. One hundred completed datasets will be imputed using multiple imputation.

a. For ICEs of a use of prohibited antipsychotic medication or early discontinuation due to insufficient clinical response, imputations will be done assuming MNAR in order to estimate what would have happened if patients who discontinued early had remained in the study on placebo treatment.

b. For ICEs of early discontinuation due to a reason that is not lack of efficacy or death, a multiple imputation assuming that the clinical effect in these patients is similar to those not experiencing ICE during the study (ie. assuming MAR) will be employed.

   Full details of the methods employed for the 2 types of ICEs and underlining assumptions will be detailed in the statistical analysis plan.

2. MMRM on change from baseline to week 8: least squares means of change from baseline to week 8, for each of the 4 treatment arms and for the differences between each of the TV-44749 arms to placebo, 95% confidence interval, and p-values will be calculated using MMRM analysis for each complete dataset. The model will include treatment arm, study visit, treatment-visit interaction, stratification variables, and PANSS total score at baseline as covariates. Unless otherwise specified, unstructured covariance matrix will be used as a covariance matrix. Further details about the analysis will be presented in the statistical analysis plan.
3. Summary statistics for the primary efficacy endpoint will be based on Rubin's rule summary of least squares means of change from baseline to week 8, for each of the 4 treatment arms and for the differences between each of the TV-44749 arms to placebo, 95% confidence interval, and p-values. The Rubin's-derived p-values that will be adjusted according to truncated Hochberg method (Section 10.6) will be used for the primary efficacy analysis.

10.5.6.2. Sensitivity Analysis

[redacted]

10.5.6.3. Supplementary Analysis

The primary and key secondary endpoints will be repeated using treatment policy estimand (ie, intention to treat). The treatment policy estimand will be defined as:

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 from baseline to week 8 in the PANSS total score, regardless of the ICEs patients experienced during Period 1.

d. **Population-level summary**: Least squares means of the difference in the change from baseline to week 8 between treatment groups according to the randomization assignment, regardless of the treatment actually received.

Assuming that missing data generated in the study, such as ET, follow the MAR assumption, this analysis complies with estimation of the mean treatment effect comprised with the intention to treat principle.

10.5.6.4. Key Secondary Efficacy Analysis

[redacted]

10.5.6.5. Secondary Efficacy Analysis

[redacted]

10.5.6.6. Other Efficacy Analysis

[redacted]

10.6. Multiple Comparisons and Multiplicity

[redacted]

[redacted]

10.7. Safety Analysis

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

The safety analysis will be by period with the respective randomization (for Period 1, randomization to Period 1 and for Period 2, randomization to Period 2). In addition, a safety analysis of the 2 periods together may be conducted; in this analysis, placebo patients in Period 1 will be counted as placebo, and after the randomization to Period 2, they will be assigned the actual dose in Period 2.

In case of dose adjustment, the patient may be regarded according to the randomized dose until the day of the dose adjustment, and from the first administration of the adjusted dose, the patient will be regarded according to the adjusted dose.

Safety assessments and time points are provided in Table 1 and Table 2.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events related to test IMP and/or device (ie, reasonable possibility defined by the investigator as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device events, and adverse events and adverse device events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

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

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

For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, ISRs, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

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

10.8. Tolerability Analysis

[redacted]

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

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

Tolerability analyses will be performed on the safety analysis set by treatment group and period.

10.9. Pharmacokinetic, Population Pharmacokinetic, Pharmacodynamic, and Pharmacokinetic/Pharmacodynamic Analysis

Plasma concentrations will be tabulated at each planned sampling time point by treatment group.

In addition, the pharmacokinetics of TV-44749 will be evaluated using a population pharmacokinetics approach. [redacted]

Importantly, independent pharmacokinetic and population-based modeling analysis will take place during the study conduct, while maintaining the blind during Period 1, as will be described in the separate predefined unblinded pharmacokinetic analyses plan. Pharmacodynamic data from Period 1 will not be shared before database lock and unblinding for the efficacy analysis.

[redacted]

The population pharmacokinetic/pharmacodynamic analysis of relevant pharmacodynamic variables and/or exposure-response analysis of relevant efficacy or safety endpoints may be performed and reported in a separate pharmacometrics report.

Samples collected at 2.5 to 3 hours post IMP administration will not be analyzed routinely during the study but rather only in the event of potential PDSS that will be evaluated by the IDMC.

10.10. Biomarker and Pharmacogenetic Analysis

[redacted]

10.11. [redacted]

[redacted]

10.12. Planned Interim Analysis

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. Based on these 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. Full details of the approach will be depicted in the IDMC charter and the statistical analysis plan.

10.13. Reporting Deviations from the Statistical Plan

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

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

Refer to Appendix I for the definition of a clinical product complaint or device deficiency and investigator responsibilities in the management of a clinical product complaint or device deficiency.

12. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6 (R2), and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, Regulation (EU) No 536/2014 [Clinical Trial Regulation, as applicable], regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

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

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

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

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

13. DATA MANAGEMENT AND RECORD-KEEPING

See Appendix J for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

14. FINANCING AND INSURANCE

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

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

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

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

15. PUBLICATION POLICY

See Appendix K for information regarding the publication policy.

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APPENDIX A. 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. They will have the right to recommend termination of the study for safety reasons.

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

Further details are given in the IDMC charter.

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. Procedures for Screening/Visit 1 (Day -8, Weeks -2 to -1)

The screening visit (visit 1) will take place not more than 8 days before the baseline visit (visit 2).

Note: 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 (eg, extreme weather) after receiving approval from the MM or the sponsor. In case the site faces a delay in obtaining the central laboratory results for the clinical laboratory tests performed during screening that are needed to determine eligibility, additional screening blood samples (specifically those with delayed results) may be collected as soon as possible and analyzed in a local laboratory to allow study eligibility determination within the 8-day screening window. Refer to Section 8.4 for more details.

The following procedures and assessments will be performed at visit 1:

- Informed consent
- Inclusion and exclusion criteria
- Medical and psychiatric history (including the number of relapse episodes and years post diagnosis)
- Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)
- Prior medication and treatment history
- Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis)
- Virology and thyroid screening tests
- Follicle-stimulating hormone test (for women with no menses for 12 months prior to screening)
- Administration of oral olanzapine (patients who received olanzapine within the last year will not be required to receive the 2 doses of oral treatment)
- Urine drug screen
- Full physical examination, including height and weight
- 12-lead electrocardiogram (ECG)
- Vital signs measurement
- Serum beta-human chorionic gonadotropin (β-HCG) test for women of childbearing potential
- Positive and Negative Syndrome Scale (PANSS)

- Clinical Global Impression-Severity (CGI-S)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Personal and Social Performance Scale (PSP)
- Schizophrenia Quality of Life Scale (SQLS)
- [redacted]
- Calgary Depression Scale for Schizophrenia (CDSS)
- [redacted]
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Inquiry regarding alcohol consumption/illicit drug use
- Cigarette use assessment
- Site confinement (for patients who are not already hospitalized)
- Concomitant medication inquiry

2. Procedures During Double-blind Treatment Period (Acute Treatment Phase; Period 1)

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 investigational medicinal product [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).

a. Procedures for Baseline/Visit 2 (Day 1, Week 0)

Patients who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2, when baseline assessments will be conducted.

The following procedures and assessments will be performed at visit 2:

- Inclusion and exclusion criteria
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Randomization
- Urine drug screen
- Abbreviated physical examination, including weight
- 12-lead ECG
- Vital signs measurement
- Urine β-HCG test for women of childbearing potential
- PANSS
- CGI-S
- AIMS
- BARS
- SAS
- C-SSRS
- PSP
- SQLS
- [redacted]
- CDSS
- [redacted]
- Abdominal fat measurement (waist-to-hip ratio)
- Blood samples for plasma concentration of IMP
- Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose
- Blood samples for biomarker analysis
- Blood samples for pharmacogenetics
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use
- Cigarette use assessment
- IMP administration
- Concomitant medication inquiry

b. Procedures for Visit 3 (Day 2, Week 0)

The following procedures and assessments will be performed at visit 3:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Abbreviated physical examination
- Vital signs measurement
- Blood samples for plasma concentration of IMP
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Concomitant medication inquiry

c. Procedures for Visit 4 (Day 8, Week 1), Visit 5 (Day 15, Week 2), Visit 6 (Day 22, Week 3), Visit 8 (Day 36, Week 5), Visit 9 (Day 43, Week 6), and Visit 10 (Day 50, Week 7)

The following procedures and assessments will be performed at visits 4, 5, 6, 8, 9, and 10:

- Vital signs measurement
- PANSS
- CGI-S
- AIMS
- BARS
- SAS
- C-SSRS
- Patient Global Impression-Improvement (PGI-I) (visit 5 only)
- [redacted]
- Blood samples for plasma concentration of IMP
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use (for outpatients only)
- Concomitant medication inquiry

d. Procedures for Visit 7 (Day 29, Week 4) and Visit 11 (Day 57, Week 8)

The following procedures and assessments will be performed at visits 7 and 11:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Thyroid test (visit 11 only)
- Randomization (visit 11 only)

  - Note: Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, Clinical Global Impression of Improvement (CGI-I), AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, adverse event inquiry, injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry. Procedures and assessments that need to be performed after randomization into Period 2 at visit 11 (week 8) include IMP administration and blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose. Remaining procedures and assessments at visit 11 (week 8) may be performed either before or after randomization

- Urine drug screen
- Abbreviated physical examination, including weight
- 12-lead ECG
- Vital signs measurement
- Urine β-HCG test for women of childbearing potential
- PANSS
- CGI-S
- CGI-I
- AIMS
- BARS
- SAS
- C-SSRS
- PSP
- SQLS
- [redacted]
- CDSS
- PGI-I
- [redacted]
- Abdominal fat measurement (waist-to-hip ratio)
- Blood samples for plasma concentration of IMP
- Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose
- Blood samples for biomarker analysis (visit 11 only)

- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use (for outpatients only)
- Cigarette use assessment
- IMP administration
- Readiness for Discharge Questionnaire (RDQ)-discharge from site confinement (visit 7 only; see note above under "2. Procedures During Double-blind Treatment Period [Acute Treatment Phase; Period 1]")
- Concomitant medication inquiry
- Review of eligibility (stability) criteria (visit 11 only)

3. Procedures During Safety Period (Long-term Safety Phase; Period 2)

The open-label safety period in Period 2 will be up to 48 weeks, with patients continuing until the end of Period 2 or until they meet 1 or more of the study discontinuation or withdrawal criteria. Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) should be invited to perform the ET visit as soon as possible.

Visit 11 (week 8) assessments are included in both Table 1 (Period 1) and Table 2 (Period 2) for completeness; however, they need to be performed only once, prior to randomization to Period 2. They are listed only once in this appendix (under Period 1).

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 early termination (ET) and follow-up (FU) visits.

a. Visit 12 (Week 12), Visit 14 (Week 20), Visit 16 (Week 28), Visit 18 (Week 36), Visit 20 (Week 44), and Visit 22 (Week 52)

The following procedures and assessments will be performed at visits 12, 14, 16, 18, and 20:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis) (visits 14 and 20 only)
- Urine drug screen
- Concomitant medication inquiry
- Abbreviated physical examination, including weight
- Abdominal fat measurement (waist-to-hip ratio)
- Vital signs measurement

- Urine β-HCG test for women of childbearing potential
- PANSS
- CGI-S
- CGI-I (visits 14 and 20 only)
- AIMS (visits 14 and 20 only)
- BARS (visits 14 and 20 only)
- SAS (visits 14 and 20 only)
- C-SSRS
- PSP (visits 14 and 20 only)
- SQLS (visits 14 and 20 only)
- [redacted] (visits 14 and 20 only)
- CDSS
- [redacted]
- Blood samples for plasma concentration of IMP
- Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose
- IMP administration
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use
- Cigarette use assessment

b. Visit 13 (Week 16), Visit 15 (Week 24), Visit 17 (Week 32), Visit 19 (Week 40), and Visit 21 (Week 48)

The following procedures and assessments will be performed at visits 13, 15, 17, 19, and 21:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis) (visit 17 only)
- Urine drug screen
- Concomitant medication inquiry
- Abbreviated physical examination, including weight
- Abdominal fat measurement (waist-to-hip ratio)
- Vital signs measurement
- 12-lead ECG
- Urine β-HCG test for women of childbearing potential

- PANSS
- CGI-S
- CGI-I (visit 17 only)
- AIMS (visit 17 only)
- BARS (visit 17 only)
- SAS (visit 17 only)
- C-SSRS
- PSP (visit 17 only)
- SQLS (visit 17 only)
- [redacted] (visit 17 only)
- CDSS
- [redacted]
- Blood samples for plasma concentration of IMP
- Blood samples for plasma concentration of IMP at 2.5 to 3 hours postdose
- IMP administration
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use
- Cigarette use assessment

c. Telephone visits (Visit 11a [Week 9], Visit 11b [Week 10], Visit 11c [Week 11], Visit 12a [Week 13], Visit 12b [Week 14], Visit 12c [Week 15], Visit 13a [Week 17], Visit 13b [Week 18], Visit 13c [Week 19], Visit 14a [Week 21], Visit 14b [Week 22], Visit 14c [Week 23], Visit 15a [Week 25], Visit 15b [Week 26], Visit 15c [Week 27], Visit 16a [Week 29], Visit 16b [Week 30], Visit 16c [Week 31], Visit 17a [Week 33], Visit 17b [Week 34], Visit 17c [Week 35], Visit 18a [Week 37], Visit 18b [Week 38], Visit 18c [Week 39], Visit 19a [Week 41], Visit 19b [Week 42], Visit 19c [Week 43], Visit 20a [Week 45], Visit 20b [Week 46], Visit 20c [Week 47], Visit 21a [Week 49], Visit 21b [Week 50], Visit 21c [Week 51], Visit 22a [Week 53], Visit 22b [Week 54], and Visit 22c [Week 55])

Telephone contacts (or other comparable form of remote communication) will occur weekly between clinic visits. These contacts will be referred to by the previous visit number and a letter (eg, the telephone contacts that take place 1, 2, and 3 weeks after visit 11 (week 8) will be referred to as “visit 11a,” “visit 11b,” and “visit 11c,” respectively).

For patients who are inpatients (for up to the first 8 weeks of Period 2), in-clinic visits will take place instead of phone visits, using the same assessments specified for the phone visits.

The following procedures and assessments will be performed at each telephone contact:

- Inquiry about pregnancy status (for women of childbearing potential)
- C-SSRS
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Inquiry regarding alcohol consumption/illicit drug use
- Brief set of clinical questions to detect psychotic symptoms

d. End-of-Treatment Visit (4 weeks after the last dose of IMP)

The following procedures and assessments will be performed at the end-of-treatment (EOT) visit:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Thyroid test
- Urine drug screen
- Concomitant medication inquiry
- Abbreviated physical examination, including weight
- Abdominal fat measurement (waist-to-hip ratio)
- Vital signs measurement
- 12-lead ECG
- Urine β-HCG test for women of childbearing potential
- PANSS
- CGI-S
- CGI-I
- AIMS
- BARS
- SAS
- C-SSRS
- PSP
- SQLS
- [redacted]
- CDSS
- PGI-I
- [redacted]

- Blood samples for biomarker analysis
- Blood samples for plasma concentration of IMP
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment
- Inquiry regarding alcohol consumption/illicit drug use

4. Follow-up (8 Weeks After the Last Dose of IMP)/Early Termination

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] for the ET and EOT visits must be performed).

The following procedures and assessments will be performed at the FU visit or ET visit:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Thyroid test (ET visit only)
- Urine drug screen (ET visit only)
- Concomitant medication inquiry
- Abbreviated physical examination, including weight
- Abdominal fat measurement (waist-to-hip ratio)
- Vital signs measurement
- 12-lead ECG
- Serum β-HCG test for women of childbearing potential (FU visit only)
- Urine β-HCG test for women of childbearing potential (ET visit only)
- PANSS
- CGI-S
- CGI-I
- AIMS
- BARS
- SAS
- C-SSRS
- PSP
- SQLS
- [redacted]

- CDSS
- PGI-I (ET visit only)
- [redacted]
- Blood samples for biomarker analysis (FU visit only)
- Blood samples for plasma concentration of IMP
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Injection site findings and pain assessment (ET visit only)
- Inquiry regarding alcohol consumption/illicit drug use

5. Unscheduled Visits

An unscheduled visit may be performed at any time per investigator decision. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits include:

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Concomitant medication inquiry
- Full physical examination, including weight
- Abdominal fat measurement (waist-to-hip ratio)
- Vital signs measurement
- PANSS
- CGI-S
- CGI-I
- C-SSRS
- CDSS
- [redacted]
- Blood samples for plasma concentration of IMP
- Blood samples for biomarker analysis (for patients with ISRs that require an unscheduled visit, ie, pus-containing lesion [abscess, infection, or inflammation], ulceration, necrosis, atrophy, or severe ISR)
- Adverse events inquiry (including serious adverse event reporting and injection site related events [including pain])
- Inquiry regarding alcohol consumption/illicit drug use

Other procedures and assessments may be performed according to the discretion of the investigator. However, in order to reduce patient burden and to avoid unnecessary data collection, the investigator will have discretion in determining whether all unscheduled visit procedures should be performed during the unscheduled visit in the event that (i) the unscheduled visit is one of multiple in-clinic visits that are deemed necessary in close proximity (ie, 2 or more visits within 1 week) or (ii) the visit is for administrative purposes (eg, reconsenting) or technical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event) and not due to a change in the patient's medical status per clinical judgment.

6. Short-term Leave

The following procedures and assessments will be performed following short-term leave:

- Urine drug screen
- Abbreviated physical examination, including weight
- Inquiry regarding alcohol consumption/illicit drug use
- Concomitant medication inquiry

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

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

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety or the physical or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product administration; use of prohibited medications. Important protocol deviations will be documented by investigational center personnel. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

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

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

Information to Study Personnel

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

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

Study Monitoring

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

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

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

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

Audit and Inspection

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

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

Appendix D. ETHICS

Informed Consent

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

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

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Confidentiality Regarding Study Patients

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

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

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on clinical trial registries, if applicable.

APPENDIX E. BIRTH CONTROL METHODS

Highly Effective Birth Control Methods in Females

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

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at the screening visit (for both investigational medicinal products [IMPs] with and without suspected reproductive toxicity) before the first dose of IMP.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at the screening visit (for IMPs with or without suspected reproductive toxicity) before the first dose of IMP.
- Intrauterine device and intrauterine hormone-releasing system; these need to be in place at least 2 months before screening.
- Bilateral tubal occlusion, except for hysteroscopic bi-tubal ligation [Essure®], for which a hysterosalpingogram is required 3 months post-procedure to assess surgical success.
- Vasectomized partner, provided he is the sole sexual partner and has received medical assessment of the surgical process.
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Minimum time adherence prior to first dosing is 3 months.
- 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) may be allowed not to use contraceptives during the study. An FSH test will be performed at the screening visit for any female who has been without menses for at least 12 months prior to screening to confirm postmenopausal status.

Unacceptable Birth Control Methods

Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

APPENDIX F. LOST TO FOLLOW-UP

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

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

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

APPENDIX G. 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 H. PHARMACOGENETIC ASSESSMENTS

[redacted]

APPENDIX I. PRODUCT COMPLAINTS

I. Clinical Product Complaints

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

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- Device deficiency (eg, any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance). This includes malfunctions, use errors, and inadequate labeling (eg, unintelligible label, incorrect expiry date)

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to TevaProductComplaintAndPotentialSB@teva.co.il as soon as possible of becoming aware of the issue.

For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

If the clinical product complaint is related to a device, rescue medication, or any other product planned in the protocol not manufactured by Teva, the complaint will be forwarded to the manufacturer/wholesaler of that product.

1. Product Complaint Information Needed from the Investigational Center

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

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies

- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

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

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

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

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

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

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

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 8.1.2 and Section 8.1.6, respectively).

4. **Documenting a Product Complaint**

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

5. **Device Deficiency That Could Have Led to Serious Adverse Event**

Device deficiencies that could have led to serious adverse events are defined as deficiencies that might have led to a serious adverse device effect if:

- suitable action had not been taken (or)
- intervention had not been made (or)
- if circumstances had been less fortunate.

These device deficiencies shall be reported to the IRB/IEC by the investigator and to the regulatory authorities by the sponsor according to national and local regulations. Device complaints related to potential device malfunctions will be initially assessed by the sponsor to determine the root cause of the complaint. Device complaints that are assessed to be caused specifically by device deficiencies will be reported to the device manufacturer for evaluation and further reported according to national and local regulations.

The investigator will record in the source documentation a description of the complaint, the initial determination whether the device deficiency could have led to a serious adverse event, and any actions taken to resolve the complaint and to preserve the safety of the patient.

APPENDIX J. DATA MANAGEMENT AND RECORD KEEPING

Data protection and confidentiality

All personal data will be processed in accordance with applicable data protection law.

Teva has implemented measures to ensure that data will be adequately protected and confidentiality will be appropriately maintained, including the following:

a. In addition to the measures set out in this appendix and the wider protocol, Teva has implemented technical measures (including encryption for data and emails) and organizational measures (including a robust governance structure, staff training, and policies dealing with document management and acceptable use) in order to prevent data loss and to ensure the integrity of data that it holds. Teva consults with independent data security experts to ensure the adequacy of these technical and organizational measures, and Teva's Information Security team keeps the measures under continuous review to ensure the measures in place continue to be state of the art, taking into account the nature and context of the processing.

b. Teva has completed Data Protection Impact Assessments in respect of the processing of personal data gathered in the course of clinical studies.

c. Teva trains all of its staff regarding the handling of personal data in accordance with applicable law.

d. Teva has implemented role-based access, which means that personal data will only be available to those who need access.

e. There are appropriate technical and organizational measures in place to protect the confidentiality of patient data. For example, patient data will be randomized and blinded in accordance with Section 6.9 and Section 6.10 above, and Teva staff are subject to a contractual obligation of confidentiality.

f. Teva has policies and procedures in place to identify and respond to data breaches, including internal reporting within Teva as well as reporting from partners and other involved third parties (contract research organizations, monitors, etc). In particular, Teva has adopted a data breach response policy that details internal reporting channels and immediate mitigation step; a data breach log that records all breaches; and a back-up and restore policy that details the measures in place to avoid data loss in the event of a service outage.

Teva ensures that all contracts into which it enters with third parties involved in the data processing with or on behalf of Teva include provisions to ensure that such parties comply with applicable law, including General Data Protection Regulation. These contracts will effectively extend obligations that are equivalent to the above to all third parties who process patient data with or on behalf of Teva.

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded

directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

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

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

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

Data Collection

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

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

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

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

Data Quality Control

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

may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

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

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

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

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

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

Investigator Responsibilities

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

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the investigational medicinal products
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the contract research organization or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of

destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX K. PUBLICATION POLICY

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

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

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data.

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

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

The publications committee established by the sponsor will oversee this process.

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

Additional information and instructions concerning confidentiality, publication and intellectual property are subject to the clinical trial agreement.

Appendix L. MANAGEMENT OF STUDY ACTIVITIES DURING COVID-19 OUTBREAKS

This appendix is to address the modifications set-up in study conduct during coronavirus disease 2019 (COVID-19) outbreaks.

The changes will be effective for the period of the COVID-19 outbreaks and will be implemented exclusively at the sites impacted by COVID-19. Once the situation at specific sites/countries allows for a return to regular study activities, this appendix will become void for those sites/countries, except in the case of COVID-19 resurgence.

The following sections of the protocol are affected:

Section 2.3. Known and Potential Benefits and Risks to Patients

In the event of COVID-19 outbreaks, the sponsor, in close collaboration with the investigators, will determine if the benefit-risk assessment remains positive as a whole, and will assess any additional risks on a patient-by-patient basis, as needed. The measures outlined in this appendix are aimed at further mitigating the additional risks in the event of a COVID-19 outbreak.

It should be noted that patients diagnosed with active COVID-19 at screening may not be included in the study as they may meet exclusion criterion “n.” A patient may be rescreened once he/she fully recovers in the opinion of the investigator.

If, in the opinion of the investigator, the patient’s diagnosis could jeopardize or would compromise the patient’s ability to participate in the study or their continued participation in the study, the patient should be early terminated.

If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection according to the investigator or the patient’s physician, the patient may be tested for active COVID-19 infection (according to local requirements for conditions that warrant testing). If the patient tests positive, the patient should be managed and treated according to standard of care and local regulations.

Section 4.1. General Study Design and Study Schematic Diagram; Section 4.5. Schedule of Study Procedures and Assessments

In the event of COVID-19 outbreaks, in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient’s concern, active COVID-19 infection, or closure of the site clinic) within the pre-specified visit windows in Period 1 or within 35 days from the previous IMP administration in Period 2, the patient will be discontinued from the IMP, scheduled adverse event and concomitant medication monitoring will be continued, and the patient will attend an ET visit when that becomes possible. Remote assessment of safety via teleconference (TC) and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends the ET visit. All other tests (including safety laboratories, pharmacokinetics, and biomarkers (if applicable) are to be conducted once the patient can return to the study center for the ET visit.

In the event that a patient completes the screening procedures but cannot come to the site for visit 2 (eg, due to quarantine, isolation, patient’s concern, or closure of the site clinic), the patient may be rescreened according to rescreening procedures described in Section 5.6 of this protocol following discussion between the investigator and the sponsor.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to a COVID-19 outbreak. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 5.2. Patient Exclusion Criteria; Section 6.7. Prior and Concomitant Medication or Therapy

The eligibility criteria and list of prohibited medications can be updated to reflect new data on COVID-19 therapies. If a patient receives new COVID-19 therapies not in compliance with the eligibility criteria and list of prohibited medications at the time of the patient's participation in the study, the investigator and sponsor will discuss how to proceed on a case-by-case basis.

Section 5.5. Replacement of Patients

In the event of COVID-19 outbreaks resulting in high rate of patients' ET, the number of patients to be randomized may be increased to ensure the targeted number of completers per treatment group.

Section 6.10. Maintenance of Randomization and Blinding

Unblinded data review of COVID-19 patients by member(s) not part of the blinded study team (during Period 1) may be conducted upon Independent Data Monitoring Committee recommendations and Teva's discretion.

Section 7. Assessment of Efficacy

In the event of COVID-19 outbreaks, in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic) within the pre-specified visit windows in Period 1 or within 35 days from the previous IMP administration in Period 2, the patient will be discontinued from IMP, remote monitoring will be performed, and the patient will attend for an ET visit when that becomes possible.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to a COVID-19 outbreak. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 8. Assessment of Safety

In the event of COVID-19 outbreaks, in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), remote assessment of safety (ie, inquiries regarding adverse events and use of concomitant medication) via TC and/or VC, with VC being the preferred method (if local regulations allow), may be allowed. The results will be directly entered into the patient's source document and reported in the case report form per the usual process.

These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to a COVID-19 outbreak. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.

Section 8.4. Clinical Laboratory Tests

For ET patients (patients who cannot be administered the IMP), all required samples scheduled for ET will be collected once the patient can return to the study center.

Section 10.5.6. Planned Method of Analysis

Sensitivity and supplementary analyses will be conducted to evaluate the impact of the change to remote monitoring (TC/VC visits) and the impact of COVID-19 on primary efficacy measurements. The analysis will include subgroup analysis (eg, pre-, during, and post-COVID-19 outbreak, where each patient will be classified into 1 of the levels), a multivariate model (eg, Cox regression with time dependent covariates for COVID-19 and/or use of remote monitoring), and/or imputation methodology for patients' attrition due to the COVID-19, as appropriate and if data permit. Details of the supplementary and sensitivity analyses will be presented in the statistical analysis plan or addendum thereof, following a blinded review meeting (when discussing Period 1) prior to database lock.

Section 11. Quality Control and Quality Assurance

Deviations from the study conduct due to 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 clinical study report (CSR), as applicable.

Appendix C. Quality Control and Quality Assurance

Important Protocol Deviations

Deviations from the study conduct due 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.

Study Monitoring

In case of COVID-19 outbreaks, monitors may not be able to access the investigational centers for on-site visits in a timely manner. A Monitoring Manual will outline risk mitigation procedures for sites where on-site monitoring visits are not permitted due to an increased public health risk, in accordance with Institutional Review Board/Ethics Committee approval and local regulations.

Audit and Inspection

In case of a COVID-19 pandemic, where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely where allowed and in accordance with local regulations.

APPENDIX M. LIST OF SCALES

Note: Full versions of each scale will be provided in a dedicated study plan outside of the protocol.

Scale Title	PRO or ClinRO	Administration Mode	Scale Version	Reference
Abnormal Involuntary Movement Scale (AIMS)	ClinRO	eCOA	Guy 1976a 14-Item version	Guy 1976a
Rating scale for drug-induced akathisia (Barnes Akathisia Rating Scale) (BARS)	ClinRO	eCOA	Reproduced from Barnes 1989 ©1989 The Royal College of Psychiatrists	Reproduced from Barnes 1989
Simpson-Angus Scale (SAS)	ClinRO	eCOA	SAS ©Munksgaard, managed by Wiley Simpson and Angus 1970	Simpson and Angus 1970 Janno et al 2005
Clinical Global Impression – Improvement (CGI-I)	ClinRO	eCOA	Guy et al 1976b Public domain	Reproduced from Guy et al 1976b
Clinical Global Impression of Severity (CGI-S)	ClinRO	eCOA	Guy et al 1976b Public domain	Reproduced from Guy et al 1976b
Positive and Negative Syndrome Scale (PANSS) Rating Criteria, PANSS Rating and Profile forms (ex Quickscore), SCI-PANSS	ClinRO	PANSS Rating Criteria + Rating and Profile form (eCOA) SCI-PANSS (Paper)	Positive and Negative Syndrome Scale (PANSS™). ©2022 NCS Pearson, Inc. All rights reserved.	Kay et al 1987
Personal and Social Performance Scale (PSP)	ClinRO	eCOA	Morosini et al 2000	Morosini et al 2000
Columbia Suicide Severity Rating Scale (C-SSRS)	ClinRO	eCOA	Since Last Visit version 1/14/09	Posner et al 2011
	ClinRO	eCOA	Baseline/Screening version 1/14/09	Posner et al 2011
Calgary Depression Scale for Schizophrenia (CDSS)	ClinRO	eCOA	©2018 (Dr. D. Addington). All rights reserved.	Addington et al 1990 Addington et al 1992 Addington et al 1993

Scale Title	PRO or ClinRO	Administration Mode	Scale Version	Reference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SQLS R4 - Schizophrenia Quality of Life Scale Revision 4	PRO	eCOA	SQLS-R4 (circle response version)	Martin and Allan 2007
Patient Global Impression-Improvement (PGI-I)	PRO	eCOA	Public domain	Steinert et al 2010
Structured Clinical Interview for DSM-5 Clinical Trials Version (SCID-5-CT)	ClinRO	Paper	SCID-5-CT for schizophrenia	First et al 2015
Readiness for Discharge Questionnaire (RDQ)	ClinRO	Paper	Potkin et al 2005	Potkin et al 2005
Numeric Pain Rating Scales 0-10 (NPRS)	ClinRO	Paper	Reproduced from Williamson and Hoggart 2005	Williamson and Hoggart 2005

ClinRO=clinician-reported outcome; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; eCOA=electronic clinical outcome assesment; [redacted]; PANSS=Positive and Negative Syndrome Scale; PRO=patient-reported outcome; SCI=Structured Clinical Interview; USA=United States of America.

APPENDIX N. PRIOR PROTOCOL AMENDMENTS AND ADMINISTRATIVE LETTERS

Administrative Letter 05 Dated 05 Sep 2023

ADMINISTRATIVE LETTER 05

Study number: TV44749-CNS-30096

Clinical Study Protocol

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

Protocol version date: 01 September 2022

IND Number: 128851; EudraCT number 2022-001865-11

5 September 2023

Dear Investigator:

The purpose of this letter is to inform you of the below clarifications to study activities, including the following.

1. *Allowed and prohibited antidepressants use during the study*

   a. **Section 6.7.1.2. Antidepressants and Mood Stabilizers**

   The sponsor would like to clarify that only antidepressants that are approved according to the study protocol are allowed to be used during the study, including the continuation of prior medications, per the conditions listed for each study period. The last statement in the section below: "The use of other antidepressants (such as tricyclic and tetracyclic antidepressants and bupropion) will be prohibited" is referring to the entire duration of the study and not exclusively to period 2.

   "Screening Period and Period 1: Patients who are currently treated with protocol-approved antidepressants and/or mood stabilizers for at least 3 months prior to screening and with no change in dose for at least 4 weeks prior to screening (except for indications excluding the patient from entering the study, such as schizoaffective disorder) may continue their treatment during the screening period/Period 1. No change of dose or new

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treatment initiation with such medications will be permitted in the screening period/Period 1.

Period 2: During Period 2, patients who received mood stabilizers and protocol-approved antidepressants prior to study entrance for at least 3 months prior to screening and with no change in dose for at least 4 weeks prior to screening and continued their treatment during Period 1 will be allowed to continue their treatment. New administrations of mood stabilizers will be not permitted; dose adjustments of mood stabilizers may be allowed on a case-by-case basis after discussion with the MM.

Dose adjustment of protocol-approved antidepressants will be allowed in Period 2 according to the investigator's clinical judgment. Patients who did not receive antidepressants previously will be allowed to initiate treatment with protocol-approved antidepressants (including selective serotonin reuptake inhibitors [other than fluvoxamine], serotonin and norepinephrine reuptake inhibitors, and trazodone) during Period 2 based on the investigator's clinical judgment. The use of other antidepressants (such as tricyclic and tetracyclic antidepressants and bupropion) will be prohibited for the entire duration of the study. Investigators are encouraged to approach the MM or the sponsor prior to initiating any new antidepressant treatment."

2. *A follow-up questionnaire regarding pus-containing lesions*

   a. **Section 8.8.1. Procedures for Injection Site Pus-Containing Lesion (Abscess, Infection, or Inflammation), Ulceration, Necrosis, or Atrophy**

[redacted]

These changes are **not considered substantial** in terms of impact on the safety or scientific value of the clinical trial and will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

Sincerely,

DocuSigned by:
[redacted]
05-Sep-2023 | 16:12 BST

[redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] www.tevapharm.com

Administrative Letter 04 Dated 31 Jul 2023

ADMINISTRATIVE LETTER 04

Study number: TV44749-CNS-30096

Clinical Study Protocol

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

Version date 01 September 2022

IND number: 128851; EudraCT number: 2022-001865-11

31 Jul 2023

Dear Investigator:

The purpose of this letter is to implement the following modifications and clarifications to Protocol TV44749-CNS-30096:

- The distinction between injection site reactions (ISRs) versus injection site findings (local tolerability assessments)
- Allowed indications for using lorazepam as a rescue medication
- Interpretation of electrocardiograms (ECGs) to assess patient eligibility for enrollment
- The order of assessments before and after randomization at visit 11
- Timeframe for treatment revealing
- Update on the assessment of adverse events related to device
- The data sources for Positive and Negative Syndrome Scale (PANSS), including informant data recording
- Safety laboratory testing during visit 3
- Total blood volume in China
- Timing of providing informed consent by the caregiver

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Revisions to the protocol are provided below with deletions signified by strikethrough and additions by underscore.

1. Injection site reactions versus injection site findings (local tolerability assessments)

   a. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1, injection site reaction and pain assessment row and footnote k:**

   "Injection site ~~reaction~~ findings and pain assessment[x]"

   Footnote k: "… Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, CGI-I, AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, AE inquiry, ~~ISRs~~ injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry. …"

   b. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 2: Study Procedures and Assessments for Period 2, injection site reaction and pain assessment row and footnote k:**

   "Injection site ~~reaction~~ findings and pain assessment[x]"

   Footnote k: "… Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, CGI-I, AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, AE inquiry, ~~ISRs~~ injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry. …"

   c. **In Section 6.9.1. Procedures and Assessments to be Performed Before and After Randomization into Period 2 at Visit 11 (Week 8):**

   "~~ISRs~~ injection site findings and pain assessment of last injection"

   d. **In Section 8. ASSESSMENT OF SAFETY:**

   "In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events (including serious adverse events, extrapyramidal symptoms, injection pain and other ~~ISRs~~ injection site findings [local tolerability]), vital signs (blood pressure, pulse and orthostatic changes, and temperature), body weight, laboratory tests, ECG, concomitant medication use, time to all-cause discontinuation, all-cause discontinuation rates and discontinuation rates due to adverse events (tolerability), and rating scales (including AIMS, BARS, SAS, C-SSRS, and CDSS)."

   e. **In Section 8.8. Assessment of Local Tolerability and Pain:**

[redacted]

[redacted]

f. **In Section 8.8. Assessment of Local Tolerability and Pain, Table 10: Assessment of Local Tolerability, title:**

[redacted]

g. **In Section 8.8. Assessment of Local Tolerability and Pain, Table 10: Assessment of Local Tolerability, footnote a:**

[redacted]

h. **In Appendix B. STUDY PROCEDURES, pages 131, 132, 134, 135, 136, 138, and 139:**

"Injection site ~~reaction~~ findings ~~(ISR)~~ and pain assessment"

i. **In Appendix B. STUDY PROCEDURES, Procedures for Visit 7 (Day 29, Week 4) and Visit 11 (Day 57, Week 8):**

"Procedures and assessments that need to be performed prior to randomization into Period 2 at visit 11 (week 8) include clinical laboratory tests, thyroid tests, physical examination, ECG, vital signs, urine β-HCG, PANSS, CGI-S, Clinical Global Impression of Improvement (CGI-I), AIMS, BARS, SAS, C-SSRS, PSP, CDSS, PGI-I, blood samples for plasma concentration of IMP, adverse event inquiry, ~~ISRs~~ injection site findings and pain assessment of last injection, inquiry regarding alcohol consumption/illicit drug use, and concomitant medication inquiry."

The purpose of these changes is to clarify the difference between the routine assessment of local tolerability/injection site findings (as specified in Table 10 in the study protocol) and ISRs, which are considered adverse events whether identified as part of the routine tolerability assessment, reported by the patient, or otherwise.

This change has no significant impact on the safety or scientific value of the clinical trial.

2. Allowed indications for using lorazepam as a rescue medication

a. **In Section 6.7.1.1. Rescue Medications:**

"In addition, during the screening period and in Period 1, use of lorazepam (up to 6 mg/day or up to the maximal daily dose allowed locally [the lower of the two]) is permitted on an as-needed basis for indications other than akathisia (eg, anxiety). Use in this context must be limited to no more than 72 consecutive hours, and lorazepam should not be taken within 8 hours prior to rating scale assessments.

In Period 2, use of lorazepam (per local label approved dose) is permitted on an as-needed basis for indications other than akathisia (eg, anxiety)."

The purpose of these changes is to clarify that there may be different indications for the use of lorazepam authorized per protocol that are not akathisia and that anxiety is only provided as an example of such an indication. This change has no significant impact on the safety or scientific value of the clinical trial.

3. Interpretation of ECGs to assess patient eligibility for enrollment.

   a. In Section 8.7. Electrocardiography:

   "A 12-lead ECG will be recorded at the time points detailed in Table 1 and Table 2. At screening and baseline, measurements will be done in triplicate (approximately 5 minutes apart). Single measurements will be performed at all other in-clinic visits where ECG recordings are taken. All ECG recordings should be sent to the central diagnostic center at screening, baseline, and throughout the study. A qualified physician at a central diagnostic center will interpret the ECG. Patients' eligibility at screening may be determined based on the investigator or designee ECG interpretation.

   In case only local ECGs interpretations are available within the screening period and they indicate that the patient is eligible for randomization, the patient may be randomized (provided all other study eligibility criteria are met). When central diagnostic ECG interpretation becomes available (after randomization), the patient's eligibility should be re-confirmed. In case the central diagnostic interpretation suggest that the patient does not meet study eligibility criteria, it is recommended to repeat the ECG and consult the MM."

   The purpose of these changes is to clarify that according to inclusion criterion p: "The patient is in adequate health as determined by medical and psychiatric history, medical examination, electrocardiogram (ECG), serum chemistry, hematology, coagulation urinalysis, and serology", the patient's eligibility for the study may be based on both central diagnostic center ECG interpretation and/or local ECG interpretation.

   This change has no significant impact on the safety or scientific value of the clinical trial.

4. Order of assessments before and after randomization at visit 11

   a. In Section 1.3. Schedule of Study Procedures and Assessments, Table 2: Study Procedures and Assessments for Period 2, footnote w:

   "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~~ as detailed in Section 6.9.1 and footnote "k" of Table 1 and Table 2). Any assessments performed after IMP administration must be completed on the day of IMP administration."

b. In Section 4.1. General Study Design and Study Schematic Diagram, page 64:

"…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~~ as detailed in Section 6.9.1 and footnote "k" of Table 1 and Table 2). Any assessments performed after IMP administration must be completed on the day of IMP administration…"

There was a discrepancy between footnote k of Tables 1 and 2, and footnote w of Table 2 regarding the order of assessment in visit 11 that is now aligned. There was no change to the order of assessments in visit 11.

This change has no significant impact on the safety or scientific value of the clinical trial.

5. Timeframe of treatment revealing

a. In Section 1.2. Study Scheme, footnote b:

"…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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

b. In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1, footnote k:

"…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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

c. In Section 1.3. Schedule of Study Procedures and Assessments, Table 2: Study Procedures and Assessments for Period 2, footnote k:

"…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), on a patient-by-patient basis.

The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

d. In Section 4.1. General Study Design and Study Schematic Diagram, page 41:

"…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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

e. In Section 4.1. General Study Design and Study Schematic Diagram, page 63:

"…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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

f. In Section 6.9. Randomization and Blinding:

"…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), on a patient-by-patient basis. The revealing of the Period 2 treatment assignment will be performed ~~between week 8 and week 12~~ after week 8 (visit 11) by the ~~sponsor or delegates~~ 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)."

g. In Section 6.9.2. Blinding Procedures:

"… 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 ~~unblinded~~ revealed."

The purpose of these changes is to clarify that although the sponsor highly encourage the sites to complete the treatment revealing process between week 8 (visit 11) and week 12 (visit 12), it is possible to reveal the treatment later in the study. The revised language is aligned with the relevant study plans and does not affect the timing or the process.

This change has no significant impact on the safety or scientific value of the clinical trial.

6. Update on assessment of adverse events related to device

a. In Section 2.1.3. Olanzapine for Subcutaneous Use (TV-44749):

[redacted]

b. In Section 6.1.1. Test Investigational Medicinal Product:

[redacted]

c. In Section 8.1.1. Definition of an Adverse Event:

"… An adverse device effect is an adverse event related to the use of a medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the medical device, including any event resulting from user error or from intentional misuse of the medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to medical devices."

d. In Section 8.1.2. Recording and Reporting of Adverse Events:

"… The investigator should make an initial determination whether the adverse event may be related to a device deficiency. If the AE/SAE could be related to the device, per

Appendix I, the details of the AE/SAE related to the device will be forwarded to the manufacturer/wholesaler of the device. Adverse device effects must be recorded on the source documentation and the CRF."

e. **In Section 8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product:**

"The relationship of an adverse event to the IMP and/or device is characterized as follows (Table 8)"

f. **In Section 8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product, Table 8: The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device, no reasonable possibility (not related):**

"This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP and/or device."

"It does not follow a reasonable temporal sequence from the administration of the IMP and/or device."

"It does not follow a known pattern of response to the IMP and/or device."

"It does not reappear or worsen when the IMP and/or device is re-administered."

g. **In Section 8.1.4. Relationship of an Adverse Event to the Investigational Medicinal Product, Table 8: The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device, reasonable possibility (related):**

"This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP and/or device cannot be ruled out with certainty."

"It follows a reasonable temporal sequence from administration of the IMP and/or device."

"It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP and/or device, yet an IMP and/or device relationship clearly exists."

"It follows a known pattern of response to the IMP and/or device."

h. **In Section 8.1.5.1. Definition of a Serious Adverse Event:**

"… A serious adverse device effect is an adverse device effect that results in any of the consequences characteristic of a serious adverse event and is reported per Section 8.1.6."

i. In Section 10.7. Safety Analysis:

"…Summaries will be presented for all adverse events (overall and by severity), adverse events related to test IMP and/or device (ie, reasonable possibility defined by the investigator as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device events, and adverse events and adverse device events causing withdrawal from the study."

j. In Section 11. QUALITY CONTROL AND QUALITY ASSURANCE:

"… Refer to Appendix I for the definition of a clinical product complaint or device deficiency and investigator responsibilities in the management of a clinical product complaint or device deficiency."

k. In Appendix I. PRODUCT COMPLAINTS, Clinical Product Complaints:

"A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical investigational medicinal product (IMP) and/or clinical device supplies used in a clinical research study sponsored by Teva.

…

Device deficiency (eg, any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance). This includes malfunctions, use errors, and inadequate labeling (eg, unintelligible label, incorrect expiry date).

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to TevaProductComplaintAndPotentialSB@teva.co.il as soon as possible ~~clinical.producteomplaints@tevapharm.com within 48 hours~~ of becoming aware of the issue.

For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

If the clinical product complaint is related to a device, rescue medication, or any other product planned in the protocol not manufactured by Teva, the complaint will be forwarded to the manufacturer/wholesaler of that product."

l. In Appendix I. PRODUCT COMPLAINTS, Handling of Investigational Medicinal Product(s) at the Investigational Center(s):

… "If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP or device.

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

m. In Appendix I. PRODUCT COMPLAINTS, Device Deficiency That Could Have Led to Serious Adverse Event [new section]:

"Device deficiencies that could have led to serious adverse events are defined as deficiencies that might have led to a serious adverse device effect if:

suitable action had not been taken (or)

intervention had not been made (or)

if circumstances had been less fortunate.

These device deficiencies shall be reported to the IRB/IEC by the investigator and to the regulatory authorities by the sponsor according to national and local regulations. Device complaints related to potential device malfunctions will be initially assessed by the sponsor to determine the root cause of the complaint. Device complaints that are assessed to be caused specifically by device deficiencies will be reported to the device manufacturer for evaluation and further reported according to national and local regulations.

The investigator will record in the source documentation a description of the complaint, the initial determination whether the device deficiency could have led to a serious adverse event, and any actions taken to resolve the complaint and to preserve the safety of the patient."

The purpose of these changes is to clarify details regarding the adverse effects that are related to device (adverse device effects) in relation to this study.

This change has no significant impact on the safety or scientific value of the clinical trial.

7. The data sources for PANSS, including informant data recording

a. In Section 7.1.1. Positive and Negative Syndrome Scale:

"The PANSS will be administered by the investigator/trained rater at screening and all the time points specified in Table 1 and Table 2.

In addition to the patient and the rater, the information used for PANSS assessment may be obtained from 3rd party sources, such as the caregiver and an informant. In such cases, the name of the person/s who had provided the information and their relation to the patient (ie, caregiver or informant) should be recorded in the source documents."

The purpose of these changes is to clarify that the information used for assessing the PANSS can be received from different sources, according to the validated PANSS version that is being used in this study, and that the source of information should be recorded in the source documents, including the name of the person who had provided the data and their relation to the patient. This information will remain confidential and will be used only for transparency purposes.

This change has no significant impact on the safety or scientific value of the clinical trial.

8. Safety laboratory tests during visit 3

   a. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1, footnote h:**

   "… At screening (prior to intake of oral olanzapine, where relevant), baseline (visit 2; week 0 [prior to IMP administration]), visit 11 (week 8 [prior to IMP administration]), and at the EOT visit, clinical laboratory tests will also include prolactin. Additionally, toxicological blood test should be collected as soon as a potential PDSS event is suspected.

   In case visit 3 safety laboratory blood samples cannot be shipped to the central laboratory on the same day, the samples may be processed in the local clinical laboratory instead. If needed, an additional set of safety laboratory tests may be collected for that purpose. In case visit 3 occurs over the weekend and the local safety laboratory tests cannot be processed on the collection day, visit 3 safety laboratory samples will be collected up to 2 days after the visit 3 nominal date and sent to the central laboratory."

   The purpose of these changes is to clarify that since visit 3 has no allowed time window, in the above specific case the patient's safety laboratory tests can be performed locally.

   This change has no significant impact on the safety or scientific value of the clinical trial.

9. Total blood volume in China

   a. **In Section 6.11. Total Blood Volume:**

   "The total blood volume for routine sampling to be collected for each patient in this study is approximately 257 mL (at maximum), including the optional samples for pharmacogenetics and biomarkers. ~~A slightly higher total blood volume is expected to be collected for patients in China.~~ "

   The purpose of this change is to clarify that the slightly higher total blood volume for patients in China initially indicated in the protocol was based on an operational requirement from the analytical laboratory that was planned to be used in China and is no longer required. As a different analytical laboratory in China was eventually selected for this study, the new operational requirements for total blood volume collected from patients in China is now identical to that collected from patients in the rest of the world.

   This change has no significant impact on the safety or scientific value of the clinical trial.

10. Timing of providing informed consent by the caregiver

    a. **In Section 4.1. General Study Design and Study Schematic Diagram:**

    "…The caregiver must have regular contact with the patient (defined as direct contact not fewer than 3 times per week), with the expectation that this frequency of contact would continue throughout the outpatient portion of Period 1 (it is also advised during the rest of

the study, including Period 2 and the FU period). The patient's caregiver will be asked to sign a caregiver ICF ~~at screening~~ during the screening period."

b. In Section 5.1. Patient Inclusion Criteria, criterion h:

" … The patient's caregiver will be asked to sign a caregiver ICF during the screening period."

The purpose of this change is to clarify that the participant's caregiver, whose presence is mandatory for the outpatient portions of the study Period 1, should sign the caregiver ICF during the screening period, prior to randomization of the patient, in order to meet inclusion criterion h.

This change has no significant impact on the safety or scientific value of the clinical trial.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

Sincerely,

DocuSigned by:

[redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel [redacted] www.tevapharm.com

Administrative Letter 03 Dated 21 Mar 2023

ADMINISTRATIVE LETTER 03

Study number: 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

Version date 01 September 2022

IND number: 128851; EudraCT number: 2022-001865-11

21 March 2023

Dear Investigator:

The purpose of this letter is to implement the following modifications and clarifications to Protocol TV44749-CNS-30096:

- update the Readiness for Discharge Questionnaire (RDQ) rater qualifications
- clarification of exclusion criterion n
- removal of carbon dioxide from Table 9, Clinical Laboratory Tests
- clarification of the PK analytes
- clarification on the Positive and Negative Syndrome Scale (PANSS) audio recording requirement and analysis
- update of end of treatment (EOT) and follow-up (FU) allowed visit windows
- update of the allowed screening period duration under certain circumstances
- clarification of allowed concomitant medications
- update of the Columbia-Suicide Severity Rating Scale (C-SSRS) rater qualifications

Modifications to the protocol are provided below with deletions signified by strikethrough and additions by underscore.

1. Update the RDQ rater qualifications
   a. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1, footnote dd:**

      Please refer to the discharge criteria (Section 4.1). The RDQ should be completed by ~~the investigator treating the patient~~ a qualified health care professional (HCP) who has a thorough knowledge of the patient's clinical condition, and has been following them throughout the duration of the hospitalization.

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b. **In Section 4.1. General Study Design and Study Schematic Diagram:**

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 by ~~the investigator treating the patient~~ a qualified health care professional (HCP) who has a thorough knowledge of the patient's clinical condition, and has been following them throughout the duration of the hospitalization.

We would like to clarify that the RDQ rater qualifications were adjusted following review of the Psychometric Evaluation of the Readiness for Discharge Questionnaire manuscript (Potkin et al 2005), suggesting the utility of the RDQ for physicians, nurses, and providers in assessing readiness for discharge in hospitalized patients with schizophrenia. This adjustment is also in line with the clinical practice, where HCPs from different educational backgrounds routinely assess the readiness for discharge in this patient population.

This change has no significant impact on the safety or scientific value of the clinical trial.

Additionally, since Clinical Global Impression–Severity (CGI-S) score is one of the Readiness for Discharge Questionnaire (RDQ) criteria, the RDQ rater qualification methodology was aligned with the CGI-S/Improvement rater qualification methodology, and may include the Doctor of Medicine, Doctor of Osteopathic Medicine, nurse practitioner, registered nurse, or other HCP depending on clinical experience, scales experience and number of scales recent administrations, as detailed in the Qualification Methodology document.

2. Clarification of exclusion criterion n

   a. **In Section 5.2. Patient Exclusion Criteria, criterion n:**

   The patient has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize study participant's safety (including in the context of local oral olanzapine label) or would compromise the patient's ability to participate in this study.

We would like to clarify that since oral olanzapine is administered during the screening period to the patients who haven't received oral olanzapine during the year prior to their participation in the study, the oral olanzapine local label language should be reviewed by the investigator for safety considerations.

3. Removal of carbon dioxide from Table 9, Clinical Laboratory Tests

   a. **In Section 8.4. Clinical Laboratory Tests, Table 9:**

   In Table 9, Clinical Laboratory Tests, ~~Carbon dioxide~~ in the serum chemistry column should be deleted.

We would like to clarify that the carbon dioxide test is being deleted, since it is redundant, and was added by mistake. The protocol already includes bicarbonate test in the serum chemistry panel (which is the same test under a different name). This change has no significant impact on the safety or scientific value of the clinical trial.

4. Clarification of the PK analytes
   a. **In Section 9.1. Pharmacokinetic Assessment**

[redacted]

5. Clarification on the PANSS audio recording requirement and analysis
   a. **In Section 4.1. General Study Design and Study Schematic Diagram, Screening (up to 8 days Prior to Randomization to Period 1):**

      …In addition, all patients will be asked to provide consent for mandatory audio recording of the PANSS assessments, which will be reviewed, as necessary, to monitor the quality of the ratings. These audio recordings will not be used for analysis, unless the patient had provided consent to participate in the optional exploratory assessment of audio recordings.

   b. **In Section 5.1. Patient Inclusion Criteria, criterion b:**

      The patient is capable of providing signed informed consent. 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. In addition, all patients will be asked to provide consent for mandatory audio recording of the PANSS assessments (which will be reviewed, as necessary, to monitor the quality of the ratings). These recordings will not be used for analysis, unless the patient had provided consent to participate in the optional exploratory assessment of audio recordings.

   c. **In Section 7.1.1. Positive and Negative Syndrome Scale**

      The audio of PANSS assessments will be recorded for all patients (which will be reviewed, as necessary, to monitor the quality of the ratings).
      [redacted]

   d. **In Appendix D. Ethics, Informed Consent:**

      In addition, all patients will be asked to provide consent for mandatory audio recording of the Positive and Negative Syndrome Scale assessments (which will be reviewed, as necessary, to monitor the quality of the ratings).
      [redacted]

We would like to clarify that the PANSS audio recordings are mandatory for all study participants, for the purpose of reviewing them, as necessary, to monitor the quality of the ratings and raters' performance. These recordings, which will be stored for 10 years, in both secure vendor facility under secure encryption and sponsor's secure cloud (which can only be accessed by authorized personnel), will not be used for the purpose of exploratory development of a model that correlates acoustic features in speech to clinically relevant patient status and safety parameters, unless the patient had provided consent via a dedicated optional ICF. This change to the protocol language is proposed for clarification reasons only, and added to all relevant sections, and does not have a significant impact on the safety or scientific value of the clinical trial.

6. Update of the EOT and FU allowed visit windows

   a. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1 (both within the table and in footnote b):**

      Allowed time window for end of treatment (EOT): ~~±3 days~~ ±1 week
      Allowed time window for follow-up visit (FU): ~~±3 days~~ -1/+2 weeks

      Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) 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 (±1 week), and a FU visit for safety evaluation will be conducted at 8 weeks (-1/+2 weeks) after the last dose of IMP.

   b. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 2: Study Procedures and Assessments for Period 2 (both within the table and in footnote b):**

      Allowed time window for end of treatment (EOT): ~~±3 days~~ ±1 week
      Allowed time window for follow-up visit (FU): ~~±3 days~~ -1/+2 weeks

      An EOT visit will be conducted at 4 weeks after the last dose of IMP (ie, 4 weeks [±1 week] after visit 22 if the patient completes the entire Period 2 or earlier if the patient ~~earlier~~early terminates or the sponsor stops the study), and a FU visit for safety evaluation will be conducted at 8 weeks (-1/+2 weeks) after the last dose of IMP.

   c. **In Section 4.1. General Study Design and Study Schematic Diagram:**

      Period 2 (up to 48 weeks):

      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.

Early Termination and Follow-up Period:

Randomized patients who meet 1 or more of the study discontinuation or withdrawal criteria (Section 5.4) 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.

We would like to clarify that the allowed time windows for EOT and FU visits have been extended since the pharmacokinetics and safety aspects allow this extension without any impact on patient's safety or scientific value of the clinical trial.

The EOT visit is scheduled to occur at the end of the last IMP exposure period ie, 4 weeks after the last IMP injection, to assess patients' safety before re-initiating their antipsychotic treatment outside the scope of the clinical study. In order to provide the patients, the caregivers, and sites the flexibility to complete all safety assessments, receive laboratory analysis results, and make necessary arrangements prior to approaching their treating physician for a timely treatment continuation, the window for EOT visit was extended to ±1 week.

The FU visit timing is aimed to assess the safety of the patients after close to complete elimination (washout) of the IMP. TV-44749 has long apparent terminal half-life of 8.5 and 16.5 days (depending on dose), with approximately 11 days terminal half-life at therapeutic dose range. Based on that, a complete elimination reached 4.5 to 5 half-lives following last IMP administration is expected to occur 50 to 55 days after visit 22 for patients completing Period 2. The extended 56 days -1week/+2 weeks window for the FU visit is aligned with the complete IMP washout timing, while allowing the patients, caregivers, and sites the flexibility in executing this visit, taking into consideration feasibility and availability constrains often associated with conducting study site visit after study completion.

This change doesn't have a significant impact on the patients' safety or scientific value of the clinical trial.

7. Update of the allowed duration of the screening period under special circumstances

   a. **In Section 1.3. Schedule of Study Procedures and Assessments, Table 1: Study Procedures and Assessments for Period 1, footnote a:**

      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 (eg, extreme weather) after receiving approval from the medical monitor (MM) or sponsor.

b. **In Section 4.1, General Study Design and Study Schematic Diagram, Screening (up to 8 days Prior to Randomization to Period 1):**

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 (eg, extreme weather) after receiving approval from the MM or sponsor.

c. **Appendix B. Study Procedures and Assessments by Visit, Procedures for Screening/Visit 1 (Day -8, Weeks -2 to -1)**

Note: 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 (eg, extreme weather) after receiving approval from the MM or the sponsor.

We would like to clarify that it was decided to allow the extension of the screening period by 2 days (until day 10 of screening) not only due to lack of screening laboratory tests results, but other unexpected situations, such as extreme weather conditions, which may preclude a timely randomization. This extension will be allowed only in exceptional cases, under special conditions, and after receiving approval from the MM or the sponsor.

8. Clarification of allowed concomitant medications

a. **In Section 6.7. Prior and Concomitant Medication or Therapy**

Medications prescribed for the treatment of chronic medical conditions, other than ~~psychiatric conditions~~ antipsychotic medications, or for the treatment of acute medical conditions (such as antibiotics) may be permitted per investigator judgment.

We would like to clarify that medications prescribed for patients for the treatment of chronic psychiatric medical conditions, which are not antipsychotic medications (eg, antihistamines to treat chronic anxiety or antidepressants) are allowed during the study per protocol. Please refer to Section 6.7, Prior and Concomitant Medication or Therapy, in the study protocol to review any special considerations regarding allowed timeframe for such medications, prior to rating scales' assessments (eg, "It is advised not to allow benzodiazepines and anticholinergics within 8 hours or 12 hours, respectively, of rating scales' assessments"), or Section 6.7.1.2, Antidepressants and Mood Stabilizers. The

current protocol language was inaccurate and the proposed change provides clarity with regards to allowed and disallowed concomitant medications, specifying that antipsychotic medications (other than the IMP) are disallowed during the study, as already stated in Appendix G, List of Disallowed Medications, without any impact on the patents' safety or study scientific value.

9. Update C-SSRS rater qualifications

   a. **In Section 8.9. 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 Baseline/Screening version will be administered by a qualified ~~clinician~~ HCP (ie, the investigator or a ~~medically~~ qualified person designated by the investigator) at screening, and the C-SSRS Since Last Visit version will be completed at all other time points, as described in Table 1 and Table 2. Following any positive finding on the C-SSRS Since Last Visit version, the patient must be evaluated by the Principal Investigator or a patient's mental health practitioner designated by the investigator ~~a physician and consult with a psychiatrist~~, which may result in the patient's withdrawal from the study. Recording of positive findings as adverse events will be per investigator decision.

We would like to clarify that the C-SSRS rater qualifications were updated to reflect the rater qualification requirements determined by the scale author. The interview and rating for the C-SSRS will be conducted by a rater specifically trained to rate the scale (per the minimum requirements outlined by the scale author), regardless of education level, who has appropriate clinical trial experience with C-SSRS administration, after review and approval by the Teva clinical study physician or designee. Study protocol Section 8.9, Assessment of Suicidality, currently states that the interview and rating for the C-SSRS will be completed by a qualified clinician specifically trained to rate the scale. However, the minimum requirements determined by the scale author, Kelly Posner Gerstenhaber, PhD, state that anyone can administer the C-SSRS for clinical trials, regardless of education level, as long as the administrator views the C-SSRS training video and gets a training certificate. Hence, the text was revised to allow raters with appropriate prior clinical trial experience with the C-SSRS administration and meet the aforementioned requirements to be eligible to administer this scale to patients participating in the TV44749-CNS-30096 study, after review and approval by the Teva clinical study physician or designee. Details regarding C-SSRS rater requirements and training can be found in the Columbia Lighthouse Project website, (http://cssrs.columbia.edu/training/training-research-setting/), ©2016.

Clinical interpretation of the C-SSRS scale should be provided by a mental health professional who has appropriate training and experience in suicide assessment and intervention. According to the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide (2013), positive finding on the C-SSRS Since Last Visit version should trigger further evaluation and immediate contact with patient's mental health practitioner. This definition may include psychologists, Licensed Clinical Social Workers (LCSWs),

Licensed Professional Counsellors (LPCs), and Psychiatric Nurse Practitioners (PNPs), in addition to physician and psychiatrist as previously defined in the protocol.

This change more accurately reflects the C-SSRS Scoring and Data Analysis Guide and has no significant impact on the safety or scientific value of the clinical trial.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

Sincerely, DocuSigned by: [redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. [redacted] www.tevapharm.com

Administrative Letter 02 Dated 15 Feb 2023

ADMINISTRATIVE LETTER 02

Study number: TV44749-CNS-30096

Clinical Study Protocol

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

Version date 01 September 2022

IND number: 128851; EudraCT number: 2022-001865-11

15 February 2023

Dear Investigator:

The purpose of this letter is to inform you that in countries where performing blood toxicology screen is not feasible due to lack of suitable analytical facilities a urine drug screen may be performed instead.

This statement will be added in the following sections as signified by underscore.

1. **In Table 1: Study Procedures and Assessments for Period 1, footnote h**:
Clinical laboratory tests (including serum chemistry, hematology, coagulation, and urinalysis) may also be performed at any time if clinically indicated. Coagulation laboratory tests are performed at screening only. Glomerular filtration rate will be calculated at screening only. At baseline (visit 2; week 0), visit 11 (week 8), and at the EOT visit, clinical laboratory tests will also include hemoglobin A1C. Patients must fast for at least 8 hours prior to baseline (visit 2; week 0), visit 11 (week 8), and the EOT visit (and preferably the ET visit). At screening (prior to intake of oral olanzapine, where relevant), baseline (visit 2; week 0 [prior to IMP administration]), visit 11 (week 8 [prior to IMP administration]), and at the EOT visit, clinical laboratory tests will also include prolactin. Additionally, toxicological blood test should be collected as soon as a potential PDSS event is suspected. In cases where performing toxicological blood test is not feasible due to a lack of suitable analytical facilities, a urine drug screen may be performed instead.
2. **In Table 2: Study Procedures and Assessments for Period 2, footnote l:**
Clinical laboratory tests (including serum chemistry, hematology, coagulation, and urinalysis) may also be performed at any time if clinically indicated. At visit 11 (week 8), visit 14 (week 20), visit 17 (week 32), visit 20 (week 44), and at the EOT visit, clinical laboratory tests will also include hemoglobin A1C. Patients must fast for at least 8 hours prior to visit 11 (week 8) and the EOT visit (and preferably the ET visit). At visit 11 (week 8 [prior to IMP administration]), visit 14 (week 20 [prior to IMP administration]),

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and at the EOT visit, clinical laboratory tests will also include prolactin. Additionally, toxicological blood test should be collected as soon as a potential PDSS event is suspected. In cases where performing toxicological blood test is not feasible due to a lack of suitable analytical facilities, a urine drug screen may be performed instead.

3. **Table 3: Study Procedures and Assessments for a Potential Post-injection Delirium/Sedation Syndrome Event, footnote d was added:**

[redacted]

4. **In section 4.1. General Study Design and Study Schematic Diagram: Procedures for Potential Post-injection Delirium/Sedation Syndrome**
During Period 1 and Period 2, following IMP administration, patients will remain in the clinic for at least 3 hours for observation. If a potential PDSS event occurs, vital signs and blood samples for plasma drug concentration and biomarkers (for patients who provided consent for biomarker collection) should be collected as soon as a potential PDSS event is suspected. In case a suspected PDSS event is reported, a toxicological blood test should be collected from the patient as soon as PDSS is suspected. In cases where performing toxicological blood test is not feasible due to lack of suitable analytical facilities, a urine drug screen may be performed instead.

5. **In section 6.11. Total Blood Volume**:
The total blood volume for routine sampling to be collected for each patient in this study is approximately 257 mL (at maximum), including the optional samples for pharmacogenetics and biomarkers. A slightly higher total blood volume is expected to be collected for patients in China.
Additional blood samples for toxicology, pharmacokinetics, and/or biomarkers should be collected in case of potential PDSS; pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy; severe ISRs; and metabolic syndrome (Table 1, Table 2, and Table 3). Details will be included in the laboratory manual. In cases where performing toxicological blood test is not feasible due to lack of suitable analytical facilities, a urine drug screen may be performed instead.

6. **In section 8.10. Post-injection Delirium/Sedation Syndrome Monitoring:**

[redacted]

[redacted]

This change will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

[redacted]

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Administrative Letter 01 Dated 27 Nov 2022

ADMINISTRATIVE LETTER 01

Study number: TV44749-CNS-30096

Clinical Study Protocol

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

Version date 01 September 2022

IND number: 128851; EudraCT number: 2022-001865-11.

27 November 2022

Dear Investigator,

The purpose of this letter is to describe:

- correction to the intended age limit for the investigation
- correction to how alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin values will be considered for exclusion
- clarification to prior and concomitant medications or therapy
- clarification to the timing of unblinding of prolactin levels during the study
- correction to how unblinding is to be performed.
- correction and clarification related to total blood volume collected from each patient
- correction to source of Glomerular filtration rate calculation
- removal of unneeded clinical laboratory tests
- [redacted]

Modifications to the protocol are provided below in bold, with deletions signified by a strikethrough and additions by underscore.

1. Section 5.1. Patient Inclusion Criteria, change of text:

   "a. The patient is a male or female of any ethnic origin, 18 to ~~65~~ 64 years of age, inclusive, at the time of screening."

   While no indication of any different tolerability of olanzapine in the elderly compared to younger patients with schizophrenia is reported, it is not the sponsor's intention to investigate TV-44749 in the elderly population (defined by ICH E7 guidance as 65 and older, inclusive).

2. Section 5.2. Patient Exclusion Criteria, change of text:

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"w. The patient has ~~known~~ alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase values ≥2 × the upper limit of normal (ULN) of the performing laboratory, and aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase values ≥2 × ULN, and total bilirubin values ≥1.5 × ULN **at screening**."

These values are exclusionary only if detected at screening. Patients with a history of elevated values, not present at screening (for example, a case of past infection with Hepatitis A) will not be exclusionary.

3. Section 6.7. Prior and Concomitant Medication or Therapy, change of text:

   "Concomitant medication and **non-pharmacological** treatment will be recorded from screening through the final visit"

   This change is to clarify that non-pharmacological concomitant treatments, such as, but not limited to, psychotherapy, should be recorded. Prior non-pharmacological treatments will be recorded only if they are still ongoing during the study. Non-pharmacological treatments which have occurred only prior to screening, will not be recorded.

4. Section 6.10.2. Blinding and Unblinding, change of text:

   "As prolactin levels are highly affected by olanzapine and reach steady state approximately 8 weeks after treatment initiation (Yang et al 2018), in order to maintain the blind, prolactin level results **obtained after first IMP administration and before visit 13 (8 weeks into Period 2)** will not be available for review by the sponsor or the sites until ~~visit 13 (8 weeks into Period 2)~~ **Period 1 database lock**. The IDMC will review the unblinded data periodically."

   Sponsor and site personnel will not be blinded to prolactin results obtained at screening and baseline, which are prior to administration of the first IMP dose, as these data does not pose any unblinding risk.

5. Section 6.10.2. Blinding and Unblinding, change of text:

   "In cases when knowledge of the IMP assignment is needed to make treatment decisions during Period 1, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes indicating the IMP assignment for each randomized patient will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, ~~both~~ via ~~telephone and~~ internet. **A back-up process will be available to the investigator in case of internet connection issues.**"

   This change clarifies that the primary method to unblind a patient is via internet, as the RTSM system no longer operates via telephone. It was further clarified that a back-up process will be available to the investigator in case of internet connection issues.

6. Section 6.11. Total Blood Volume, change of text:

   "The total blood volume for routine sampling to be collected for each patient in this study is approximately 257 mL (at maximum), **not** including the optional samples for pharmacogenetics and biomarkers."

The protocol mistakenly indicated that the optional samples for pharmacogenetics and biomarkers samples were included in the total blood volume of 257mL collected from each patient. This volume does not include optional samples, according to how it is typically reported in Teva's protocols. The study Informed Consent Form (ICF) accurately reflects the volumes collected.

7. Section 8.4. Clinical Laboratory Tests, table 9 footnote a, change of text:

   "Glomerular filtration rate (to be calculated at screening only) will be calculated based on ~~plasma~~ serum creatinine levels, weight, gender, and age using the Cockcroft-Gault equation."

   This change does not require additional blood volume collected at screening, since serum creatinine levels are already measured as part of the mandatory serum chemistry blood test.

8. Section 8.4. Clinical Laboratory Tests, table 9:

   The term "Lymphocytes atypical" should be removed from the column "Hematology and coagulation".

   The known adverse events of Olanzapine, affecting WBCs, including Leukopenia, Neutropenia, and Agranulocytosis, will be monitored closely during the trial, by hematology blood test results. Since atypical Lymphocytes have not been reported to be affected by Olanzapine, this test is not warranted to ensure study participants safety and will not be performed.

9. Section 9.3. Assessment of Exploratory Biomarkers, change of text:

[redacted]

[redacted]

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

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

Sincerely,

[redacted]

27-Nov-2022 | 10:10 GMT

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