Clinical Study Protocol

A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three SC Olanzapine Extended-release Formulations with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder

Study Number TV44749-NPC-10205

NCT06319170

Protocol with Amendment 01 Approval Date: 11 May 2024

Clinical Trial Protocol with Amendment 01

Trial Number TV44749-NPC-10205

A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three SC Olanzapine Extended-release Formulations with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder

Pharmacokinetic Trial

Phase 1

IND number: 128851; NDA number: not applicable; BLA number: not applicable; EudraCT number: not applicable; EU CT number: not applicable

EudraVigilance Code for the IMP: not applicable

EudraVigilance Code for the Drug Substance: SUB09426MIG

Version Date: 11 May 2024

Sponsor

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

Sponsor's Authorized Representative

[redacted]
Teva Pharmaceutical Industries Ltd.

Name and contact information of the Medical Monitor are provided separately.

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

Confidentiality Statement

INVESTIGATOR AGREEMENT

Clinical Trial Protocol with Amendment 01

Version Date: 11 May 2024

TV44749-NPC-10205

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IND number: 128851; NDA number: not applicable; BLA number: not applicable;

EudraCT number: not applicable; EU CT number: not applicable

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 trial. I am qualified by education, experience, and training to conduct this clinical research trial. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this trial 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 products (IMP) that were furnished to me by the Sponsor to all physicians and other trial personnel reporting to me who participate in this trial and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the trial. I agree to keep records on all participant information, IMP shipment and return forms, and all other information collected during the trial, in accordance with national and local GCP 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

Clinical Trial Protocol with Amendment 01

Version Date: 11 May 2024

TV44749-NPC-10205

A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three SC Olanzapine Extended-release Formulations with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder

IND number: 128851; NDA number: not applicable; BLA number: not applicable; EudraCT number: not applicable; EU CT number: not applicable

I have read the protocol with Amendment 01 and approve the design of this trial.

Sponsor's Authorized Representative	Signature	Date
[redacted]		

Executed signature pages are maintained within the Trial Master File

PROTOCOL AMENDMENT DETAILS

Document History	
Administrative Letter 01	26 March 2024
Protocol Revision 1	13 September 2023
Original Protocol	01 August 2023

Current Amendment 01, 11 May 2024

As of 03 May 2024, 6 participants have been enrolled into cohort 1a (sentinel cohort).

Overall Rationale for the Amendment 01:

The primary reason for this amendment is to revise Section 9.7 (Interim Analyses) to clarify that, under the Sponsor's current internal procedures and definitions, the originally planned reviews of emerging data in this open-label study are no longer considered formal interim analyses. The review of safety data of cohort 1a by the safety review committee (SRC) is described in Section 4.1.2. In addition, wording has been modified to allow more flexibility regarding the use of preliminary concentration data to initiate IVIVC modeling before database lock.

Additional minor corrections/clarifications were made. None of these changes affect the safety or rights of the participants, the scope of the investigation, and/or the scientific integrity of the trial.

One previous Administrative Letter (March 26th, 2024) was issued to provide corrections to editorial errors and clarifications; these revisions have been implemented in this protocol amendment.

The modifications and clarifications implemented to the TV44749-NCP-10205 study protocol have no significant impact on the safety or scientific value of the clinical trial.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities: Table 1. Screening, Antipsychotic Washout Period, and ZYPREXA IM Treatment Period 1: Trial Procedures and Assessments (Day -40 Through Day 4)	Footnote "c" of Table 1 was corrected to indicate that a separate written informed consent will be obtained from each participant before the biomarker samples are collected during period 3.	To provide clarification and correct a prior error
1.3 Schedule of Activities: Table 1. Screening, Antipsychotic Washout Period, and ZYPREXA IM Treatment Period 1: Trial Procedures and Assessments (Day -40 Through Day 4)	Footnote "r" of Table 1 was updated to clarify that there are no specific time windows for conducting Numeric Pain Rating Scale assessments in case of injection site reaction adverse events. (Administrative Letter 01)	To provide clarification
1.3 Schedule of Activities: Table 3. Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1A: Trial Procedures and Assessments (Day R1 through Day R25) Table 4. Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1B, Cohort 2, and Cohort 3: Trial Procedures and Assessments (Day R1 through Day R25)	"PGx" is defined in the footnotes of Table 3 and Table 4 as "pharmacogenetics". However, the synonymous term, "pharmacogenomics", is used consistently throughout the rest of the study protocol tables. As the "pharmacogenomics" term is the preferred term for use in the protocol, the footnotes will be corrected.	To correct an editorial error
1.3 Schedule of Activities: Table 7. Schedule of Assessments for Pharmacokinetic Sampling Before and After Olanzapine Extended-release SC Formulation Administration	For the pharmacokinetic sampling schedule (Table 7), the ±3-hour time window for the day 1 pre-dose sample was not feasible as this range extends beyond the time of dosing. This window was revised to ±10 minutes.	To correct an error
4.1 Description of Trial Design	Text was added to clarify that Visit 11, if deemed not necessary by the Principal Investigator and Sponsor, will be skipped and the participant will proceed to Visit 12.	To provide clarification
4.1 Description of Trial Design 6.6.2 Randomization	The number of participants in the sentinel cohort 1A was revised to be composed of "approximately" 2 to 4 participants.	To allow flexibility in participant recruiting and enrollment

Section Number and Name	Description of Change	Brief Rationale
5.3 Inclusion Criteria Criterion “k”	A technical correction was necessary to make the study protocol consistent with Section 13 (Appendix) of the Study Protocol.	To provide alignment throughout the protocol
5.4 Exclusion Criteria Criterion “b”	A procedure was added in case the QuantiFERON test result, needed for eligibility, came out indeterminate. The option to repeat the QuantiFERON test was added as the possible improper handling of the test kit may result in indeterminate result, prohibiting the completion of the eligibility process.	To provide clarification
5.4 Exclusion Criteria Criterion “r”	The revision to exclusion criterion “r” clarifies that the temperature should be collected either orally or in both ears. (Administrative Letter 01)	Each of these methods are acceptable and clarifying this provides flexibility to the sites.
5.4 Exclusion Criteria Criterion “s”	The total bilirubin's unit and value in the bracket in exclusion criterion “s” were incorrect and were deleted as their inclusion was an error. Total bilirubin's remaining value and unit, 2.5 mg/dL, are correct and will remain as a part of exclusion criterion “s”. (Administrative Letter 01)	To correct an error
5.4 Exclusion Criteria Criterion “bb”	For exclusion criterion “bb”, text was added to align it with the relevant study population, as specified in inclusion criterion “f”, the study title, and the rest of the protocol. (Administrative Letter 01)	To provide alignment throughout the protocol
6.6.2.1. Maintenance of Randomization	Text indicating that the randomization list will be maintained in a secure location has been removed.	This study is not a blinded trial, so the randomization code list is technically not blinded and therefore does not need to be held in a secure location.

Section Number and Name	Description of Change	Brief Rationale
6.8.2 Permitted Concomitant Therapy	A revision was made to clarify that the medications that are prescribed to the patients are at the discretion of the investigator and that it is highly recommended to consult the sponsor to avoid prescribing medications that could potentially affect the olanzapine pharmacokinetic levels. (Administrative Letter 01)	To provide clarification
8.3.3 Electrocardiograms	More flexibility was allowed regarding the interpretation of the ECGs by physician or designee.	To provide clarification
8.3.6 Assessment of Local Tolerability and Pain	Sentences related to multiple injection sites were removed as there is only one (1) TV-44749 subcutaneous injection in the trial. (Administrative Letter 01)	To correct an error
8.3.7 Procedures for Injection Site Pus-containing Lesion (Abscess, Infection, or Inflammation), Ulceration, Necrosis, or Atrophy	This was the only section in the protocol where the protocol-defined adverse event of special interest (PDAESI) terms “necrosis or atrophy” were mistakenly not included. This revision aligns section text with other locations in the protocol where these terms are listed. (Administrative Letter 01)	To provide consistency across the document
9.1.2 Pharmacokinetics Analysis Set	A sentence related olanzapine formulations in the pharmacokinetics analysis set description was revised to clarify the routes of administration and formulations used. (Administrative Letter 01)	To provide clarification
9.7 Interim Analyses	Redundant interim analysis text was removed. The review of safety data of cohort 1a by the safety review committee (SRC) is described in Section 4.1.2. In addition, wording has been modified to allow more flexibility regarding the use of preliminary concentration data to initiate IVIVC modeling before database lock.	To clarify that under the Sponsor’s current internal procedures and definitions the originally planned reviews of emerging data in this open-label study are no longer considered formal interim analyses.

Section Number and Name	Description of Change	Brief Rationale
10.5 Early Investigational Center Closure or Trial Termination	A sentence related to investigational center closures was deleted since it was not capturing accurately all the relevant cases stated in the paragraph, which were adequately specified in the rest of the paragraph. (Administrative Letter 01)	To correct an error
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title: A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three SC Olanzapine Extended-release Formulations with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder.

Brief Title: Open-label Trial Characterizing the PK of 3 SC Olanzapine Extended-release Formulations in Participants with Schizophrenia/Schizoaffective Disorder.

Regulatory Agency Identifier Number(s): IND 128851

Rationale: To characterize the pharmacokinetics of 3 sc olanzapine extended-release injectable suspensions (TV-44749) with different release rates following single administration in participants with schizophrenia or schizoaffective disorder. The results from the current trial will be utilized for the development of an in vitro/in vivo correlation (IVIVC) model. The objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (plasma drug concentration or amount of drug absorbed), per the Food and Drug Administration (FDA) guidance (FDA, 1997) on the development, evaluation, and application of IVIVC for extended-release oral products. The results of the IVIVC analysis will be presented in a separate report.

Name of IMP: The trial will include four IMPs:

1. Olanzapine for Extended-release Injectable Suspension D (TV-44749) (hereafter referred to as Fast-D)
2. Olanzapine for Extended-release Injectable Suspension (TV-44749) (hereafter referred to as the to-be-marketed formulation)
3. Olanzapine for Extended-release Injectable Suspension C (TV-44749) (hereafter referred to as Slow-C)
4. ZYPREXA IntraMuscular (olanzapine) Injection, Powder, for Solution for im use (immediate-release) (hereafter referred to as ZYPREXA im)

Intervention Type: Drug

Primary and Secondary Objectives, Endpoints:

The primary and secondary objectives and measures are presented below:

Objectives	Measures
Primary	
To characterize the pharmacokinetics of 3 extended-release sc olanzapine formulations with different release rates following single administration in participants with schizophrenia or schizoaffective disorder.	The following pharmacokinetic parameters will be calculated for olanzapine, following single administration of 3 sc olanzapine extended-release formulations to support the primary objective of the trial: • Maximum observed plasma drug concentration (C_{max}) over the 84-day period following single-dose administration of 1 of the sc formulations to end of trial (EOT) (day R1 to day R84) • Area under the plasma drug concentration-time curve (AUC) following single-dose administration of 1 of the sc formulations to last measurable concentration (AUC_{0-t}) (day R1 to day R84) • AUC extrapolated to infinity ($AUC_{0-\infty}$) calculated from last measurable olanzapine plasma concentration following single-dose administration of 1 of the sc formulations from time 0 to EOT (day R1 to day R84)
Secondary	
To evaluate the safety and tolerability of 3 extended-release sc olanzapine formulations with different release rates in participants with schizophrenia or schizoaffective disorder.	The following safety and tolerability measures/parameters will be evaluated: • Number (%) of participants with at least 1 treatment-emergent adverse event (TEAE) over the 28-day period following administration of 1 of the sc olanzapine formulations (day R1 to day R29) • Number (%) of participants with at least 1 serious adverse event (SAE) over the 28-day period following administration of 1 of the sc olanzapine formulations (day R1 to day R29)

To characterize the pharmacokinetics of immediate-release ZYPREXA im in participants with schizophrenia or schizoaffective disorder.	The following pharmacokinetic parameters will be calculated for ZYPREXA im to support the secondary objective of the trial:
	• C_{max} over the 24-hour period following single-dose administration of the im formulation (day 4)
	  • AUC following single-dose administration of ZYPREXA im to last measurable concentration (AUC_{0-t}) (pre-dose ZYPREXA im to 216 hours post im administration)
	  • Apparent plasma terminal elimination rate constant (λ_z) over the 216-hour period (9 days) following single-dose administration of ZYPREXA im (pre-dose ZYPREXA im to 216 hours post im administration)

Overall Design: This is a multi-center, open-label, randomized, parallel-group trial to characterize the pharmacokinetics profile of 3 subcutaneous (sc) olanzapine extended-release formulations with different release rates, in participants with schizophrenia or schizoaffective disorder. The trial population will include clinically stable participants 18 to 64 years of age, not currently on antipsychotic treatment, with the exception of treatment with oral antipsychotics including aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone. The trial will be conducted in the US at approximately 5 investigational centers.

Participants currently treated with 1 of the antipsychotics allowed per the trial protocol (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) and who meet screening eligibility will undergo a 3-day inpatient washout (WO) period of the current antipsychotic treatment. Thereafter, participants will continue to period 1 that will include a single injection of 5 mg of ZYPREXA im (day 4). Subsequently, participants will continue to the follow-up period 2 (day 5 to day 12) during which they will resume treatment with 1 of the allowed antipsychotics at the Investigator's discretion. Period 2 can be extended by up to 7 days maximum, post Visit 10 (Visit 10 counts as extension day 1, so extension day 7 is R1, at maximum) for all cohorts. Follow-up period 2 is followed by a 28-day treatment period (period 3: day R1 to R29, where R1 is the first day post-randomization and the beginning of period 3), during which participants will be treated with 1 of the 3 single-dose sc olanzapine for extended-release IMP formulations (cohorts 1A and 1B will be treated with Fast-D; cohort 2 with the to-be-marketed formulation; cohort 3 will be treated with Slow-C). During period 3, participants will discontinue treatment with the allowed antipsychotic medication received during period 2. Period 3 will be initiated with treatment of a sentinel cohort, cohort 1A (2-4 participants). Cohort 1A will serve for initial evaluation of systemic safety and tolerability of the Fast-D formulation. If no safety concerns are raised based on the review of cohort 1A safety data up to 15 days (R15) inclusive, period 3 for cohort 1B (n~16) may be initiated. Randomization to cohort 2 (n~20) and cohort 3 (n~20) will be initiated in parallel to cohort 1B. Following completion of period 3, all participants enter a 56-day follow-up period during which they will resume treatment with the allowed antipsychotics at the Investigator’s discretion (day R29 to day R84).

The trial schematic diagram is presented in Figure 1.

Number of Participants: Approximately 95 participants are planned to be enrolled. The aim is to achieve approximately 20 completers in each of the single-dose sc olanzapine extended-release cohorts, for a total of approximately 60 completers. Completers are defined as participants who have completed the procedures and assessments required through the follow-up period of sc olanzapine extended-release (ie, the 84 days after the sc injection, up to and including day R84).

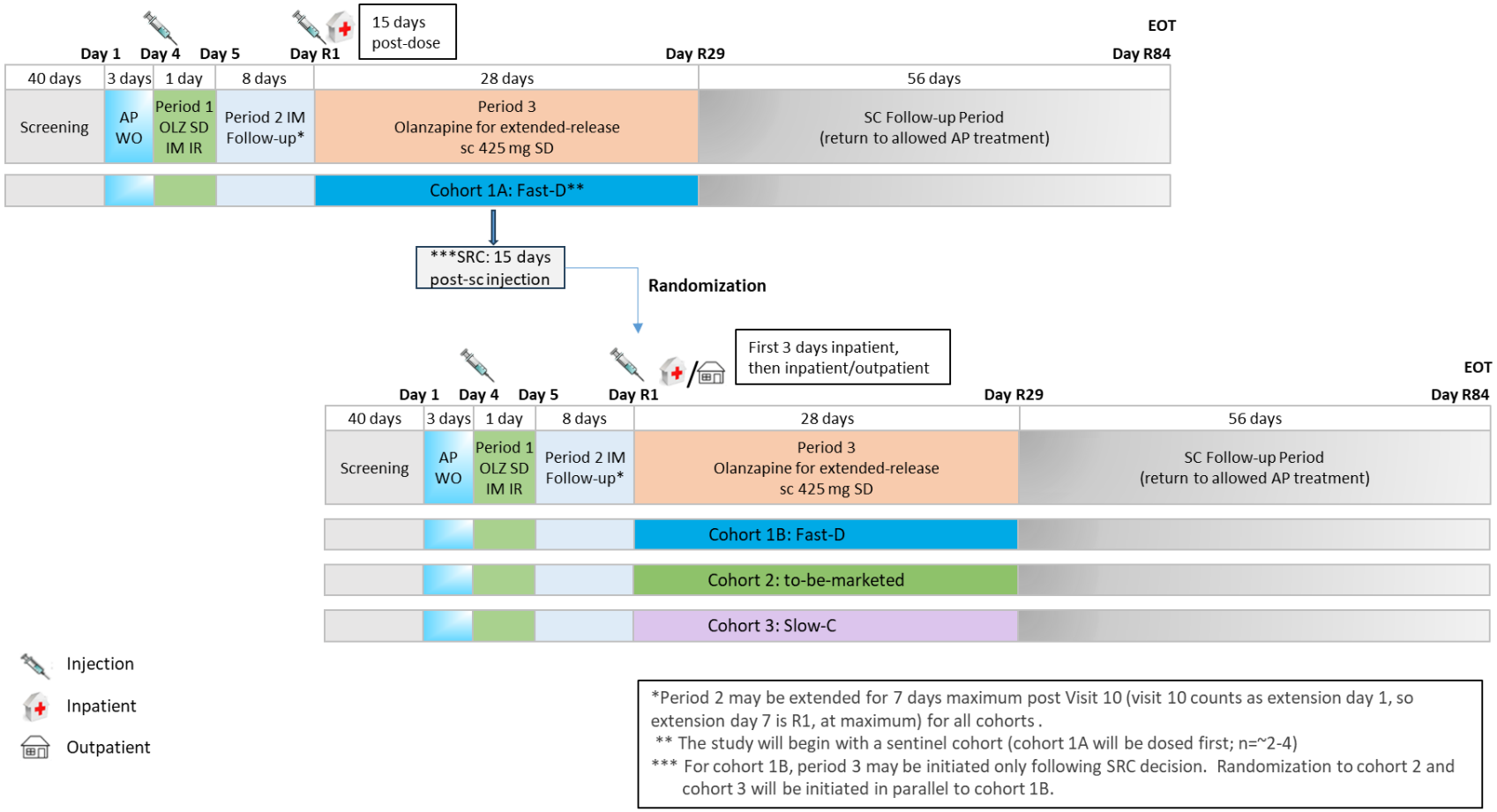
Trial Arms and Duration: Participants are expected to participate in this trial for its entire duration of approximately 19 weeks. The trial will consist of a screening period (up to 40 days), a 3-day WO period (day 1 to day 3), an open-label 1-day treatment period with ZYPREXA im (period 1: day 4), an 8-day follow-up period (period 2: day 5 to day 12), an open-label randomized 28-day treatment period with 1 of the 3 sc olanzapine (TV-44749) for extended-release formulations (period 3: day R1 to day R29), and an up to approximately 8-week follow-up period (day R29 to day R84). During the follow-up periods (period 2 and follow-up period post-sc injection), treatment with 1 of the allowed antipsychotics (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) will be resumed as per the Investigator’s discretion.

Data Monitoring/Other Committee: A safety review committee composed of the Sponsor’s clinical trial physician, clinical leader, pharmacovigilance physician, and other relevant experts has been appointed for this trial. The committee will review all safety data available upon completion of the first 15 days of the sentinel cohort (cohort 1A), and no other ongoing safety monitoring by the committee is expected.

Ethical Considerations: The trial design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect participant safety. The results of this trial may facilitate the development of TV-44749 with potential benefits for participants with schizophrenia and schizoaffective disorder. The availability of an extended-release antipsychotic agent may increase compliance in participants with schizophrenia.

1.2. Trial Schema

Figure 1: Trial Schematic Diagram



AP=antipsychotic; EOT=end of treatment; IM=intramuscular; IR=immediate-release; OLZ=olanzapine; sc=subcutaneous; SD=single-dose; SRC=safety review committee; WO=washout

1.3. Schedule of Activities

Trial procedures and assessments with their time points during screening, the antipsychotic washout period and treatment period 1 are presented in Table 1. Trial procedures and assessments with their time points during period 2 are presented in Table 2. Trial procedures and assessments during treatment period 3 for the Fast-D cohort 1A are presented in Table 3, and for cohorts 1B, 2, and 3 in Table 4. Trial procedures and assessments during the follow-up period following administration of sc olanzapine for extended-release are presented in Table 5.

Trial procedures and assessments for pharmacokinetic sampling windows after ZYPREXA im administration are presented in Table 6, while those after olanzapine sc formulation administration are presented in Table 7.

Trial procedures and assessments to be performed in the case of a suspected post-injection delirium/sedation syndrome (PDSS) event are present in Table 8.

Detailed descriptions of each method of procedures and assessments are provided in Section 8 (Trial Assessments and Procedures).

Table 1: Screening, Antipsychotic Washout Period, and ZYPREXA IM Treatment Period 1: Trial Procedures and Assessments (Day -40 Through Day 4)

APPLICABLE TO ALL COHORTS: 1A, 1B, 2, and 3				
Procedures and assessments	**Screening**	**Antipsychotic washout period**		**Period 1: ZYPREXA IM**
	Outpatient[a]	**Inpatient**		
Visit number	**V1**	**V2**	**V3**	**V4**
Trial day	**-40 through -1**	**1[b]**	**3**	**4**
Informed consent[c]	X			
Demographics	X			
Medical and psychiatric history	X			
Prior medication history	X			
Inclusion and exclusion criteria	X			X[d]
Enrollment		X		
ZYPREXA IM injection[e]				X
Vital sign measurements[f]	X		X	X
12-lead ECG[g]	X		X	X
Physical examination[h]	X		X	
Physical measurements[i]	X		X	
Clinical laboratory tests[j]	X	X		X[k]
Alcohol and drug screen[l]	X	X	X	
Pregnancy test[m]	X	X	X	
Serology test[n]	X			
FSH test[o]	X			
[redacted]	X	X		

Table 1: Screening, Antipsychotic Washout Period, and ZYPREXA IM Treatment Period 1: Trial Procedures and Assessments (Day -40 Through Day 4) (Continued)

APPLICABLE TO ALL COHORTS: 1A, 1B, 2, and 3				
Procedures and assessments	**Screening**	**Antipsychotic washout period**		**Period 1: ZYPREXA IM**
	Outpatient[a]	**Inpatient**		
Visit number	**V1**	**V2**	**V3**	**V4**
Trial day	**-40 through -1**	**1[b]**	**3**	**4**
[redacted]	X	X		X[p]
[redacted]	X	X		X[p]
[redacted]	X	X		X[p]
[redacted]	X	X		
[redacted]	X[q]	X		
NPRS for pain[r]				X
Adverse event recording		X	X	X
Concomitant medication review		X	X	X
Pharmacokinetic blood sample collection[s]				X
Admission to CU		X		
Inpatient in CU			X	X

[a] Participants will visit the CU for screening as an outpatient.
[b] Participant enrollment occurs on day 1. On day 1 of the washout period of antipsychotics, participants will be admitted to the CU for trial procedures and assessments.
[c] Written informed consent will be obtained from each participant before any trial-specific procedures or assessments are performed. A separate written informed consent will be obtained from each participant before the biomarker samples are collected during period 3.
[d] Participants' continued eligibility will be reconfirmed by review of abbreviated inclusion and exclusion criteria prior to administration of ZYPREXA im. The abbreviated list will include the following inclusion criteria (g, h) and exclusion criterion (a); the clinical scales and laboratory tests taken on day 1 will be used to confirm eligibility on day 3. In case of a delay, laboratory results can be reviewed to perform abbreviated eligibility assessment on day 4, as long as this is done prior to administration of ZYPREXA im. Laboratory results from blood samples collected on day 4 are not required prior to initiating ZYPREXA im. Day 4 central clinical laboratory assessments will serve as baseline values and are based on samples collected prior to dosing of ZYPREXA im. Serology to support eligibility criteria will only be done at screening.
[e] ZYPREXA im injection will be administered into the gluteal muscle.

[f] Vital signs include body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure. Pulse, blood pressure, and respiratory rate will be measured after the patient has been supine or semi-supine for at least 5 min. Orthostatic vital signs will be determined with measurements obtained after the patient has been supine or semi-supine for at least 5 min and repeated after the patient has been standing for 3 min. Body temperature will be measured only in the supine or semi-supine body position. Vital signs will be measured at screening on day 3 and on day 4. On day 4 vital signs will be measured at 45 min and at 6 h post-dose. Vital signs will be measured after ECGs but before scheduled blood draws, up to 30 min prior to the time point, when applicable.

[g] ECGs will be performed at screening, day 3, and day 4 after the participant has been in a supine or semi-supine position for at least 5 min. At screening only, the ECG will be obtained in triplicate at 5-min intervals. On day 4 ECG will be performed at 0.5 h and 6 h post-dose. The ECGs will be recorded before vital sign assessments and scheduled blood draws, up to 30 min prior to the time point, when applicable.

[h] A complete physical examination will be performed at screening and an abbreviated physical examination will be performed on day 3. The abbreviated physical examination will include general appearance, HEENT, lung, heart, skin, extremities, and a brief neurological examination.

[i] Includes height, weight, and calculation of BMI at screening; on day 3 only weight will be measured.

[j] Clinical laboratory tests will be performed following an overnight fast of at least 8 h and will include chemistry, hematology, coagulation, and urinalysis. HbA1c will be collected at screening. On day 1 and day 4 clinical laboratory tests may be performed via both local and central laboratories, as applicable. Non-fasting blood collection is permitted as needed, per Investigator assessment of adverse events. At each urinalysis collection, females will be asked if they are currently menstruating. Day 1 results will be used to confirm eligibility on day 3. In case of a delay, laboratory results can be reviewed to perform abbreviated eligibility assessment on day 4, as long as this is done prior to administration of ZYPREXA im.

[k] Blood samples will be collected prior to dosing. Laboratory results from blood samples collected on day 4 are not required prior to initiating ZYPREXA im, but are required prior to initiating period 3. Serology to support eligibility criteria will only be done at screening.

[l] Serum alcohol and serum drug screen will be performed at screening; urine dipstick for prohibited drugs and breathalyzer for alcohol will be performed on day 1 and day 3. Drug and alcohol screens may be conducted at additional time points at the discretion of the Investigator.

[m] Serum pregnancy tests will be performed for all female participants at screening and on day 1. Serum or urine dipstick pregnancy tests will be performed for all women of childbearing potential on day 3. Negative result is required prior to ZYPREXA im injection. Additional pregnancy tests may be performed if clinically indicated.

[n] Includes HBsAg, hepatitis C virus antibody, HIV-1 antibodies, and HIV-2 antibodies.

[o] For confirmation of postmenopausal status (an increased concentration of FSH of more than 35 IU/L in women not using hormonal contraception or hormonal replacement therapy).

[p] [redacted]

[q] [redacted]

[r] On day 4, pain will be assessed 30 min after the completion of ZYPREXA im administration, and pain and injection site findings will be assessed 3 h after the completion of administration. Allowed time windows for these local tolerability assessments are ±15 min. In case an adverse event associated with an ISR is reported, pain may be assessed periodically using an NPRS until resolution. No time windows are specified for these assessments.

[s] Pharmacokinetic blood samples will be collected on day 4 pre-dose (up to 30 min prior to dosing); 10, 20, 30, 45 min and 1, 2, 3, 4, 6, 8, and 12 h post-dose relative to the single-dose of ZYPREXA im. For allowable time windows of sample collection, refer to Table 6.

[redacted] BMI=body mass index; [redacted] CU=clinical unit; [redacted] ECG=electrocardiogram; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HEENT=head, eyes, ears, nose, throat; HIV=human immunodeficiency virus; im=intramuscular; ISR=injection site reaction; NPRS=numeric pain rating scale; [redacted];

Table 2: ZYPREXA IM Follow-up Period 2: Trial Procedures and Assessments (Day 5 through Day 12)

APPLICABLE TO ALL COHORTS: 1A, 1B, 2, and 3								
Procedures and assessments	**ZYPREXA IM Follow-Up Period 2 (Day 5 through Day 12)**						**Period 2 Extension (as needed)[a]**	**Unscheduled visit[b]**
Visit number	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	
Trial day	**5**	**6**	**7**	**8**	**9**	**12[c]**	**13**	
Vital sign measurements[d]	X		X			X		X
12-lead ECG[e]	X		X			X		
Physical examination[f]			X			X		
Physical measurements[g]						X		
Clinical laboratory tests[h]	X		X			X		
Pregnancy test[i]						X		
Alcohol screen[j]						X		
Drug screen[k]						X		
[redacted]						X		
[redacted]						X		
[redacted]						X		
[redacted]						X		
[redacted]						X		
[redacted][l]						X		X
Resumption of antipsychotic[m]	X	X	X	X	X	X	X	
Pharmacokinetic blood sample collection[n]	X	X	X	X	X	X	X	X
Smoking status[o]	X					X		

Table 2: ZYPREXA IM Follow-up Period 2: Trial Procedures and Assessments (Day 5 through Day 12) (Continued)

APPLICABLE TO ALL COHORTS: 1A, 1B, 2, and 3								
Procedures and assessments	**ZYPREXA IM Follow-Up Period 2 (Day 5 through Day 12)**						**Period 2 Extension (as needed)[a]**	**Unscheduled visit[b]**
Visit number	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	
Trial day	**5**	**6**	**7**	**8**	**9**	**12[c]**	**13**	
Biomarker blood sample collection						X		
Inpatient in CU	X	X						
Discharge from CU[p]			X					
Outpatient visits[q]				X	X			
Admission to CU[r]						X		
Adverse event recording	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X

[a] Period 2 may be extended up to an additional maximum of 7 days, post V10 (V10 counts as extension day 1, so extension day 7 is R1 at maximum) for all cohorts as needed, prior to allowing participants to begin period 3. Participants who enter this extension period and do not proceed directly into period 3 (outlined in Table 3 for cohort 1A and Table 4 for cohorts 1B, 2, and 3), should return to the clinic for a PK sample collection on day 13 (V11) at 216±3 h post the ZYPREXA im dosing.

[b] All procedures marked in the table are mandatory during unscheduled visits. Other procedures may be performed at the discretion of the Investigator. In addition, to reduce patient burden and to avoid unnecessary data collection, the Investigator will have discretion in determining whether the procedures that are marked as mandatory actually need to be performed during the unscheduled visit in the case that the visit is for administrative purposes (eg, reconsenting) or clinical 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).

[c] All participants should attend the day 12 visit at the clinic.

[d] Vital signs include body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure. Pulse, blood pressure, and respiratory rate will be measured after the patient has been supine or semi-supine for at least 5 min. Body temperature will be measured only in the supine or semi-supine body position. Vital signs will be measured on days 5, 7, 12, and during unscheduled visits (if applicable). On day 5, vital signs will be measured 24 h following administration of ZYPREXA im. Vital signs will be measured after ECGs but before scheduled blood draws, up to 30 min prior to the time point, when applicable.

[e] ECGs will be obtained after the patient has been in a supine or semi-supine position for at least 5 min. The ECG will be recorded before vital sign assessments and scheduled blood draws, up to 30 min prior to the time point, when applicable. On day 5, the ECG will be performed 24 h following administration of ZYPREXA im.

[f] The abbreviated physical examination will include general appearance, HEENT, lung, heart, skin, extremities, and a brief neurological examination.

[g] Includes weight measurement only.

[h] Clinical laboratory tests will be performed following an overnight fast of at least 8 h and will include chemistry, hematology, coagulation, and urinalysis. Non-fasting blood collection is permitted as needed, per Investigator assessment of adverse events. At each urinalysis collection, females will be asked if they are currently menstruating.

[i] A serum pregnancy test will be performed for all women, regardless of childbearing potential, only on day 12 (V10) and will be performed both in central and local laboratories. A negative result is required prior to administering olanzapine extended-release sc injection on day R1. Additional pregnancy tests may be performed if clinically indicated.

[j] Breathalyzer for alcohol, to be conducted at the discretion of the Investigator. Alcohol screens may be conducted at additional time points at the discretion of the Investigator.
[k] In-house urine dipstick for prohibited drugs, to be conducted at the discretion of the Investigator. Drug screens may be conducted at additional time points at the discretion of the Investigator.
[l] [redacted]
[m] Dosing (initial dose and any dose modifications) and administration of the allowed antipsychotic (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) at the discretion of the Investigator. At each visit, participants will be asked about whether or not they are taking 1 of the allowed antipsychotics and their response will be entered in the eCRF.
[n] Pharmacokinetic blood samples to continue to characterize the elimination phase of the IM injection will be collected post-dose at the following time points: 24, 48, 72, 96, 120, and 192 h, at approximately the same time relative to the single-dose of ZYPREXA im. For participants who enter the optional extension period, a PK sample will also be collected at 216±3 h post-dose on day 13 (V11); for those who proceed directly to period 3, the 216 h post-dose sample will be collected prior to sc dosing as shown in Table 3 for cohort 1A and Table 4 for cohorts 1B, 2, and 3. After 24 h of ZYPREXA im administration, where applicable, PK samples should be collected at approximately the same time of day as dosing. For allowable time windows of sample collection, refer to Table 6.
[o] Data on smoking status will be collected using the following questions if cigars, pipes, or cigarettes are used: “How many cigarettes, cigars, or pipes did you smoke over the past 7 days?” and "Has your smoking status/tobacco use remained the same compared to at the time of screening”? Use of cigars and pipes will be converted into cigarette use with a ratio of 1 cigar or pipe = 2.5 cigarettes.
[p] Participants will be followed up in the CU until day 3 after ZYPREXA im (day 7), when they be discharged from the CU after completion of day 7 assessments.
[q] Day 8 and day 9 can be inpatient or outpatient per the Investigator’s discretion.
[r] Participants will be readmitted to the CU on day 12 prior to administration of olanzapine extended-release sc.

[redacted]CU=clinical unit; [redacted] ECG=electrocardiogram; eCRF=electronic case report form; HEENT=head, eyes, ears, nose, throat; im=intramuscular; [redacted]; [redacted] sc=subcutaneous.

Table 3: Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1A: Trial Procedures and Assessments (Day R1 through Day R25)

APPLICABLE TO COHORT 1A (Fast-D): SC Olanzapine for Extended-release																
Procedures and assessments	**SC olanzapine extended-release treatment period 3 (day R1 through day R25)**															**Unscheduled visit[a]**
Visit number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	
Day from sc injection (visit window)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R10**	**R11**	**R13**	**R15[b] (±1)**	**R18 (±1)**	**R22 (±1)**	**R25 (±2)**	
PGx blood sample collection[c]	X															
Vital sign measurements[d]	X	X	X					X				X		X		X
12-lead ECG[e]	X	X						X				X				
Physical examination[f]	X		X					X				X				
Clinical laboratory tests[g]	X							X				X				
Pregnancy test[h]	X											X				
Alcohol screen[i]	X											X				
Drug screen[j]	X											X				
[redacted]												X				
[redacted]												X				
[redacted]												X				
[redacted]												X				
[redacted]												X				
[redacted][k]								X				X		X		X
Olanzapine extended-release administration	X															

Table 3: Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1A: Trial Procedures and Assessments (Day R1 through Day R25) (Continued)

APPLICABLE TO COHORT 1A (Fast-D): SC Olanzapine for Extended-release																
Procedures and assessments	**SC olanzapine extended-release treatment period 3 (day R1 through day R25)**															**Unscheduled visit[a]**
Visit number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	
Day from sc injection (visit window)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8**	**R10**	**R11**	**R13**	**R15[b] (±1)**	**R18 (±1)**	**R22 (±1)**	**R25 (±2)**	
Post-injection delirium/sedation syndrome monitoring[l]	X															
Injection site tolerability and pain assessment[m]	X							X				X		X		X
Smoking status[n]								X				X		X		
Pharmacokinetic blood sample collection[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker blood sample collection[p]								X								
Inpatient period CU[q]	X	X	X	X	X	X	X	X	X	X	X					
Discharge from CU												X				
Outpatient visits[r]													X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All procedures marked in the table are mandatory during unscheduled visits. Other procedures may be performed at the discretion of the Investigator. In addition, to reduce participant burden and to avoid unnecessary data collection, the Investigator will have discretion in determining whether the procedures that are marked as mandatory actually need to be performed during the unscheduled visit in the case that the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event and not due to a change in the participant's medical status per clinical judgment).

[b] The SRC will review safety data available up to day R15, inclusive, for cohort 1A. For participants who miss this visit, all assessments must be performed on the immediate next visit performed.
[c] In case the pharmacogenomics sample cannot be collected on R1, it should be collected at the next possible visit.
[d] Vital signs include body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure (systolic and diastolic), and their orthostatic changes. On R1, vital signs will be measured pre-dose. Pulse, blood pressure, and respiratory rate will be measured after the participant has been supine or semi-supine for at least 5 min. Orthostatic vital signs will be determined with measurements obtained after the participant has been supine or semi-supine for at least 5 min and repeated after the participant has been standing for 3 min. Vital signs will be measured after ECGs but before scheduled blood draws, up to 30 min prior to the time point, when applicable.
[e] ECGs will be obtained after the participant has been in a supine or semi-supine position for at least 5 min. The ECG will be recorded before vital sign assessments and scheduled blood draws, up to 30 min prior to the time point, when applicable. On R1, the ECG will be performed pre-dose. On R2, the ECG will be performed 24 h following administration of the sc olanzapine extended-release formulation.
[f] An abbreviated physical examination will be performed. The abbreviated physical examination will include general appearance, HEENT, lung, heart, skin, extremities, and a brief neurological examination. On R1, the abbreviated physical examination will be performed pre-dose.
[g] Clinical laboratory tests will be performed following an overnight fast of at least 8 h and will include chemistry, hematology, coagulation, and urinalysis. HbA1c will be collected at day R1 pre-dose. Non-fasting blood collection is permitted as needed, per Investigator assessment of adverse events. At each urinalysis collection, females will be asked if they are currently menstruating. Blood and urine samples will be collected prior to dosing on day R1. Laboratory results from blood samples collected on day R1 are not required pre-dose. Day R1 central clinical laboratory assessments will serve as the baseline values for the sc olanzapine extended-release formulation.
[h] A urine dipstick pregnancy test will be performed for all women of childbearing potential. In case period 2 is extended, a urine dipstick pregnancy test will be performed for all women of childbearing potential at visit R1 with a confirmation test of negative results prior to dosing. Additional pregnancy tests may be performed if clinically indicated.
[i] Breathalyzer for alcohol. In case period 2 is extended, the alcohol screen will be performed on day R1. Alcohol screens may be performed at additional time points at the discretion of the Investigator.
[j] An in-house urine dipstick screen for prohibited drugs. In case period 2 is extended, in-house urine dipstick screen for prohibited drugs will be performed on day R1. Drug screens may be performed at additional time points at the discretion of the Investigator.
[k] [redacted]
[l] Participants will remain under clinical observation for at least 3 h after injection to monitor for any potential symptoms of PDSS. In any event of suspected PDSS, unscheduled pharmacokinetic samples will be collected as soon as PDSS is suspected and at 3, 6, 12, and 24 h after the onset of the event and 24 h after resolution, or when feasible. Vital signs should be measured as soon as a suspected PDSS event is suspected and at the same time points that additional pharmacokinetic samples are collected. Additionally, a toxicological blood test will be performed as soon as PDSS is suspected, and unscheduled biomarker samples will be collected as soon as PDSS is suspected, 24 h after the onset of the event, and 24 h after resolution, or when feasible.
[m] On R1, pain will be assessed 30 min after the completion of administration of any of the 3 olanzapine for extended-release sc formulations, and pain and injection site findings will be assessed 3 h after the completion of olanzapine sc administration. Allowed time windows for these local tolerability assessments are ±15 min. In case an adverse event associated with an ISR is reported, pain may be assessed periodically using an NPRS until resolution. Thereafter the site of injection will be assessed for local tolerability weekly (R8, R15, R22).
[n] Data on smoking status will be collected using the following questions if cigars, pipes, or cigarettes are used: “How many cigarettes, cigars, or pipes did you smoke over the past 7 days?” and "Has your smoking status/tobacco use remained the same compared to at the time of screening”? Use of cigars and pipes will be converted into cigarette use with a ratio of 1 cigar or pipe = 2.5 cigarettes.
[o] Pharmacokinetic blood samples will be collected pre-dose (up to 1 h prior to dosing of sc olanzapine at approximately 216±3 h post the ZYPREXA im dosing) (applicable ONLY for participants who have entered period 3 directly from period 2), at 3 h post-dose, and on R2, R3, R4, R5, R6, R7, R8, R10, R11, R13, R15, R18, R22, and R25 at approximately the same hour of the day as dosing.
[p] Blood samples will be collected for biomarker assessment on R8 and in the event of the appearance of an adverse event related to pus-containing injection site lesions. Blood for biomarker analyses will be collected as follows: 6 mL for plasma and 2.5 mL for PAXgene RNA.
[q] Participants will be treated in the CU until R15, when they will be discharged from the CU after completion of R15 assessments.
[r] Participants will return to the CU on an outpatient basis for scheduled assessments. All visits must be scheduled within the provided windows and 2 visits cannot occur on the same day.

[redacted] BMI=body mass index; [redacted] CU=clinical unit; [redacted]; ECG=electrocardiogram; HEENT=head, eyes, ears, nose, throat; im=intramuscular; ISR=injection site

reaction; NPRS=Numeric Pain Rating Scale; [redacted] PDSS=post-injection delirium/sedation syndrome; PGx=pharmacogenomics; RNA=ribonucleic acid; [redacted]; sc=subcutaneous; SRC=safety review committee.

Table 4: Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1B, Cohort 2, and Cohort 3: Trial Procedures and Assessments (Day R1 through Day R25)

APPLICABLE TO COHORT 1B (Fast-D), COHORT 2 (to-be-marketed), AND COHORT 3 (Slow-C): SC Olanzapine for Extended-release																
Procedures and assessments	**SC olanzapine extended-release treatment period 3 (day R1 through day R25)**															**Unscheduled visit[a]**
Visit number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	
Day from sc injection (visit window)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8 (+1)**	**R10 (±1)**	**R11 (±1)**	**R13 (±1)**	**R15 (±1)**	**R18 (±1)**	**R22 (±1)**	**R25 (±2)**	
Randomization	X															
PGx blood sample collection[b]	X															
Vital sign measurements[c]	X	X	X					X				X		X		X
12-lead ECG[d]	X	X						X				X				
Physical examination[e]	X		X					X				X				
Clinical laboratory tests[f]	X							X				X				
Pregnancy[g]	X											X				
Alcohol screen[h]	X											X				
Drug screen[i]	X											X				
[redacted]												X				
[redacted]												X				
[redacted]												X				
[redacted]												X				
[redacted]												X				

Table 4: Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1B, Cohort 2, and Cohort 3: Trial Procedures and Assessments (Day R1 through Day R25) (Continued)

APPLICABLE TO COHORT 1B (Fast-D), COHORT 2 (to-be-marketed), AND COHORT 3 (Slow-C): SC Olanzapine for Extended-release																
Procedures and assessments	**SC olanzapine extended-release treatment period 3 (day R1 through day R25)**															**Unscheduled visit[a]**
Visit number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	
Day from sc injection (visit window)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8 (+1)**	**R10 (±1)**	**R11 (±1)**	**R13 (±1)**	**R15 (±1)**	**R18 (±1)**	**R22 (±1)**	**R25 (±2)**	
[redacted]			X					X				X		X		X
Olanzapine extended-release administration	X															
Post-injection delirium/sedation syndrome monitoring[k]	X															
Injection site tolerability and pain assessment[l]	X							X				X		X		X
Smoking status[m]								X				X		X		
Pharmacokinetic blood sample collection[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker blood sample collection[o]								X								
Inpatient in CU[p]	X	X														
Discharge from CU			X													
Outpatient visit[q]				X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4: Subcutaneous Olanzapine for Extended-release Treatment Period 3 for Cohort 1B, Cohort 2, and Cohort 3: Trial Procedures and Assessments (Day R1 through Day R25) (Continued)

APPLICABLE TO COHORT 1B (Fast-D), COHORT 2 (to-be-marketed), AND COHORT 3 (Slow-C): SC Olanzapine for Extended-release																
Procedures and assessments	**SC olanzapine extended-release treatment period 3 (day R1 through day R25)**															**Unscheduled visit[a]**
Visit number	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	
Day from sc injection (visit window)	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**R8 (+1)**	**R10 (±1)**	**R11 (±1)**	**R13 (±1)**	**R15 (±1)**	**R18 (±1)**	**R22 (±1)**	**R25 (±2)**	
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All procedures marked in the table are mandatory during unscheduled visits. Other procedures may be performed at the discretion of the Investigator. In addition, to reduce participant burden and to avoid unnecessary data collection, the Investigator will have discretion in determining whether the procedures that are marked as mandatory actually need to be performed during the unscheduled visit in the case that the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event and not due to a change in the participant's medical status per clinical judgment).

[b] In case the PGx sample cannot be collected on R1, it should be collected at the next possible visit.

[c] Vital signs include body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure (systolic and diastolic), and their orthostatic changes. On R1 vital signs will be measured pre-dose. Pulse, blood pressure, and respiratory rate will be measured after the participant has been supine or semi-supine for at least 5 min. Orthostatic vital signs will be determined with measurements obtained after the participant has been supine or semi-supine for at least 5 min and repeated after the participant has been standing for 3 min. Vital signs will be measured after ECGs but before scheduled blood draws, up to 30 min prior to the time point, when applicable.

[d] ECGs will be obtained after the participant has been in a supine or semi-supine position for at least 5 min. The ECGs will be recorded before vital sign assessments and scheduled blood draws, up to 30 min prior to the time point, when applicable. On R1, ECG will be performed pre-dose. On R2, the ECG will be performed 24 h following administration of the sc olanzapine extended-release formulation.

[e] An abbreviated physical examination be performed. The abbreviated physical examination will include general appearance, HEENT, lung, heart, skin, extremities, and a brief neurological examination. On R1, the abbreviated physical examination will be performed pre-dose.

[f] Clinical laboratory tests will be performed following an overnight fast of at least 8 h and will include chemistry, hematology, coagulation, and urinalysis. HbA1c will be collected at day R1 pre-dose. Non-fasting blood collection is permitted as needed, per Investigator assessment of adverse events. At each urinalysis collection, females will be asked if they are currently menstruating. Blood and urine samples will be collected prior to dosing on day R1. Laboratory results from blood samples collected on day R1 are not required pre-dose. Day R1 central clinical laboratory assessments will serve as baseline values for the sc olanzapine extended-release formulation.

[g] A urine dipstick pregnancy test will be performed for all women of childbearing potential. In case period 2 is extended, a urine dipstick pregnancy test will be performed for all women of childbearing potential at visit 12 (R1) with a confirmation test of negative results prior to dosing. Additional pregnancy tests may be performed if clinically indicated.

[h] Breathalyzer for alcohol. In case period 2 is extended, the alcohol screen will be performed on day R1. Alcohol screens may be performed at additional time points at the discretion of the Investigator.

[i] An in-house urine dipstick screen for prohibited drugs. In case period 2 is extended, in-house urine dipstick screen for prohibited drugs will be performed on day R1. Drug screens may be performed at additional time points at the discretion of the Investigator.

[j] [redacted]

[k] Participants will remain under clinical observation for at least 3 h after injection to monitor for any potential symptoms of PDSS. In any event of suspected PDSS, unscheduled pharmacokinetic samples will be collected as soon as PDSS is suspected and at 3, 6, 12, and 24 h after the onset of the event and 24 h after resolution, or when feasible. Vital signs should be measured as soon as a suspected PDSS event is suspected and at the same time points that additional pharmacokinetic samples are collected. Additionally, a toxicological blood test will be performed as soon as PDSS is suspected, and unscheduled biomarker samples will be collected as soon as PDSS is suspected, 24 h after the onset of the event, and 24 h after resolution, or when feasible.

[l] On R1, pain will be assessed 30 min after the completion of administration of any of the 3 olanzapine for extended-release sc formulations, and pain and injection site findings will be assessed 3 h after the completion of olanzapine sc administration. Allowed time windows for these local tolerability assessments are ±15 min. In case an adverse event associated with an ISR is reported, pain may be assessed periodically using an NPRS until resolution. Thereafter the site of injection will be assessed for local tolerability weekly (R8, R15, R22).

[m] Data on smoking status will be collected using the following questions if cigars, pipes, or cigarettes are used: “How many cigarettes, cigars, or pipes did you smoke over the past 7 days?” and "Has your smoking status/tobacco use remained the same compared to at the time of screening”? Use of cigars and pipes will be converted into cigarette use with a ratio of 1 cigar or pipe = 2.5 cigarettes.

[n] Pharmacokinetic blood samples will be collected pre-dose (up to 1 h prior to dosing of sc olanzapine at approximately 216 ±3 h post the ZYPREXA im dosing) (applicable ONLY for participants who have entered period 3 directly from period 2), at 3 h post-dose, and on R2, R3, R4, R5, R6, R7, R8, R10, R11, R13, R15, R18, R22, and R25 at approximately the same hour of the day as dosing.

[o] Blood samples will be collected for biomarker assessment on R8 and in the event of the appearance of an adverse event related to pus-containing injection site lesions. Blood for biomarker analyses will be collected as follows: 6 mL for plasma and 2.5 mL for PAXgene RNA.

[p] Participants will be treated in the CU until R3, when they will be discharged from the CU after completion of R3 assessments.

[q] Participants will return to the CU on an outpatient basis for scheduled assessments. All visits must be scheduled within the provided windows and 2 visits cannot occur on the same day.

[redacted] CU=clinical unit; [redacted] ECG=electrocardiogram; HEENT=head, eyes, ears, nose, throat; NPRS=Numeric Pain Rating Scale; [redacted] PDSS=post-injection delirium/sedation syndrome; PGx=pharmacogenomics; RNA=ribonucleic acid; [redacted]; sc=subcutaneous.

Table 5: Subcutaneous Olanzapine Extended-release Follow-up Period: Trial Procedures and Assessments (Day R29 through Day R84)

Applicable to all cohorts: 1A, 1B, 2, and 3										
Procedures and assessments	**SC olanzapine extended-release follow-up period (day R29 through day R84)**									**Unscheduled Visit[a]**
Visit	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	
Trial day (visit window)	**R29[b] (±1)**	**R36 (±2)**	**R43 (±2)**	**R50 (±2)**	**R57 (±2)**	**R64 (±2)**	**R71 (±2)**	**R78 (±2)**	**EOT (R84±2) /ET**	
Vital sign measurements[c]	X								X	X
12-lead ECG[d]	X								X	
Physical examination[e]	X								X	
Physical measurements[f]									X	
Clinical laboratory tests[g]	X								X	
Pregnancy test[h]									X	
Alcohol screen[i]									X	
Drug screen[j]									X	
[redacted]	X								X	
[redacted]	X								X	
[redacted]	X								X	
[redacted]	X								X	
[redacted]	X								X	
[redacted]	X	X	X	X	X	X	X	X	X	X
Resumption of antipsychotic[l]	X	X	X	X	X	X	X	X	X	
Smoking status[m]	X			X					X	

Table 5: Subcutaneous Olanzapine Extended-release Follow-up Period: Trial Procedures and Assessments (Day R29 through Day R84) (Continued)

Applicable to all cohorts: 1A, 1B, 2, and 3										
Procedures and assessments	**SC olanzapine extended-release follow-up period (day R29 through day R84)**									**Unscheduled Visit[a]**
Visit	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	
Trial day (visit window)	**R29[b] (±1)**	**R36 (±2)**	**R43 (±2)**	**R50 (±2)**	**R57 (±2)**	**R64 (±2)**	**R71 (±2)**	**R78 (±2)**	**EOT (R84±2) /ET**	
Pharmacokinetic blood sample collection[n]	X	X	X	X	X	X	X	X	X	X
Biomarker blood sample collection[o]									X	
Outpatient visits[p]	X	X	X	X	X	X	X	X	X	
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X

[a] All procedures marked in the table are mandatory during unscheduled visits. Other procedures may be performed at the discretion of the Investigator. In addition, to reduce participant burden and to avoid unnecessary data collection, the Investigator will have discretion in determining whether the procedures that are marked as mandatory actually need to be performed during the unscheduled visit in the case that the visit is for administrative purposes (eg, reconsenting) or clinical reasons (eg, repeat laboratory sample collection for reasons unrelated to an adverse event and not due to a change in the participant's medical status per clinical judgment).

[b] All assessments must be performed prior to returning a participant to antipsychotic treatment.

[c] Vital signs include body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure (systolic and diastolic), and their orthostatic changes. Pulse, blood pressure, and respiratory rate will be measured after the participant has been supine or semi-supine for at least 5 min. Orthostatic vital signs will be determined with measurements obtained after the participant has been supine or semi-supine for at least 5 min and repeated after the participant has been standing for 3 min. Vital signs will be measured after ECGs but before scheduled blood draws, up to 30 min prior to the time point, when applicable. At the discretion of the Investigator, vital signs may be checked at every visit during this follow-up period.

[d] ECGs will be obtained after the participant has been in a supine or semi-supine position for at least 5 min. The ECGs will be recorded before vital sign assessments and scheduled blood draws, up to 30 min prior to the time point, when applicable. At the discretion of the Investigator, an ECG may be performed at every visit during this follow-up period.

[e] A complete physical examination will be performed at EOT/ET and an abbreviated physical examination at other time points. The abbreviated physical examination will include general appearance, HEENT, lung, heart, skin, extremities, and a brief neurological examination. At the discretion of the Investigator, a physical exam may be performed at every visit during this follow-up period.

[f] Includes weight measurement only, except for at EOT/ET when height measurement and BMI calculation will also be performed.

[g] Clinical laboratory tests will be performed following an overnight fast of at least 8 h and will include chemistry, hematology, coagulation, and urinalysis. Non-fasting blood collection is permitted as needed, per Investigator assessment of adverse events. At each urinalysis collection, females will be asked if they are currently menstruating. Clinical laboratory tests can be performed at every visit during this follow-up period.

[h] A serum pregnancy test will be performed for all women, regardless of childbearing potential, on R84 (EOT). Additional pregnancy tests may be performed if clinically indicated.

[i] Breathalyzer for alcohol. Alcohol screens may be performed at additional time points at the discretion of the Investigator.

[j] An in-house urine dipstick screen for prohibited drugs. Drug screens may be performed at additional time points at the discretion of the Investigator.

[k] [redacted]

[l] Dosing (initial dose and any dose modifications) and administration of the allowed antipsychotic (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) at the discretion of the Investigator. At each visit, participants will be asked about whether or not they are taking 1 of the allowed antipsychotics and their response will be entered in the eCRF.

[m] Data on smoking status will be collected using the following questions if cigars, pipes, or cigarettes are used: “How many cigarettes, cigars, or pipes did you smoke over the past 7 days?” and "Has your smoking status/tobacco use remained the same compared to at the time of screening”? Use of cigars and pipes will be converted into cigarette use with a ratio of 1 cigar or pipe = 2.5 cigarettes.

[n] Pharmacokinetic blood samples will be collected on R29, R36, R43, R50, R57, R64, R71, R78, and on R84 (EOT) or early termination, at approximately the same time of the day as dosing as specified in Table 7.

[o] Blood samples will be collected for biomarker assessment on R84 (EOT) and in the event of the appearance of an adverse event related to pus-containing injection site lesions. Blood for biomarker analyses will be collected as follows: 6 mL for plasma and 2.5 mL for PAXgene RNA.

[p] Participants will return to the CU on an outpatient basis for scheduled assessments.

[redacted] BMI=body mass index; [redacted] CU=clinical unit; [redacted]; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of trial (visit); ET=early termination (visit); HEENT=head, eyes, ears, nose, throat; [redacted]; RNA=ribonucleic acid; [redacted]; sc=subcutaneous.

Table 6: Schedule of Assessments for Pharmacokinetic Sampling Before and After ZYPREXA IM Administration

Time points		Time window	Pharmacokinetic sample
ZYPREXA im Treatment Period 1			
Day 4 pre-dose	-30 min	±10 min	X
Day 4	10, 20, 30, 45 min	±3 min	X
Day 4	1, 2, 3, 4 h	±15 min	X
Days 4-5[a]	6, 8, 12, 24 h	±30 min	X
Days 6-12[b]	48, 72, 96, 120, 192 h	±3 h	X
In case Period 2 is extended optional Day 13[c]	216	±3 h	X

[a] It is recommended that the PK samples collected at 24 h post-injection should be collected at approximately the same hour of day that the ZYPREXA im injection was performed on day 4.
[b] It is recommended that the PK samples collected at 48, 72, 96, 120, 192 h post-injection should be collected at approximately the same hour of the day that the ZYPREXA im injection was performed on day 4.
[c] In the event of extension of period 2, participants will return to the clinic on day 13 (V11) for an unscheduled visit to collect the 216 h PK sample. For those who proceed directly to period 3, the 216 h post-dose sample will be collected prior to sc dosing as shown in Table 7.
im=intramuscular.

Table 7: Schedule of Assessments for Pharmacokinetic Sampling Before and After Olanzapine Extended-release SC Formulation Administration

Time points		Time window	Pharmacokinetic sample
Olanzapine Extended-release sc Treatment Period 3			
Day R1 pre-dose	-1 h	±10 min	X
Day R1	3 h	±15 min	X
Days R2-R13	Days R2, R3, R4, R5, R6, R7, R8, R10, R11, R13	±4 h	X
Days R14-R23	Days R15, R18, R22	±1 day at approximately the same time of day as dosing	X
Days R24-R84 (EOT/ET)	Days R25, R29, R36, R43, R50, R57, R64, R71, R78, R84	±2 days at approximately the same time of day as dosing	X

EOT=end of trial; ET=early termination; sc= subcutaneous.

Table 8: Trial Procedures and Assessments in Case of a Suspected Post-injection Delirium/Sedation Syndrome Event

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

[redacted]

2. INTRODUCTION

2.1. Purpose of Trial

2.1.1. Background on Schizophrenia

Schizophrenia is a severely debilitating psychotic disorder characterized by positive symptoms (eg, delusions, hallucinations, and grossly disorganized or catatonic behavior) and negative symptoms (eg, affective flattening, alogia, and avolition) (New York State Office of Mental Health 2018, Stefan et al 2002). Cognitive deficits are common; they include impairments of executive functioning and attention, and difficulties with short- and long-term memory.

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

Noncompliance and high discontinuation rates are particularly problematic in patients with schizophrenia. Premature discontinuation of antipsychotic drug therapy is a common phenomenon; in the Clinical Antipsychotic Trials of Intervention Effectiveness trial, 74% of patients discontinued their drug within 18 months due to either poor tolerability or lack of efficacy. 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. As a result, many of these patients do not experience the full benefit of antipsychotic drug therapy and suffer frequent relapses or exacerbations that require rehospitalization, often in the context of psychiatric emergency (Rainer 2008).

Thus, the availability of a long-acting injectable antipsychotic agent may increase compliance in patients with schizophrenia (Barnes and Curson 1994, Hughes 2008, Keith and Kane 2003, Walburn et al 2001).

Note that the terms ‘long-acting’, ‘extended-release’, and ‘prolonged-release’ are used interchangeably within this document.

The purpose of this trial is to characterize the pharmacokinetics (PK) of 3 subcutaneous (sc) olanzapine extended-release formulations with different release rates (described in Section 2.1.3) in participants with schizophrenia or schizoaffective disorder, with the purpose of establishing in vitro/in vivo correlation (IVIVC).

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; it has not yet been approved for use as a subcutaneous (sc) injection.

Oral formulations of olanzapine 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 tablets (ZYPREXA® 2.5, 5, 7.5, 10, 15, and 20 mg); orally disintegrating tablets (ZYPREXA® ZYDIS® 5, 10, 15, and 20 mg); and immediate-release ZYPREXA® IntraMuscular (Olanzapine) Injection (10 mg/mL) (ZYPREXA USPI 2021).

2.1.2.2. Prolonged-release Olanzapine Formulations

A prolonged-release olanzapine pamoate powder and diluent for suspension is currently marketed in the US as ZYPREXA® RELPREVV™ (150, 210, 300, and 405 mg) (ZYPREXA RELPREVV USPI 2021). Both products are administered by deep im gluteal injection either every 2 or 4 weeks, depending on the target oral olanzapine dose. ZYPREXA RELPREVV is currently only available through a restricted distribution program in the US.

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 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 Extended-release Injectable Suspensions (TV-44749) for Subcutaneous Use

To-be-marketed formulation

Teva is developing a new formulation of olanzapine as a prolonged-release injectable suspension for sc use that is intended for the treatment of schizophrenia. The product is coded the “to-be-marketed” formulation of Olanzapine for Extended-release Injectable Suspension (TV-44749) throughout this document. During period 3 of the trial, participants in cohort 2 will receive a single-dose of this formulation (the trial schematic is shown in Figure 1).

The TV-44749 to-be-marketed formulation is a co-packaged drug/device combination product that requires reconstitution (Section 6.1.1). Before administration, the drug product is reconstituted in the vial by adding the vehicle from the prefilled syringe (PFS) and mixing. A yellow, viscous suspension is obtained.

Upon sc injection of this olanzapine suspension, dimethyl sulfoxide (DMSO) diffuses away and the block copolymers, which are not soluble in aqueous medium, precipitate and form a depot that entraps olanzapine. From this depot, olanzapine is slowly released to achieve and maintain therapeutic levels of the drug, resulting from drug diffusion and/or gradual depot degradation, over the period of 1 month.

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 (ZYPADHERA SmPC 2022), which is identical to ZYPREXA RELPREVV, was also used to support the nonclinical development of TV-44749.

The clinical program of the to-be-marketed TV-44749 formulation was initiated with Trial TV44749-SAD-10154. The objective of this trial was to evaluate the safety, tolerability, and PK of single doses and multiple doses of TV-44749 for sc use in healthy participants and participants with schizophrenia or schizoaffective disorder.

Overall, 127 participants were enrolled in this trial and TV-44749 was administered to 101 participants. The trial applied an adaptive dose escalation design in which healthy volunteers (n=30) received oral olanzapine (2.5 and 5 mg/day) for 7 days, followed by a 7-day washout period, and then received single injections of TV-44749 (70 or 105 mg). Participants with schizophrenia or schizoaffective disorder (n=71) received oral olanzapine (10, 15, or 20 mg/day) for 7 days followed by a washout period of 2 days for all cohorts, except for the cohort that was to receive 425 mg TV-44749 for which the washout period was 7 days. This washout period was followed by a treatment period during which participants received either a single injection of TV-44749 (318, 425, or 531 mg) or 3 once-monthly injections of 283 or 566 mg. The trial included safety assessments and PK sampling for all.

Main PK observations:

- [redacted]
- There was no burst or unexpected rise in olanzapine plasma concentrations following TV-44749 sc administration.
- TV-44749 systemic exposure (C_{max} and AUC) increased in an approximate dose-proportional manner over the clinically relevant dose range of 283 mg to 566 mg. Steady-state was attained after the second dosing interval (day 57), indicating modest accumulation.
- At steady-state conditions over the 28-day dosing interval, the systemic exposure of TV-44749 at doses of 318, 425, and 531 mg was shown to be comparable to corresponding daily oral doses of 10 mg, 15 mg, and 20 mg, respectively.

The results of this trial supported the dose strengths of TV-44749 administered in the ongoing Phase 3 trial (Trial TV44749-CNS-30096; SOLARIS) of 318, 425, and 531 mg, which are comparable to corresponding daily oral doses of 10 mg, 15 mg, and 20 mg, respectively. SOLARIS is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled trial with an open-label, long-term safety phase evaluating the efficacy, safety, and tolerability of TV-44749 in adult participants with schizophrenia.

Additionally, a Phase 1, 21-week, open-label, multiple-dose trial to assess the comparative bioavailability of olanzapine prolonged-release suspension for subcutaneous administration (TV-44749) to oral olanzapine (European Reference) in participants with schizophrenia is currently planned.

Background information on completed nonclinical studies and clinical trials is provided in the current version of the Investigator's Brochure (IB).

Two additional formulations with different release rates relative to the to-be marketed formulation

This trial will also characterize the PK of two additional sc olanzapine for extended-release formulations, Fast-D and Slow-C, with different release rates relative to the to-be-marketed TV-44749 formulation, in participants with schizophrenia or schizoaffective disorder. During period 3 of the trial, participants in cohorts 1A and 1B will receive a single-dose of the Fast-D formulation and participants in cohort 3 will receive a single-dose of the Slow-C formulation (the trial schematic is shown in Figure 1). Based on beagle PK data and in vitro release (IVR) data, it is expected that both of these formulations will provide extended-release of olanzapine during the 84-day period following single-dose sc administration. The formulations are expected to have the same bioavailability (ie, similar AUC at day R84) and differ only in C_{max} as a consequence of different release rate relative to the to-be-marketed formulation, with no burst present. The Fast-D formulation is expected to exhibit a faster release rate (ie, higher C_{max}), while the Slow-C formulation is expected to exhibit a slower release rate (ie, lower C_{max}) relative to the to-be-marketed formulation.

2.2. Summary of Benefits and Risks

2.2.1. Known and Potential Risks of TV-44749

Olanzapine is a well-characterized and commonly prescribed atypical antipsychotic drug available as oral and im formulations. Oral formulations (Section 2.1.2.1) are approved for the treatment of adults and adolescents with schizophrenia. The prolonged-release im depot preparation containing olanzapine pamoate (Section 2.1.2.2) is approved for the treatment of adults with schizophrenia, while an immediate-release im formulation of olanzapine (Section 2.1.2.1) is approved for the treatment of adults with acute agitation associated with schizophrenia.

Data from Trial TV44749-SAD-10154, including PK, safety, and tolerability associated with TV-44749 are available (Section 2.1.3). The safety profile emerging from these data is consistent with that seen with other olanzapine formulations, with the exception of the identification of injection site reactions (ISRs). None of these were identified as serious events, and they do not significantly impact the benefit-risk profile of TV-44749. Overall, the Sponsor believes that the

safety data present no concerns that preclude continuation of TV-44749 clinical development. The anticipated risks are similar to those associated with the use of any other formulations of olanzapine.

The current ZYPREXA tablet label contains warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations.

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 (McDonnell et al 2010). Because the prolonged duration of release of TV-44749 arises as a consequence of slow degradation of the precipitated polymer depot (the water insoluble polymer matrix entraps and slowly releases olanzapine, rather than low tissue solubility of olanzapine pamoate salt) and because it is injected sc, the hypothesized causes of PDSS resulting from ZYPREXA RELPREVV administration are not relevant for TV-44749. No suspected PDSS events occurred in Trial TV44749-SAD-10154.

Additional information regarding risks to participants may be found in the IB.

2.2.2. Known and Potential Risks of ZYPREXA IntraMuscular (Olanzapine) Injection

Information regarding benefits and risks to participants from use of ZYPREXA IntraMuscular (olanzapine) Injection, Powder, for Solution for im use in this trial during period 1 are available in the prescribing information (ZYPREXA USPI 2021).

Specific risks associated with ZYPREXA im are similar to oral formulations. ZYPREXA im has not been shown to cause PDSS that has been seen with ZYPREXA RELPREVV.

2.2.3. Potential Benefits of TV-44749

Participating in a clinical trial can provide a number of benefits to patients, regardless of the effectiveness of the treatment. Clinical trial participants are closely monitored for their psychiatric and general health in a highly monitored clinical setting by medical professionals, including doctors, nurses, and research staff. This level of attention and care can help ensure that participants receive the best possible medical treatment and support. In addition, clinical trial participants have an opportunity to take an active role in their own healthcare. By working closely with medical professionals, participants can gain a deeper understanding of their condition and treatment options, and may feel more empowered to manage their health. Finally, clinical trials are a critical part of the process of developing new treatments and understanding how existing treatments work. By participating in a clinical trial, patients contribute to the body of medical knowledge, and help improve healthcare for future generations.

2.2.4. Overall Benefit-Risk Conclusion

The trial will be conducted in participants with schizophrenia or schizoaffective disorder. The trial design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect participant safety. The results of this trial may facilitate the development of TV-44749 with potential benefits for patients with schizophrenia and schizoaffective disorder.

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

3. TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Primary and Secondary Trial Objectives and Endpoints

The primary and secondary objectives and measures are presented in the table below:

Objectives	Measures
Primary	
To characterize the PK of 3 extended-release sc olanzapine formulations with different release rates following single administration in participants with schizophrenia or schizoaffective disorder.	The following PK parameters will be calculated for olanzapine, following single administration of 3 sc olanzapine extended-release formulations to support the primary objective of the trial: • Maximum observed plasma drug concentration (C_{max}) over the 84-day period following single-dose administration of 1 of the sc formulations to EOT (day R1 to day R84) • Area under the plasma drug concentration-time curve (AUC) following single-dose administration of 1 of the sc formulations to last measurable concentration (AUC_{0-t}) (day R1 to day R84) • AUC extrapolated to infinity ($AUC_{0-\infty}$) calculated from last measurable olanzapine plasma concentration following single-dose administration of 1 of the sc formulations from time 0 to EOT (day R1 to day R84)
Secondary	
To evaluate the safety and tolerability of 3 extended-release sc olanzapine formulations with different release rates in participants with schizophrenia or schizoaffective disorder.	The following safety and tolerability measures/parameters will be evaluated: • Number (%) of participants with at least 1 TEAE over the 28-day period following administration of 1 of the sc olanzapine formulations (day R1 to day R29) • Number (%) of participants with at least 1 serious adverse event (SAE) over the 28-day period following administration of 1 of the sc olanzapine formulations (day R1 to day R29)
To characterize the PK of immediate-release ZYPREXA im in participants with schizophrenia or schizoaffective disorder.	The following PK parameters will be calculated for ZYPREXA im to support the secondary objective of the trial: • C_{max} over the 24-hour period following single-dose administration of ZYPREXA im (day 4) • AUC following single-dose administration of ZYPREXA im to last measurable concentration (AUC_{0-t}) (pre-dose ZYPREXA im to 216 hours post im administration) • Apparent plasma terminal elimination rate constant (λ_z) over the 216-hour period (9 days) following single-dose administration of ZYPREXA im (pre-dose ZYPREXA im to 216 hours post im administration)

3.2. Primary Estimand

For the primary objectives, the estimand is described by the following attributes:

a. Population – adult participants, 18 to 64 years of age, with a clinically stable diagnosis of schizophrenia or schizoaffective disorder, not currently on antipsychotic

treatment, with the exception of oral treatment with aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone, and meeting all trial eligibility criteria. For intercurrent events which could adversely affect the calculation of the PK parameters, the participant will be excluded.

b. Endpoint – see parameters in Section 3.1.

c. Treatment – the 3 formulations of Olanzapine for Extended-release Injectable Suspension, with different release rates, over the 84-day olanzapine sc treatment period (day R1 to day R84) following single-dose administration.

d. Population level summary – descriptive statistics (n, mean, standard deviation, geometric mean [if appropriate], geometric coefficient of variation (%CV) [if appropriate], median, minimum, and maximum).

Rationale for estimand: To characterize the PK of 3 olanzapine extended-release sc formulations with different release rates, following single administration in participants with schizophrenia or schizoaffective disorder, who are clinically stable and are not on antipsychotic treatment, with the exception of oral treatment with aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone, and who meet all trial eligibility criteria.

3.3. Secondary Estimand(s)

There are no secondary estimands defined for this trial.

3.4. Exploratory Objectives and Endpoints

Exploratory Objectives	Measures/Parameters
To further evaluate the safety and tolerability of single doses of 3 extended-release sc olanzapine formulations with different release rates in participants with schizophrenia or schizoaffective disorder.	The following safety and tolerability parameters will be assessed: • Number (%) of participants with at least 1 injection site adverse event from baseline to the end of period 3 (day R1 to day R29) • Change in clinical laboratory parameters (chemistry, hematology) from baseline to the end of period 3 (day R1 to day R29) • Change in vital signs parameters (body temperature, respiratory rate, pulse rate, and blood pressure) from baseline to the end of period 3 (day R1 to day R29) • Number (%) of participants with QT interval corrected for heart rate using Fridericia's formula (QTcF) change of ≥30 and ≥ 60 msec from baseline to the end of period 3 (day R1 to day R29) • Number (%) of participants who reported use of concomitant medications from baseline to the end of period 3 (day R1 to day R29) • Number (%) of participants who discontinued from the trial for any reason from baseline to the end of period 3 (day R1 to day R29) • Number (%) of participants who discontinued from the trial due to an adverse event from baseline to the end of period 3 (day R1 to day R29) [redacted]

Exploratory Objectives	Measures/Parameters
To evaluate the safety and tolerability following a single-dose of immediate-release ZYPREXA im in participants with schizophrenia or schizoaffective disorder.	The safety and tolerability measures/parameters are: • Occurrence of adverse events during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • Change in clinical laboratory (chemistry, hematology) tests, vital sign measurements (body temperature, respiratory rate, pulse rate, and blood pressure) during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • ECG findings during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • Use of concomitant medication during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • Discontinuation for any reason during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • Discontinuation due to an adverse event during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) • Local tolerability and pain during the 24-hour period following administration of ZYPREXA im (day 4 to day 5) [redacted]
To evaluate the overall safety of the trial in participants with schizophrenia or schizoaffective disorder.	The safety measures/parameters are: • Occurrence of adverse events during trial participation (day 1 to day R84) • Change in clinical laboratory (chemistry, hematology) tests, vital sign measurements (body temperature, respiratory rate, pulse rate, and blood pressure) during trial participation (day 1 to day R84) • ECG findings during trial participation (day 1 to day R84) • Use of concomitant medication during trial participation (day 1 to day R84) • Discontinuation for any reason during trial participation (day 1 to day R84) • Discontinuation due to an adverse event during trial participation (day 1 to day R84) [redacted]

[redacted]

4. TRIAL DESIGN

4.1. Description of Trial Design

This is a multi-center, open-label, randomized, parallel-group trial to characterize the PK profile of 3 olanzapine extended-release formulations for sc use with different release rates, in participants with schizophrenia or schizoaffective disorder. The trial will consist of a screening period (up to 40 days), a 3-day washout (WO) period (day 1 to day 3), a 1-day treatment period with immediate-release ZYPREXA im (period 1: day 4), an 8-day follow-up period (period 2: day 5 to day 12), a 28-day treatment period with 1 of the 3 extended-release sc olanzapine formulations (period 3: day R1 to day R29), and an up to approximately 8-week follow-up period (day R29 to day R84).

The total duration of individual participation in the trial is planned to be approximately 19 weeks. Participants are expected to participate in this trial for its entire duration. See Section 4.4 for the definition of the EOT.

The trial population will include clinically stable participants 18-64 years old, not currently on antipsychotic treatment, with the exception of oral treatment with an oral antipsychotic including aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone.

The screening period of up to 40 days in duration will be performed in an outpatient setting. Participants who meet screening eligibility will undergo an inpatient WO of 3 days from their current antipsychotic treatment. Thereafter, participants will remain in the clinical unit (CU) and will continue to period 1 (day 4) that will include a single injection of 5 mg of ZYPREXA im, immediate-release solution, administered to the gluteal muscle. Prior to the im injection, participants' eligibility will be reconfirmed (Table 1). Subsequently, participants will continue to the follow-up period 2 (day 5 to day 12). The first 3 days of period 2 will be performed in an inpatient setting. Participants will be discharged on day 7. The remaining visits of period 2 (day 8 and day 9) may be performed in an inpatient or an outpatient setting per Investigator's discretion and participants' preference. Participants will be readmitted to the CU on day 12, which is a mandatory visit for all patients. Period 2 may be extended up to 7 days maximum, post Visit 10 (Visit 10 counts as day 1, so day 7 is R1, at maximum) for all cohorts per Principal Investigator and Sponsor discretion. In the event of extension of period 2, participants will return to the clinic on day 13 (Visit 11) for an unscheduled visit to collect the 216 h PK sample; if this extension is not required, participants will skip Visit 11 and proceed to Visit 12. For those who proceed directly to period 3, the 216 h post-dose sample will be collected prior to sc dosing as shown in Table 3 for cohort 1A and Table 4 for cohorts 1B, 2, and 3. During period 2, participants will resume treatment with the allowed antipsychotic treatments and discontinue 24 h prior to sc injection on day R1. Participants will be readmitted to the CU on day 12 (Table 2).

Thereafter, on day R1, participants will enter treatment period 3 (day R1 to day R29). During this period participants will discontinue treatment with any of the allowed antipsychotics they were receiving during period 2. On day R1 of this period, participants will be assigned to 1 of the 3 single-dose cohorts and will be administered 1 of 3 olanzapine extended-release sc formulations (TV-44749) in the abdomen. Period 3 includes both an inpatient and an outpatient period.

During period 3, participants will be treated with 1 of the following olanzapine extended-release (TV-44749) formulations:

1. Cohort 1: Olanzapine for Extended-release Injectable Suspension D (TV-44749) (Fast-D)
2. Cohort 2: Olanzapine for Extended-release Injectable Suspension (TV-44749) (to-be-marketed)
3. Cohort 3: Olanzapine for Extended-release Injectable Suspension C (TV-44749) (Slow-C)

The aim is to achieve approximately 20 completers in each cohort. Period 3 will be initiated with a sentinel cohort 1A (Fast-D) composed of approximately 2 to 4 participants. A safety review committee (SRC) composed of the Sponsor's clinical trial physician, clinical leader, PV physician, and other relevant experts, will be summoned to review all safety data (including demography, vital signs, clinical laboratory tests, ECGs, adverse events (AEs), concomitant medications local tolerability and pain, leakage assessment) available upon completion of the first 15 days of the sentinel cohort (day R1 to day R15, inclusive) (cohort 1A). The sentinel cohort will serve for initial evaluation of the systemic safety and tolerability of the Fast-D formulation. Participants assigned to cohort 1A will be in an inpatient setting for 15 days following administration of the Fast-D formulation, to allow safety review prior to dosing of the rest of the Fast-D cohort (cohort 1B).

For cohort 1B (n~16 participants), period 3 may be initiated only following SRC decision. Randomization to cohort 2 (n~20 participants) and cohort 3 (n~20 participants) will be initiated in parallel to cohort 1B. If no safety concern is raised from review of data from cohort 1A, the inpatient period of cohorts 1B, 2, and 3 will be identical and will include an inpatient period of 3 days (day R1 to day R3) followed by a 25-day outpatient period (day R4 to day R29).

Period 3 will include PK blood sampling and safety assessments (Table 3 and Table 4).

In the case that a safety concern arises following a review of the safety results from cohort 1A, or one of the stopping rules in participants as detailed below (Section 7.4) is met, the following may be considered:

- Adjust the olanzapine extended-release sc dose
- Pause olanzapine extended-release sc dosing until additional data become available
- Maintain the inpatient period of cohort 1B as in cohort 1A
- Modification of the inpatient period of cohorts 1A and 1B to up to 28 days for close safety monitoring
- Stop the trial

At any time, the SRC may request additional evaluation including PK data before allowing continued dosing.

Following completion of period 3, all participants enter a 56-day follow-up period during which they will resume treatment with 1 of the allowed antipsychotics at the Investigator's discretion (day R29 to day R84). The follow-up period will be performed in an outpatient setting, and will include PK blood sampling, safety assessments, and an EOT visit on day R84 (Table 5). During

the follow-up period participants will resume treatment with 1 of the allowed antipsychotics (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) at the Investigator's discretion.

The trial schematic diagram is presented in Figure 1.

4.1.1. Planned Number of Participants and Countries

Approximately 95 adult participants are planned to be enrolled in order to achieve approximately 60 completers. Details on the definition of completers and the sample size are given in Section 9.

The trial is planned to be conducted in the US in approximately 5 investigational centers.

4.1.2. Data Monitoring Committee/Safety Review Committee

An SRC comprising the Sponsor's clinical trial physician, clinical leader, PV physician, and other relevant experts will be summoned to review all safety data (including demography, vital signs, clinical laboratory tests and ECGs, AEs, concomitant medications use, local tolerability and pain, leakage assessment) available upon from the beginning of the study to completion of the first 15 days, inclusive of the sentinel cohort (cohort 1A). Following SRC decision that no safety concerns are raised based on the safety review of cohort 1A safety data up to day R15, inclusive, period 3 for cohort 1B may be initiated. Randomization to cohorts 2 and 3 will be initiated in parallel to cohort 1B.

Further details are provided in Section 10.2.

4.2. Rationale for Trial Design

The trial design follows the recommendations provided in the FDA Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (FDA, 1997). The objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (plasma drug concentration or amount of drug absorbed), per the FDA guidance (FDA, 1997) on the development, evaluation and application of IVIVC for extended-release oral products.

With the purpose of establishing IVIVC, the PK of 3 olanzapine extended-release sc formulations with different release rates will be characterized following a single-dose administration in participants with schizophrenia or schizoaffective disorder. The trial design will include extensive characterization of the PK profiles over 84 days after olanzapine sc administration (day R1 to day R84) to characterize fully the absorption kinetics of all 3 formulations for the purpose of IVIVC. All 3 formulations are expected to provide extended-release of olanzapine during the 84-day treatment period following single-dose sc administration and are expected to differ only in C_{max} as a consequence of a different release rate, with no burst present. The trial design also includes a single-dose administration of ZYPREXA im, before sc administration of one of the 3 sc olanzapine extended-release formulations. The obtained PK data of this im immediate-release formulation will be used to characterize olanzapine disposition for the purpose of IVIVC analysis. These analyses will be conducted and reported separately from the main trial results.

4.3. Access to Trial Intervention After End of Trial

Upon the completion of Follow-up Period on day R84, investigators should advise participants to return to the care of their primary physician for continuation of treatment with available medications.

4.4. Start of Trial and End of Trial

The trial start date is the date on which the clinical trial will be open for recruitment of participants. The first act of recruitment is the first investigational center open and will be the trial start date. EOT is defined as the last follow-up visit of the last participant.

5. TRIAL POPULATION

5.1. Selection of Trial Population

The trial population will include participants 18 to 64 years of age, with a diagnosis of schizophrenia or schizoaffective disorder. Participants must be clinically stable, not currently on antipsychotic treatment, with the exception of oral treatment with aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone, and meet all trial eligibility criteria. During period 3, participants will be treated with 1 of 3 single-dose sc olanzapine extended-release formulations. For details regarding the study design, refer to Section 4.1.

5.2. Rationale for Trial Population

The selected trial population is representative of the demographics and disease state of individuals who are likely to be treated with TV-44749 in a clinical setting.

5.3. Inclusion Criteria

Participants may be included in this trial only if they meet all of the following criteria:

a. Capable of giving signed informed consent as follows:
   - Able to understand the nature of the trial and any possible hazards in participating; willing to provide written informed consent to participate; and after reading the trial information and consent form and having the opportunity to discuss the trial with the Investigator or assigned delegate, sign the informed consent form (ICF).
   - Able to follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, sc depot injection, and discontinuation of prohibited concomitant medications; able to participate in and comply with the requirements of the entire trial; able to read and understand the written word in order to complete participant-reported outcomes measures; and can be reliably rated on assessment scales.

b. Males or females of any ethnic origin aged 18 to 64 years, inclusive, at the time of screening.

c. Body weight >50 kg and body mass index (BMI) within the range 18.5 to 38.0 kg/m^2, inclusive, at the time of screening.

d. Agree to maintain current smoking or nonsmoking status at the time informed consent is obtained and throughout the trial until completion of the end of treatment or early termination (ET) visit (ie, nonsmoking participants must agree not to start smoking and participants who smoke will be excluded if they plan to discontinue smoking during the trial.

e. Agree to the inpatient periods required during the trial period.

f. Have a current confirmed diagnosis of schizophrenia or schizoaffective disorder according to an evaluation by the Investigator, using the Diagnostic and Statistical

Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013a).

g. Are clinically stable, on oral aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone (ie, dose has not changed in the last 4 weeks prior to screening) and not currently on other antipsychotic including olanzapine treatment at the time of screening.

h. Have a [redacted] score ≤70 and a [redacted] score ≤3 at the time of screening.

i. Have had no hospitalization for worsening of schizophrenic symptoms and no significant exacerbation of schizophrenic symptoms, as judged by the Investigator, within the 3 months prior to screening.

j. Have no ongoing or expected significant life events (eg, pending loss of housing, marital status change, long travel abroad, surgery) that could affect trial outcomes throughout the period of trial participation.

k. [Revision 1] Women may be included only if they have a negative serum beta human chorionic gonadotropin (HCG) test result at screening; they are surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or postmenopausal (postmenopausal status will be confirmed by a follicle-stimulating hormone screen according to the clinical laboratory standard value) for at least 1 year; or they are practicing a highly effective method of birth control and not planning pregnancy for at least 30 days before the trial, for the duration of the trial, and for 70 days after the last dose administration, if they are sexually active and of childbearing potential (Section 13.1).

l. Men must be sterile; or if they are potentially of reproductive competence and have sexual relationship with female partners of childbearing potential, they must use, together with their female partners, highly effective birth control methods for the duration of the trial and for 70 days after the last dose administration.

m. Willing and able to comply with trial restrictions and to remain at the investigational center for the required durations during the trial period and willing to return to the investigational center for the follow-up procedures and assessments as specified.

5.4. Exclusion Criteria

Participants will be excluded from participating in this trial if they meet any of the following criteria**:**

a. Presence or have a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, or musculoskeletal system, or presence or history of clinically significant immunological, endocrine, or metabolic diseases, neurological or psychiatric disorder(s) (other than schizophrenia), or a history of any illness that, in the opinion of the Principal Investigator, might pose additional risk to the participant by participation in the trial or confound the results of the trial.

b. Infectious disease:

   – Acute infection and/or antibiotic treatment must be resolved 28 days prior to the first dose of IMP.

   – Any chronic infection.

   – [Revision 1] Known history of, or a positive test result for hepatitis B surface antigen and/or core antibody, known history of, or positive serology for hepatitis C and positive ribonucleic acid (RNA) test*, human immunodeficiency virus Types 1 or 2 antibody (according to enzyme-linked immunosorbent assay test), or active/latent tuberculosis (as determined by a positive result of the QuantiFERON test). If the QuantiFERON test result is indeterminate, then the test may be repeated once. If the second QuantiFERON test result is indeterminate also, the participant will be excluded from the study.

     *Note: If serology is positive but the 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.

c. History or known risk of narrow-angle glaucoma.

d. Uncontrolled diabetes (hemoglobin A1c 6.5% or above and/or fasting plasma glucose 126 mg/dL or above).

e. Major trauma or surgery in the 2 months before screening or at any time between screening and the first dose of IMP, or surgery scheduled during the trial or follow-up period, or open biopsy within 4 months prior to screening.

f. History of malignancy or treatment of malignancy in the last 5 years, excluding resected basal cell or squamous cell carcinoma of the skin.

g. The participant is a pregnant or lactating woman or plans to become pregnant during the trial or within 70 days after the last dose administration.

h. 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, or ZYPREXA im in any formulation.

i. Presence of excessive pigment, bruises, scars, or tattoos around the potential injection area.

j. Presence of any local skin infection, rash, or anything else that limits injection administration and assessment of injection site.

k. Donated or received any blood or blood products (eg, white blood cells, platelets) within 60 days prior to screening, or has donated blood or blood products on 2 or more occasions within 6 months prior to IMP administration, or has donated plasma within 7 days prior to screening, or has planned donations during the 56 days or 5 half-lives following the last dose administration, whichever is longer. The minimum reference volume of whole blood lost or donated is 500 mL.

l. Vulnerable participants (eg, prisoners or institutionalized individuals), participants who pose a significant risk of suicide attempt in the Investigator's judgment based on

medical history, answered "yes" to Suicidal Ideation items 4 or 5 on the [redacted] for "current" or "within 3 months prior to screening," or had a suicide attempt or hospitalization due to suicide risk within 12 months prior to screening.

m. 12-lead electrocardiogram (ECG) demonstrating intraventricular conduction delays (QRS interval ≥110 msec or PR interval ≥200 msec) and have a mean of triplicate QTcF values >450 msec for males and >470 msec for females at screening or other clinically significant ECG findings that would interfere with trial participation as judged by the Investigator.

n. Personal or family history of arrhythmia, sudden unexplained death at a young age (before 40 years) in a first-degree relative, long QT syndrome, personal history of syncope, or history of uncontrolled high blood pressure. Participants with history of high blood pressure who no longer require treatment or participants who are treated with antihypertensive medications and whose blood pressure is currently well-controlled, may be enrolled.

o. Supine or semi-supine blood pressure outside the range of 90 to 140 mm Hg for systolic or 50 to 90 mm Hg for diastolic (following at least a 5-minute rest). Note: If either value is out of range, blood pressure measurements may be repeated in the supine or semi-supine position at intervals of 5 to 10 minutes up to 2 times. If the systolic or diastolic measurement continues to exceed the stated limits, the participant will be excluded.

p. Orthostatic hypotension defined as a decrease exceeding 20 mmHg in systolic blood pressure or 10 mm Hg in diastolic blood pressure, or both, occurring within 3 minutes of changing from supine to standing position, or orthostatic intolerance (only 2 rechecks of orthostatic blood pressure are permitted for eligibility purposes).

q. Postural tachycardia defined as a sustained heart rate increment of 30 beats per minute within 10 minutes of standing (only 2 rechecks allowed).

r. [Revision 1] Body temperature (measurement performed either orally or on both ears, recording the highest value) outside the interval of 35.4°C to 37.5°C at the screening visit.

s. [Revision 1] Clinical laboratory test abnormalities as listed below:

   - Clinical laboratory values with Common Terminology Criteria for AEs (CTCAE) Grade 2 or above
   - Blood urea nitrogen >31 mg/dL
   - Lactate dehydrogenase ≥3 × upper limit of normal (ULN)
   - Urinalysis with any clinically significant finding
   - Total bilirubin >2.5 mg/dL
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN
   - Creatinine >2 × ULN

- Creatine phosphokinase (CPK) >3 × ULN. Participants with CPK levels >1.5 × ULN and ≤3 × ULN may be enrolled, if the results are not clinically significant according to the Investigator's review and judgment, in consultation with the Sponsor's medical representative.
- International normalized ratio ≥2.0
- Absolute neutrophil count $<1.5 \times 10^9$/L

Any laboratory abnormality may be retested once per the Investigator's clinical discretion. If the retested value is within normal limits, the participant does not need to be excluded from the trial. The retest limitation applies to the same day laboratory assessments but not to monitoring for trends (eg, CPK). Abnormal laboratory values that meet CTCAE Grades 1 and 2 may be accepted per consultation with Sponsor and where safety is not compromised. The severity of each clinical laboratory AE will be graded according to CTCAE, version 5.0.

t. Any procedure or disorder that may interfere with drug absorption, distribution, metabolism, or excretion (appendectomies are acceptable procedures at the discretion of the Investigator).

u. Received a prolonged-release formulation of olanzapine within 5 half-lives prior to screening.

v. Use of an investigational drug or marketed drug (new chemical entity) within 30 days or 5 half-lives (whichever is longer) or in case of biologics (eg, tumor necrosis factor-alpha inhibitors such as adalimumab, etanercept, or infliximab) within 3 months or 5 half-lives (whichever is longer) prior to the administration of ZYPREXA im.

w. Using or consuming the following concurrent medications, over-the-counter (OTC) products, prescription drugs (any route of administration: eg, oral, topical), or foods:

- strong and moderate inducers or inhibitors of CYP1A2 (Section 13.4) within 30 days or 5 half-lives (whichever is longer) prior to the administration of ZYPREXA im.
- dopamine reuptake inhibitors or prescription psychostimulants within 30 days prior to screening.
- opioids or opioid-containing analgesics within 30 days prior to screening.
- medications, in addition to those listed above, that may be expected to significantly interfere with the metabolism or excretion of olanzapine, that may be associated with a significant drug interaction with olanzapine, or that may pose a significant risk to participants if they were enrolled in the trial.

x. 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 participant does not meet the criteria for substance use disorder, a positive result on the serum drug test is not exclusionary. Participant's eligibility in cases of a positive

result, without medical explanation, will be determined by the Investigator based on the participant's background, history of substance use, and the Investigator's discussions with family members, caregivers, or healthcare professionals, as applicable (American Psychiatric Association 2013b).

y. Treatment-resistant schizophrenia according to medical and psychiatric history as judged by the Investigator or have taken clozapine for treatment-resistant schizophrenia.

z. A significant sedation or delirium post-antipsychotic treatment according to medical and psychiatric history and as judged by the Investigator or suffered from delirium due to a medical condition.

aa. A significant risk of violent behavior based on the participant's medical and psychiatric history as judged by the Investigator.

bb. [Revision 1] A current clinically significant DSM-5 diagnosis other than schizophrenia or schizoaffective disorder.

cc. History of or a current active medical condition that may either compromise the participant's safety or interfere with the safety or outcome evaluation of the trial drug, including, but not limited to, traumatic brain injury or seizure (excluding a single febrile or withdrawal seizure), neuroleptic malignant syndrome, clinically significant tardive dyskinesia, or are suffering with a clinically significant neurological disorder.

dd. The participant cannot participate or successfully complete the trial, in the opinion of the Investigator, for any of the following reasons:

- The participant is under the legal age of consent, mentally or legally incapacitated, or unable to give consent for any reason (unless a legal guardian is able to provide consent according to local requirements).
- The participant is in custody due to an administrative or a legal decision, or under tutelage, or being admitted to a sanitarium or social institution.
- The participant is unable to be contacted in case of emergency or in case a follow-up assessment is required within 30 days after trial completion.
- The participant is an employee of the Sponsor or the site or a relative of an employee at the site conducting the trial.
- Any other reason, at the discretion of the Investigator.

5.5. Ongoing Confirmation of Participant Eligibility

Participants' continued eligibility will be reconfirmed by review of abbreviated inclusion and exclusion criteria prior to administration of ZYPREXA im. The abbreviated list will include the following inclusion criteria (g, h) and exclusion criterion (a). Clinical scales and laboratory tests taken on day 1 will be used to confirm eligibility on day 3. In case of a delay, laboratory results can be reviewed to perform abbreviated eligibility assessment on day 4, as long as this is done prior to administration of ZYPREXA im. Laboratory results from blood samples collected on day 4 are not required prior to initiating ZYPREXA im. Day 4 central clinical laboratory

assessments will serve as baseline values and are based on samples collected prior to dosing of ZYPREXA im. Serology to support eligibility criteria will only be done at screening.

5.6. Lifestyle Considerations

Participants will be required to comply with the following restrictions.

5.6.1. Meals and Dietary Restrictions

Participants are not required to fast before ZYPREXA im or any of the sc olanzapine extended-release injectable formulations.

Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis) will be performed following an overnight fast of at least eight hours at the time points detailed in Table 1 to Table 5. Non-fasting blood collection is permitted as needed, per the Investigator's assessment of AEs.

5.6.2. Caffeine, Alcohol, Tobacco, and Other Habits

It is recommended that participants do not consume alcohol and cannabis-derived products (such as marijuana) during the treatment period (excluding follow-up). Any positive result will be managed according to the Investigator's review and judgment, in consultation with the Sponsor's medical representative.

Excessive consumption of coffee, tea, and/or caffeine-containing beverages or food (ie, 600 mg or more of caffeine per day or five or more cups of coffee per day) will be prohibited for a minimum of 2 weeks before the first dose of trial drug and during the treatment period (excluding follow-up).

Participants must agree to maintain current smoking or nonsmoking status at the time informed consent is obtained and during the treatment period (excluding follow-up).

The use of tobacco products will be recorded at the visits indicated in Table 1 to Table 5. Use of cigars and pipes will be converted into cigarette use with a ratio of 1 cigar or pipe = 2.5 cigarettes. Use of vapes, e-cigarettes, nicotine gums, heat-non-burn tobacco products, snuffs, and nicotine patches will also be recorded but not be converted into cigarette use as these have minimal effect on CYP1A2 induction.

5.6.3. Physical Activity

Participants must remain lying down or semi-recumbent for safety reasons during administration of any of the 3 Olanzapine for Extended-release Injectable Suspensions (Fast-D, to-be-marketed, or Slow-C), and will remain under clinical observation for at least 3 hours after injection to monitor any possible symptom of PDSS.

Following the administration of ZYPREXA im or olanzapine extended-release sc injectable formulations, the participants should be advised to stand up from the lying position after waiting for 30 to 60 seconds in a sitting position at the bed margin, in order to reduce the risk of occurrence of orthostatic hypotension often associated with olanzapine treatment.

Participants will be instructed to not touch, rub, massage, or compress the injection site during the first 2 hours after administration of ZYPREXA im or olanzapine extended-release sc

injectable formulations. Participants may cover the injection site with loose-fitting clothing immediately after trial drug administration. Participants will not be allowed to lie on the injection site for the first 6 hours after the injection. Adhesive bandages may not be used during the period of leakage assessment following administration of olanzapine extended-release sc formulations.

During all treatment periods (excluding follow-up), participants are not to engage in strenuous exercise, and the use of hot tubs, steam baths, and saunas are prohibited.

5.6.4. Other Activity

There are no additional restrictions in this trial.

5.7. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently enrolled in the trial. The minimum information to be collected on screen failures includes, but is not limited to, demography, screening failure details, eligibility criteria, and AEs from the time of informed consent.

At screening, abnormal laboratory values may be retested once per the Investigator's clinical discretion. Vital signs may be repeated twice if initial values are out of range, to determine whether the participant is eligible for inclusion.

A participant who is screened but not enrolled because enrollment did not occur within the specified time may be considered for screening again. Likewise, a participant who is screened and does not meet trial entry criteria may be considered for rescreening in consultation with the clinical leader and the clinical trial physician.

The Investigator, in consultation with the Sponsor, will decide whether a participant can be rescreened. In the event a participant is rescreened, the following procedures will be followed:

- a new screening number will be used for the participant
- a participant may be rescreened only once
- the participant must be reconsented at the second screening visit

In the event of a participant being rescreened, all screening procedures will be repeated. Procedures performed during the screening period are listed in Table 1.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1. Description of Trial Intervention(s)

6.1.1. Investigational Medicinal Products Used in the Trial

The IMPs in this trial are 3 sc formulations of Olanzapine for Extended-release Injectable Suspensions (TV-44749) with different release rates that are administered during period 3, and ZYPREXA IntraMuscular (olanzapine) Injection, immediate-release solution, administered to the gluteal muscle during period 1; these are described in Table 9.

Table 9: Investigational Medicinal Products used in the Trial

IMP name	**Fast-D**	**To-be-marketed formulation**	**Slow-C**	**ZYPREXA IM**
Trade name and INN, if applicable, or company-assigned number	Olanzapine	Olanzapine	Olanzapine	ZYPREXA (olanzapine)
Formulation	[redacted]	[redacted]	[redacted]	[redacted]
Unit dose strength(s)/Dosage level(s)	425 mg [redacted]	425 mg [redacted]	425 mg [redacted]	10 mg (5 mg to be administered)
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Intramuscular
Dosing instructions	Single-dose injection during treatment period 3	Single-dose injection during treatment period 3	Single-dose injection during treatment period 3	Single-dose injection during treatment period 1
Intervention type	Drug	Drug	Drug	Drug
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.	IMP will be provided in a blister tray in a carton box.	IMP will be provided in a vial in a carton box.
Storage conditions	2°C to 8°C	2°C to 8°C	2°C to 8°C	20°C to 25°C, protect from light, do not freeze

IM=intramuscular; IMP=Investigational Medicinal Product; INN=international nonproprietary name.

6.1.1.1. Olanzapine for Extended-Release Injectable Suspension Formulations

[redacted]

6.1.1.2. ZYPREXA IntraMuscular (Olanzapine) Injection

[redacted]

6.2. Rationale for Trial Intervention(s)

6.2.1. Justification for Investigational Medicinal Product and Dose

Olanzapine extended-release formulations will be administered sc. The 3 formulations differ in the content of excipients which is expected to result in different release rates of olanzapine from depot. The dosage of olanzapine to be administered in these formulations was selected on the basis of the existing safety and PK profile of olanzapine in trial TV44749-SAD-10154.

The TV-44749 dose in this trial (425 mg) is comparable to 15 mg/day of oral olanzapine administered over a 28-day period and represents the intermediate dose within the range of clinically approved doses of oral olanzapine (10-20 mg/day). All 3 formulations are expected to have comparable overall exposure (AUC) over the dosing period.

Based on PK studies conducted in beagles and in vitro release (IVR) data, it is expected that all formulations will provide extended-release of olanzapine during the 28-day period following single-dose sc administration. The Fast-D and Slow-C formulations are expected to have the same bioavailability (ie, similar AUC at day R84) and differ only in C_{max} as a consequence of different release rate relative to the to-be-marketed formulation, with no burst or uncontrolled release expected. The C_{max} for the Fast-D formulation is expected to be higher than the C_{max} of the corresponding dose of the to-be-marketed formulation that has been assessed in previous clinical trials. However, the expected plasma concentration range of Fast-D is expected to be within that of the higher clinical dose of the to-be-marketed formulation previously established as safe and tolerable – 566 mg Q1M dose that was administered in trial TV44749-SAD-10154 for 3 consecutive months. Similarly, the C_{max} for olanzapine for the Slow-C formulation is expected to be lower than that of the to-be-marketed formulation, while still within the clinically relevant range of plasma concentrations. Slow-C plasma concentration is expected to be within that of the low clinical dose of the to-be-marketed formulation previously established as safe and tolerable – 283 mg Q1M dose that was administered in trial TV44749-SAD-10154 for 3 consecutive months.

Per the FDA guidance (FDA, 1997) on the development, evaluation, and application of IVIVC for extended-release oral products, the IVIVC should be demonstrated consistently with 2 or more formulations with different release rates to result in corresponding differences in absorption profiles. Although an IVIVC can be defined with a minimum of 2 formulations with different release rates, 3 or more formulations with different release rates are recommended. Thus, inclusion of 1 dose strength at the 425 mg at 2 different release rates (1 faster and 1 slower) relative to the to-be-marketed TV-44749 (intermediate-release) is considered appropriate in the current trial.

Therefore, the 3 olanzapine extended-release formulations administered to the participants of this trial are expected to result in therapeutic plasma olanzapine concentrations throughout the dosing interval. These concentrations are expected to be achieved within 1-2 days from IMP administration, as previously demonstrated in trial TV44749-SAD-10154.

It is noted that the to-be-marketed formulation of TV-44749 exhibited dose linearity in the therapeutic dose range tested in participants with schizophrenia of 283 to 566 mg in trial TV44749-SAD-10154.

6.3. Dosing and Administration

The dose of olanzapine extended-release sc formulations to be administered in treatment period 3 is 425 mg. The volume per syringe are provided in Table 10. Detailed instructions relating to the preparation of the syringes and dose administration will be fully described in the Pharmacy Manual and provided separately.

Table 10: Dose Administration Details for Olanzapine in Treatment Period 3

Olanzapine dose level (subcutaneous injection in the abdomen)	Dosing volume (mL)
Olanzapine for Extended-release Injectable Suspension D (TV-44749) (Fast-D): 425 mg	[redacted]
Olanzapine for Extended-release Injectable Suspension (TV-44749) (to-be-marketed): 425 mg	[redacted]
Olanzapine for Extended-release Injectable Suspension C (TV-44749) (Slow-C): 425 mg	[redacted]

The sc olanzapine extended-release formulations will be administered using a sterile stainless-steel needle closed with a sterile protective cap. For all participants, olanzapine extended-release will be injected sc in the abdomen. Dosing at the abdomen should be done below or at the level of the umbilicus to the left or right of the midline.

The administration will be performed by a trained medical professional according to local regulations. The same person at each site, preferably, will administer the trial drug to all participants at their respective trial site. Participants should be instructed to not touch, rub, massage, or compress the injection site(s) for the first 2 hours following administration. Adhesive bandages may not be used during the period of leakage assessment. If leaked IMP is seen at the injection site 10 minutes post-injection, it should be gently wiped, while avoiding pressure or squeezing the injection site (see Section 8.14). A leakage score of 4 should be reported to the Medical Monitor (MM) within 24 hours. The leakage score will also be recorded in the eCRF.

A leakage score of 4 is a criterion for exclusion from PK analysis set and the participant will be replaced (refer to Section 7.1).

The dose of ZYPREXA im to be administered in period 1 is 5 mg. The contents of the vial should be reconstituted using 2.1 mL of sterile water for injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. A volume of 1 mL of the reconstituted solution will be administered to the gluteal muscle.

More detailed information will be provided in the Pharmacy Manual for this trial.

Refer to Section 5.6.3 for restrictions on physical activity.

6.4. Treatment of Overdose

For this trial, any dose of olanzapine extended-release sc formulations greater than 425 mg or any dose of ZYPREXA im greater than 5 mg will be considered an overdose. There is no specific antidote to olanzapine.

In the event of an overdose, the Investigator/treating physician should take the following actions:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Obtain a plasma sample for PK analysis immediately and obtain further sample(s) as requested by the MM and the Sponsor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.
- Follow the instructions specified in Table 8 and in Section 8.3.8 for suspected PDSS monitoring.

In the event of acute overdose, appropriate supportive measures should be initiated and the Sponsor/MM should be notified. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents; do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade. Respiratory support, including ventilation, may be required. Close medical supervision and monitoring should continue until the participant recovers.

The possibility of multiple drug involvement should be considered. In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias.

6.5. Preparation, Handling, Labeling, Storage, and Accountability

6.5.1. Preparation of Investigational Medicinal Product

Detailed instructions relating to the preparation of the syringes and dose administration will be fully described in the Pharmacy Manual and provided separately from the protocol.

6.5.2. Handling, Storage, and Security

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

All IMPs (ZYPREXA im and sc olanzapine extended-release formulations) must be stored according to the specifications listed in the Pharmacy Manual in a securely-locked, temperature-controlled, and monitored storage area.

Diversion is considered to have occurred when the legal supply chain of prescription medicinal products is broken, and medicinal products are transferred from a licit to an illicit channel of distribution or use.

Further guidance and information are provided in the Pharmacy Manual.

6.5.3. Labeling

Supplies of IMPs (ZYPREXA im and sc olanzapine extended-release formulations) will be labeled according to the current ICH guidelines on GCP, Good Manufacturing Practice, Regulation (EU) No. 536/2014 Annex VI (for EU Clinical Trial Application submissions) and will include any locally required statements. If necessary, labels will be translated into the local language.

6.5.4. Accountability

Each IMP (ZYPREXA im and sc olanzapine extended-release formulations) shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

The Investigator is responsible for ensuring that deliveries of IMP and other trial materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the local regulations and used in accordance with this protocol.

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

IMP can be destroyed at the investigational center in accordance with its SOPs, with Sponsor approval. In the event that the investigational center is unable to destroy the empty and/or unused units of IMP, the IMP will be disposed of, retained, or returned to the Sponsor or designee per Sponsor instructions.

Further guidance and information are provided in the Pharmacy Manual.

6.6. Participant Assignment, Randomization, and Blinding

6.6.1. Participant Assignment

Potential participants will be screened against the inclusion and exclusion criteria, and those individuals who have a successful screen will be enrolled into the trial. Individuals who do not meet criteria for trial eligibility must not be enrolled via protocol waivers or exemptions.

6.6.2. Randomization

Period 3 will be initiated with the sentinel cohort 1A (Fast-D) composed of approximately 2-4 participants. Upon completion of the first 15 days (day R1 to day R15, inclusive) following sc administration of olanzapine to cohort 1A participants, the SRC will review all available safety and tolerability data from the beginning of the study, as described in Section 4.1. If no safety concern is raised by the SRC, period 3 can be initiated for cohort 1B participants (n~16).

Randomization to cohort 2 (n~20) and cohort 3 (n~20) will be initiated in parallel to cohort 1B. In order to achieve approximately 20 completers in cohorts 1, 2, and 3, participants for cohorts 1B, 2, and 3 will be randomized at a ratio of 4:5:5.

The randomization list will be generated by a qualified service provider under the oversight of the responsible function at Teva. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

6.6.2.1. Maintenance of Randomization

Participant randomization codes will be maintained by the service provider contracted to generate the codes.

6.6.3. Blinding and Unblinding

This is an open-label trial.

6.7. Trial Intervention Compliance

All IMPs will be administered by the Investigator or other clinical personnel to ensure compliance with IMP administration.

6.8. Prior and Concomitant Therapy

Any prior or concomitant therapy, medication, or procedure a participant has had within 30 days before ZYPREXA im and up to the EOT, including follow-up, will be recorded on the case report form (CRF). Generic or trade name, indication, and dosage will be recorded. The Sponsor will encode all therapy and medication according to the World Health Organization Drug Dictionary (WHO Drug).

At each clinic visit after the screening visit, the Investigator or designee will ask participants whether they have taken any medications (other than IMPs), including prescription and OTC medications, vitamins, herbal or nutritional supplements and whether there has been any change in dosing regimen for previously reported medications, since the previous visit. Indication, dosage, and start and end dates should be entered on the CRF.

6.8.1. Prohibited Concomitant Therapy

Participants will be excluded from participating in this trial if they are using or consuming the following concurrent medications, OTC products, prescription drugs (any route of administration: eg, oral, topical), or foods during the treatment periods (excluding follow-up):

- olanzapine products other than the IMPs of this trial.
- any antipsychotic medications other than the trial drug (excluding allowed antipsychotics during period 2 and follow-up period after period 3, and rescue medications that may be required to ensure the safety of participants during the trial, as described in Section 6.8.2).
- any of the following concurrent medications, OTC products, prescription drugs, or foods:

- strong or moderate inducers or inhibitors of CYP1A2 (Section 13.4) within 30 days or five half-lives (whichever is longer) prior to the administration of ZYPREXA im, whichever is longer
- dopamine reuptake inhibitors or prescription psychostimulants within 30 days prior to screening
- opioids or opioid-containing analgesics within 30 days prior to screening
- medications, in addition to those listed above, that may be expected to significantly interfere with the metabolism or excretion of olanzapine, that may be associated with a significant drug interaction with olanzapine, or that may pose a significant risk to participants in the trial

During the treatment periods, participants may not receive treatment with any other formulations or doses of olanzapine. Antipsychotics other than aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone are not allowed during the screening period.

Any medications that interfere with the absorption, excretion, or metabolism of olanzapine, either directly or by liver enzyme induction or inhibition, are prohibited. A partial list of prohibited drugs can be found in Section 13.4.

In addition, during the follow-up periods, any restrictions on concomitant medications use that are included in the US labels of any of the antipsychotics allowed to be received per protocol (ie, aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) should be applied.

6.8.2. Permitted Concomitant Therapy

Allowed rescue medications will include zolpidem, zopiclone, zaleplon, and diphenhydramine for insomnia; benztropine, trihexyphenidyl, and diphenhydramine for parkinsonian symptoms; and benzodiazepines for akathisia. Lorazepam (at the approved dose per the local label) is permitted on an as -needed basis for indications other than akathisia (anxiety). The dose and duration of treatment with rescue medications will be at the discretion of the Investigator’s clinical judgment, based on acceptable practice standards in accordance with the local prescribing information.

If additional rescue medications are needed, the following oral antipsychotics may be added at the Investigator's discretion: aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone. These should be used in accordance with the local prescribing information per Investigator's judgment/discretion. Dosing (initial dose and any dose modifications) and administration of the allowed antipsychotic (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) is at the discretion of the Investigator. During visits to the CU, the participant will be asked whether or not they are receiving an antipsychotic from the list of allowed medications (yes/no question format), and the information will be recorded in the eCRF. Details regarding the antipsychotic, including name, dose, and date, will be recorded in a manner similar to that of all other permitted concomitant medications.

Medications prescribed for the treatment of chronic medical conditions or for the treatment of acute medical conditions (such as antibiotics) may be permitted per Investigator judgment. The Sponsor may be consulted to avoid any effect on the olanzapine PK assessments. Medications

required for the treatment of any AEs, and contraceptives as per Section 13.1.2 are allowed (as long as they do not interfere with the absorption, excretion, or metabolism of olanzapine).

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1. Discontinuation of Trial Intervention

A participant will be discontinued from trial IMP if any of the following criteria are fulfilled:

- The participant withdraws consent to continue in the trial for any reason.
- A serious or intolerable AE develops that necessitates discontinuation from treatment at the discretion of the Investigator.
- The Investigator believes continued participation is not in the best interest of the participant.
- The Investigator believes that the participant has not adhered to the trial procedures or restrictions.
- An important protocol deviation occurs that, in the opinion of the Investigator, warrants discontinuation from treatment.
- A participant requires concomitant medication that may interfere with the PK of the trial drug.
- A participant demonstrates a significant clinical deterioration that cannot be managed with rescue medication, as judged by the Investigator, based on any relevant history or observation made by the investigative site, including rating scales.
- A participant meets 1 or more of the following hepatic enzyme criteria:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of the normal range (ULN)
  - ALT or AST >5 × ULN for more than 2 weeks
  - ALT or AST >3 × ULN and total bilirubin level >2 × ULN
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

  Participants who meet any of these hepatic enzyme criteria at any time during the trial will remain in the trial, and monitoring will be continued at the discretion of the Investigator until the criterion leading to treatment discontinuation has resolved, stabilized, or returned to baseline. If this occurs during either of the treatment periods (periods 1or 3), no further treatment will be administered to the participant.
- A participant experiences a confirmed PDSS event.
- A leakage score of 4 is reported after sc injection of 1 of the 3 olanzapine for extended-release formulations. A leakage score of 4 should be reported to the MM within 24 hours (refer to Section 8.14).
- A participant becomes pregnant during the trial.

Note: Treatment discontinuation under any of the above criteria will be discussed and mutually agreed upon by the Investigator and the Sponsor.

Participants discontinued following im immediate-release olanzapine injection due to AE will be monitored for safety until the event leading to discontinuation has resolved, and for PK until at least 9 days after the im immediate-release injection was administered, unless consent is withdrawn.

Participants discontinued following olanzapine extended-release formulation injection due to AE will be monitored for safety until the event leading to discontinuation has resolved, and for PK until at least 56 days, after sc injection administration, unless consent is withdrawn.

Participants who meet 1 or more of the treatment discontinuation criteria should be invited to perform the ET visit as soon as possible. Participants who discontinue during treatment period 3 should be encouraged to also complete the EOT visit on day R84 (see Section 7.2 for details).

Participants who destabilize should be referred directly to a psychiatric clinic or to a hospital emergency room with psychiatric capabilities if they are not deemed stable to return home.

7.2. Participant Withdrawal from the Trial

In accordance with the Declaration of Helsinki (and in accordance with the applicable country's acceptance), each participant is free to withdraw from the trial at any time. The Investigator also has the right to withdraw a participant from the trial for any reason. Reasons for participant withdrawal include but are not limited to the following:

1. Participant withdraws consent or requests discontinuation from the trial for any reason.
2. Participant develops an AE that would interfere with his/her continued participation.
3. Participant is noncompliant with the trial procedures and assessments or administration of IMP in the opinion of the Investigator.
4. Confirmed pregnancy in a female participant.
5. The Sponsor requests withdrawal of the participant.
6. Participant experiences an AE or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the participant.

Participants should be treated with standard of care after withdrawal from the trial as appropriate.

If a participant withdraws consent, every attempt will be made to determine the reason. For participants withdrawn from the trial, all efforts will be made to complete and report all observations up to the time of withdrawal. EOT procedures should be completed at the time of the participant's withdrawal (assuming consent is not withdrawn) and an explanation given as to why the participant is withdrawing or being withdrawn from the trial. Participants who discontinue during treatment period 3 should be encouraged to also complete the EOT visit on day R84.

If the reason for withdrawal is an AE and/or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the Investigator (eg, until the event has

resolved, stabilized, or returned to baseline; until the participant is referred to the care of a health care professional; or until a determination of a cause unrelated to any of the IMPs or trial 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. If the Investigator determines that the AE is related to the IMP, monitoring should continue until the AE has resolved or stabilized.

The Investigator must inform the clinical trial physician/clinical leader as soon as possible of all participants who are being considered for withdrawal due to AEs. Additional reports must be provided when requested.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the investigational center. The following actions must be taken if a participant fails to return to the investigational center for a required trial visit:

- The investigational center must attempt to contact the participant and/or the participant's caregiver and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant and/or the participant's caregiver in accordance with the clinical site standard procedures. These contact attempts should be documented in the participant's medical record.

Should the participant and the participant's caregiver continue to be unreachable, the participant will be considered to have withdrawn from the trial with a primary reason of "lost to follow-up."

7.4. Trial Stopping Rules

The Sponsor may suspend or terminate the trial 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
- an SAE of interest considered by the Principal Investigator and/or Sponsor as related to the IMP

If 3 or more participants meet stopping rules criteria during the trial, as described below, the Investigator, clinical lead, clinical trial physician, and pharmacovigilance physician will meet to decide on the need for trial discontinuation:

- drug-induced liver injury
- any drug-related SAE
- any CTCAE Grade 3 laboratory test result, or a CTCAE Grade 2 laboratory test result lasting over 48 hours, graded according to the National Cancer Institute (NCI)

CTCAE, version 5.0. An exception to that rule is isolated Grade 3 hypophosphatemia.

At any time during the trial, and after discussion between the Sponsor and Investigator, the trial may be stopped, if the following occur:

- previously unknown data that raise concern about the safety of the trial participants become available, and
- following administration of 1 of the olanzapine extended-release formulations, 3 or more participants (cumulative across the trial, from all cohorts) meet the definition of PDSS.

Any possible symptoms of a PDSS event will be monitored based on establishing evidence for all 5 criteria in the definition for a clinical diagnosis of a PDSS as described in Section 8.3.8 (adapted from Detke et al 2010).

8. TRIAL ASSESSMENTS AND PROCEDURES

8.1. Screening/Baseline Assessments and Procedures

A signed and dated ICF will be obtained before screening procedures commence (Section 10.3). Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. Participants will acknowledge and agree to the possible use of this information for the trial by giving informed consent. Participants will be provided with the option to provide a sample for pharmacogenomics analyses during period 3. A separate written informed consent will be obtained from each participant before pharmacogenomics samples will be collected.

After informed consent is obtained, participants who are screened will be assigned an 8-digit permanent identification number such that all participants from each investigational center are given consecutive identification numbers in successive order of inclusion. The first two digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated Investigator center number, and the last 3 digits will be assigned at the Investigator center (eg, if the number assigned to the country is 01, the third participant screened at center 5 would be given the number of 01005003).

The screening period will take place within 40 days prior to the antipsychotic's 3-day WO period. Screening procedures and assessments may be performed at any time during the screening period. Confirmation of eligibility for the trial will be performed on day 3 and determined based on an abbreviated list of eligibility criteria using laboratory and clinical scale values collected on day 1. If, due to technical reasons, laboratory results are not available by day 3, eligibility may be confirmed on day 4, prior to dosing (Table 1).

Participants who meet the inclusion criteria and do not meet the exclusion criteria at the screening visit may be enrolled in the trial.

8.2. Efficacy Assessments and Procedures

Efficacy assessments are not evaluated in this trial.

8.3. Safety Assessments and Procedures

The following safety and tolerability measures will be implemented throughout the trial at the time points listed in Table 1 to Table 5:

- inquiries about AEs (Section 8.4)
- physical examinations and physical measurement findings (Section 8.3.1)
- vital signs measurements (Section 8.3.2)
- ECG findings (Section 8.3.3)
- clinical laboratory test results (Section 8.3.4)
- neurological and clinical symptom assessments ([redacted], [redacted], and [redacted]) (Section 8.3.5)
- local injection site tolerability and pain assessments (Section 8.3.6)

- injection site pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy monitoring (Section 8.3.7)
- PDSS monitoring (Section 8.3.8)
- medication error and special situations related to the IMP (Section 8.3.9)
- overall tolerability (Section 8.3.10)
- pregnancy and postpartum information (Section 8.5)
- clinical product complaints (Section 8.6)
- concomitant medication usage (Section 6.8)

In the case of a suspected PDSS event, an adjudication committee will be summoned to review all cases of suspected PDSS. Further details on the adjudication committee are provided in Section 10.2.

8.3.1. Physical Examinations

Physical examinations and physical measurements (height, weight, and calculation of BMI) will be performed at the time points detailed in Table 1 to Table 5.

A complete physical examination will be conducted at the screening and EOT visits. Physical examinations will include, at a minimum, assessments of general appearance, head, ears, eyes, nose, throat/neck [HEENT], lymph nodes, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system including extremities, neurological system, and dermatological system. An abbreviated physical examination (general appearance, HEENT, lung, heart, skin, and extremities) will be conducted at the other time points and will include a brief neurological examination that includes assessment of mental status and 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 assessed by the Investigator as a clinically significant change (worsening) compared with a baseline value will be recorded as an AE, recorded on the CRF, and monitored as described in Section 8.4.4.

8.3.2. Vital Signs

Vital signs, including body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure (systolic and diastolic), and their orthostatic changes, will be measured at the time points detailed in Table 1 to Table 5.

Orthostatic blood pressure and heart rate will be determined with measurements obtained after the participant has been supine or semi-supine for at least five minutes and repeated after the participant has been standing for 3 minutes.

All vital sign results outside of the reference range will be interpreted by the Investigator as belonging to 1 of the following categories:

- abnormal but not clinically significant
- abnormal and clinically significant

When applicable, vital signs will be measured after ECGs but before scheduled blood draws.

Before pulse, blood pressure, and respiratory rate are measured, the participants must be in a supine or semi-supine position and resting for at least 5 minutes. The same position and arm (opposite arm from the cannula site) should be used each time vital signs are measured for a given participant, when possible. For any abnormal vital signs finding, the measurement should be repeated as soon as possible.

Any vital sign result that is assessed by the Investigator as clinically significant will be recorded on the source documentation, transcribed to the CRF as an AE, and monitored as described in Section 8.4.4. In addition, potentially clinically significant values may be predefined by the Sponsor for selected vital signs and, if so, this will be documented in the Statistical Analysis Plan or other relevant documents (eg, medical monitoring plan).

8.3.3. Electrocardiograms

ECGs will be measured at the time points detailed in Table 1 to Table 5.

All ECG results outside of the reference range will be interpreted by a qualified physician as belonging to 1 of the following categories:

- abnormal but not clinically significant
- abnormal and clinically significant

When applicable, ECGs will be performed before vital signs measurements and scheduled blood draws. Before each ECG is performed, the participants must be in a supine or semi-supine position and resting for at least 5 minutes. At screening only, the ECG will be performed in triplicate at 5-minute intervals.

A qualified physician or designee at the clinical investigational site will be responsible for interpreting the ECGs. Any ECG finding that is assessed by the Investigator as a clinically significant change (worsening) compared with a baseline value will be considered as an AE, recorded on the source documentation, transcribed onto the CRF, and monitored as described in Section 8.4.4.

8.3.4. Clinical Laboratory Tests

8.3.4.1. Chemistry, Hematology, Coagulation, and Urinalysis

Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis) will be performed following an overnight fast of at least eight hours at the time points detailed in Table 1 to Table 5. Non-fasting blood collection is permitted as needed, per the Investigator's assessment of AEs.

Clinical laboratory tests on samples collected during day 1 and day 3 may be performed via both local and central laboratories, as described below. Non-fasting blood collection is permitted as needed, per Investigator assessment of AEs.

Specific laboratory tests to be performed are listed in Section 13.2. At each urinalysis collection, females will be asked if they are currently menstruating, and this information will be recorded in the source documents and CRF.

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

- abnormal but not clinically significant
- abnormal and clinically significant (AE, as described in Section 8.4.1)

A laboratory test result that is assessed by the Investigator as clinically significant will be recorded as an AE and monitored as described in Section 8.4.4. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the participant from the trial, the temporary or permanent 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 participant from entering the trial or receiving IMP are not considered AEs).

In addition, potentially clinically significant values will be predefined by the Sponsor for selected laboratory test variables and detailed in the Statistical Analysis Plan or other relevant documents (eg, medical monitoring plan or laboratory analysis plan).

8.3.4.1.1. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as all of the criteria listed below, must be reported by the Investigator to the Sponsor as an SAE:

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

8.3.4.2. Other Laboratory Tests

8.3.4.2.1. Screening Laboratory Tests

At screening, participants will be tested for hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus (HIV)-1 antibodies, and HIV-2 antibodies.

8.3.4.2.2. Follicle-stimulating Hormone

At screening, women who have been amenorrheic for at least 1 year without an alternative medical cause will have a serum follicle-stimulating hormone (FSH) assessment to confirm postmenopausal status (an increased concentration of FSH of >35 IU/L in women not using hormonal contraception or hormonal replacement therapy [HRT]).

For pregnancy testing, see Section 13.1.3.

8.3.4.2.3. Human Chorionic Gonadotrophin Test

HCG tests in serum or urine will be performed for all women at the time points specified in Table 1 to Table 5.

A serum pregnancy test will be administered for all women, regardless of childbearing potential at screening, on day 1, day 12, and R84 (EOT). Serum or urine dipstick pregnancy tests will be

performed for all women of childbearing potential (WOCBP) on day 3. Negative pregnancy results on day 1, day 3, day 12 (which will be performed locally and centrally), and, if Period 2 is extended, day R1 are mandatory prior to IMP dosing. Additional pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the trial.

Any participant who becomes pregnant during the trial will be withdrawn. Procedures for reporting the pregnancy are provided in Section 8.5.

8.3.4.2.4. Alcohol and Drug Screen

A serum drug and alcohol screen will be performed at screening. The serum drug screen is to detect the presence of drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol.

An in-house urine dipstick screen for prohibited drugs and breathalyzer for alcohol will be performed on day 1, day 3, day 12 (to be conducted at the discretion of the Investigator), day R1 (if Period 2 is extended), day R15, and day R84 (EOT). Alcohol and drug screens may be performed at additional time points at the discretion of the Investigator.

Any positive result during trial conduct will be managed according to the Investigator's review and judgment, in consultation with the Sponsor's medical representative.

8.3.5. Neurological and Clinical Symptoms Measures

The following neurological and clinical symptoms measures ([redacted], [redacted], and [redacted]) will be administered by a trained rater at the time points specified in Table 1 to Table 5.

8.3.5.1. [redacted]

[redacted]

8.3.5.2. [redacted]

[redacted]

8.3.5.3. [redacted]

[redacted]

[redacted]

8.3.5.4. [redacted]

[redacted]

8.3.5.5. [redacted]

[redacted]

8.3.5.6. [redacted]

[redacted]

8.3.6. Assessment of Local Tolerability and Pain

Local tolerability assessments should be performed after each administration of the IMPs (olanzapine immediate-release im or any of the olanzapine for extended-release sc formulations) (Table 1 to Table 5) and should include injection site findings and pain. Injection site findings (erythema, induration/swelling, and pus-containing lesions) and pain will be assessed using the scales provided in Table 11. Pain at the injection site will be reported using a standardized 11-point NPRS for pain intensity, where 0 is "No pain" and 10 is "Worst possible pain." Participants will be asked to respond to the following question: "How much pain do you feel at the drug injection site?"

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. Pain and injection site findings will also be assessed on the planned trial days as detailed in Table 1 to Table 5.

Local tolerability should be assessed as described in Table 11. The surface diameter in millimeters should be recorded, and erythema and induration/swelling at the injection site will be measured as absent, 5 to ≤50 mm, >50 to ≤100 mm, and >100 mm. Erythema and induration/swelling under 5 mm in diameter should be assessed as absent. Care should be taken to avoid pressuring or squeezing the injection site while assessing induration via careful superficial palpation.

Injection sites may be photographed, including between visits to the clinical center, to provide visual representation in addition to comments in the source documents. The photographs will not be used for analysis but can be used to the support the Investigators with their assessments. Any features that could be used to identify the participant will not be captured in the photograph.

Injection site findings described in Table 11 and injection site pain will be recorded on the specified CRF.

Injection site findings will not be captured as AEs unless they fulfill adverse event criteria and then must be recorded and reported as specified in Section 8.4.4. Appropriate treatment may be provided, if necessary, in which case such treatments must be recorded as concomitant medication(s).

In case an AE associated with an ISR is reported, pain may be assessed periodically using an NPRS until resolution.

Site-specific training to monitor for ISRs will be provided; participants will also be educated about ISRs. Additionally, each visit at the CU will include AE inquiry, including inquiry on injection site-related events.

Refer to Section 8.4 for procedures and assessments that are performed for events of pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy.

Table 11: Assessment of Local Tolerability (Injection Site Findings)

Test	Response
Erythema[a]	Absent Surface diameter 5 to ≤50 mm Surface diameter >50 to ≤100 mm Surface diameter >100 mm
Induration/swelling[a]	Absent Surface diameter 5 to ≤50 mm Surface diameter >50 to ≤100 mm Surface diameter >100 mm
Pain[a]	0 to 10 (NPRS)
Pus-containing lesion If "Yes," it will be considered as an AESI, and the diameter should be recorded.	Yes/No <5 mm 5 to 15 mm >15 mm

[a] The decision on whether any of the above meet AE criteria and whether it should be recorded as an AE is per the Investigator's clinical judgment.
AE=adverse event; AESI=adverse event of special interest; NPRS=Numeric Pain Rating Scale.

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

In case of injection site pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy, the following procedures and assessments will be performed:

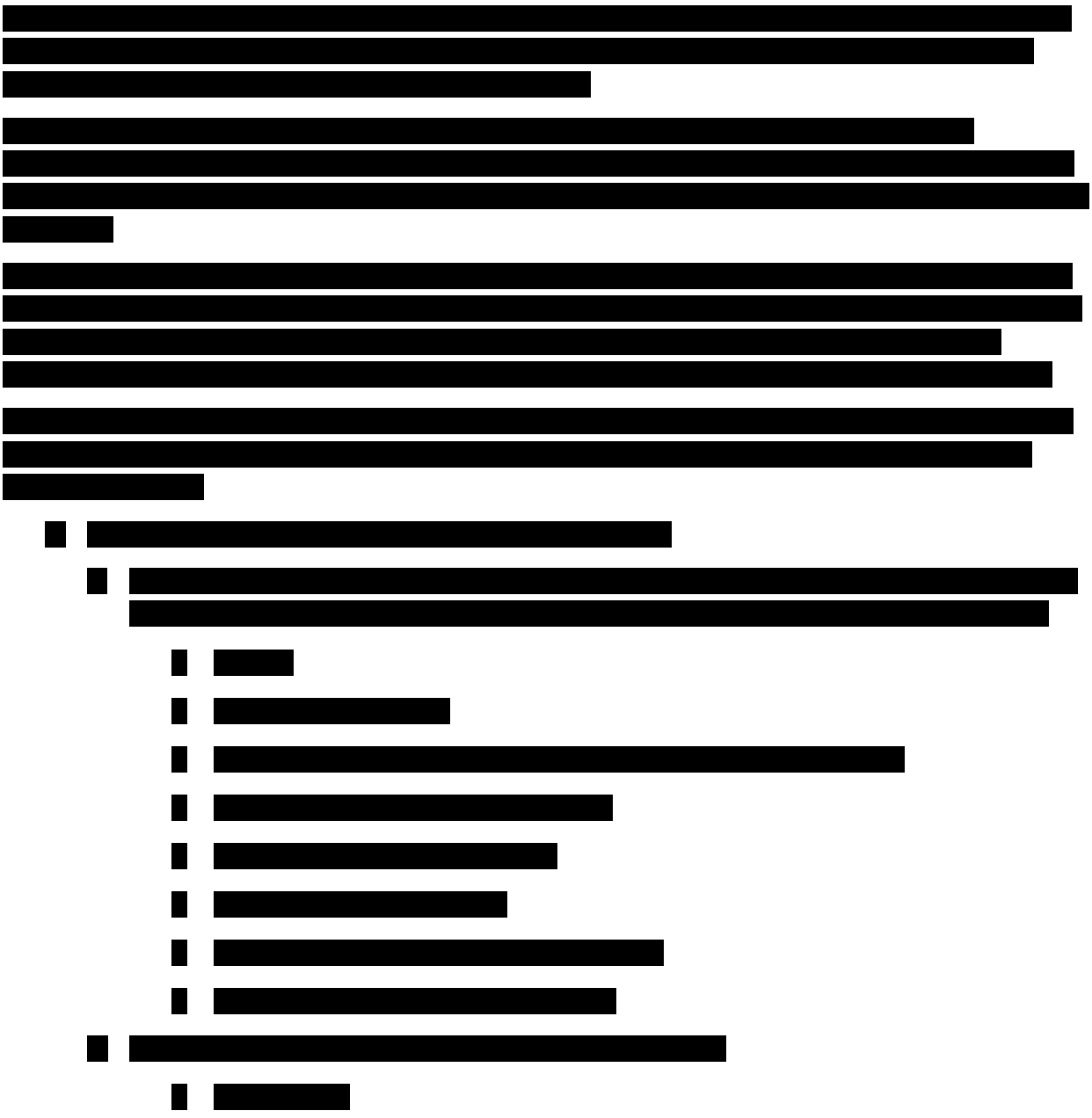
- Vital signs will be measured.
- Hematology clinical laboratory tests will be performed.
- In case of pus-containing lesion (abscess, infection, or inflammation), refer to the assessments described in the last row of Table 11.
- In case of surgical drainage of pus-containing lesion (abscess, infection, or inflammation), every effort should be made to collect a discharge sample for culture, if possible, and every effort should be made to avoid contamination.
- Treatment should be administered according to the local standard of care, with follow-up until resolution.
- It is highly recommended that site staff photograph the injection site. Photographs may be shared with the Sponsor, but data analysis will not be performed on the photographs. The photographs should be taken at a standardized distance of the camera to the skin, using a standardized light source and two perpendicular rulers to provide scale. Any features that could be used to identify the participant should not be captured in the photograph.
- Biomarker samples will be collected at any unscheduled visits as a result of the pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or

atrophy, and for 2 consecutive visits after the event is identified (where local regulations allow, unless the participant declines to provide consent).

The procedures for reporting these events to the Sponsor's Global PV is described in Section 8.4.8.1.

Investigators at sites where participants experience pus-containing lesions may be asked by the sponsor to fill out a follow-up questionnaire regarding these events to further assess the subjective perception of these AEs. In addition, a follow-up discussion with the site representative/s may be conducted, with written documentation of the meeting minutes.

8.3.8. Post-injection Delirium and Sedation Syndrome (PDSS) Monitoring



[redacted]

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

Any administration of IMP that is not in accordance with the trial protocol should be reported as a protocol deviation and documented in the participant's source documents (see Section 11.2), regardless of whether or not an AE occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, participant, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the recommended dose according to this protocol as specified in Section 6.4. Clinical judgment should always be applied. Any dose of IMP, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the Sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.

6. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the protocol or authorized product information, as applicable.
7. Breastfeeding: Suspected AEs that occur in infants following exposure to a medicinal product from breast milk.

8.3.10. Overall Tolerability

Subjective overall tolerability will be assessed after all participants have completed the final assessments and will be based upon the number (%) of participants who failed to complete the trial and the number (%) participants who failed to complete the trial due to AEs.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Definitions of Adverse Events and Serious Adverse Events

8.4.1.1. Adverse Events

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this trial, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the olanzapine sc formulations or ZYPREXA im.

Accordingly, an AE can include any of the following:

- a new condition or the worsening of a preexisting 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 trial
- laboratory or diagnostic test abnormalities

  Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a participant from entering the trial or receiving trial treatment are not considered AEs.
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions (Note: A condition recorded as preexisting that is intermittently symptomatic [eg, headache] and that occurs during this trial should be recorded as an AE).
- events occurring during diagnostic procedures

- laboratory or diagnostic test abnormalities that result in the withdrawal of the participant from the trial, are associated with clinical signs and symptoms or an SAE, require medical treatment or further diagnostic work up, or are considered by the Investigator to be clinically significant
- all events of possible drug-induced liver injury (Section 8.3.4.1.1)
- any physical examination, vital signs measurement, ECG, or other safety assessment finding that is judged by the Investigator as a clinically significant change (worsening) compared with a baseline value

8.4.1.2. Serious Adverse Events

An SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

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

  Hospitalizations scheduled before the participant signed the ICF will not be considered SAEs, unless there was worsening of the preexisting condition during the participant's participation in this trial.
- 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 participant 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; or 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.

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

8.4.1.3. Adverse Device Effects and Serious Adverse Device Effects

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

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

A serious adverse device effect results in any of the consequences characteristic of an SAE (Section 8.4.1.2) and is reported per Section 8.4.7.

8.4.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

For recording of AEs and SAEs, the trial period is defined for an individual participant as the time period from signature of the ICF to the EOT. TEAEs are defined as AEs that occurred after the first dose of IMP was administered through the EOT. SAEs occurring in a participant after the trial has ended should be reported to the Sponsor if the Investigator becomes aware of them, following the procedures described in Section 8.4.6 and Section 8.4.7.

8.4.3. Identifying Adverse Events and Serious Adverse Events

At each contact with the participant, the Investigator or designee must question the participant about AEs 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 an SAE or protocol-defined adverse event of special interest (PDAESI) for expedited reporting to Global PV, on the Serious Adverse Event and PDAESI Form.

Any clinically significant change, as judged by the Investigator, in the [redacted], [redacted] [redacted] and [redacted] scales should be reported as an AE.

During the conduct of the trial, to identify safety concerns, AEs (both serious and nonserious) will be reviewed by the clinical trial physician as they are reported from the investigational center.

8.4.4. Recording of Adverse Events and Serious Adverse Events

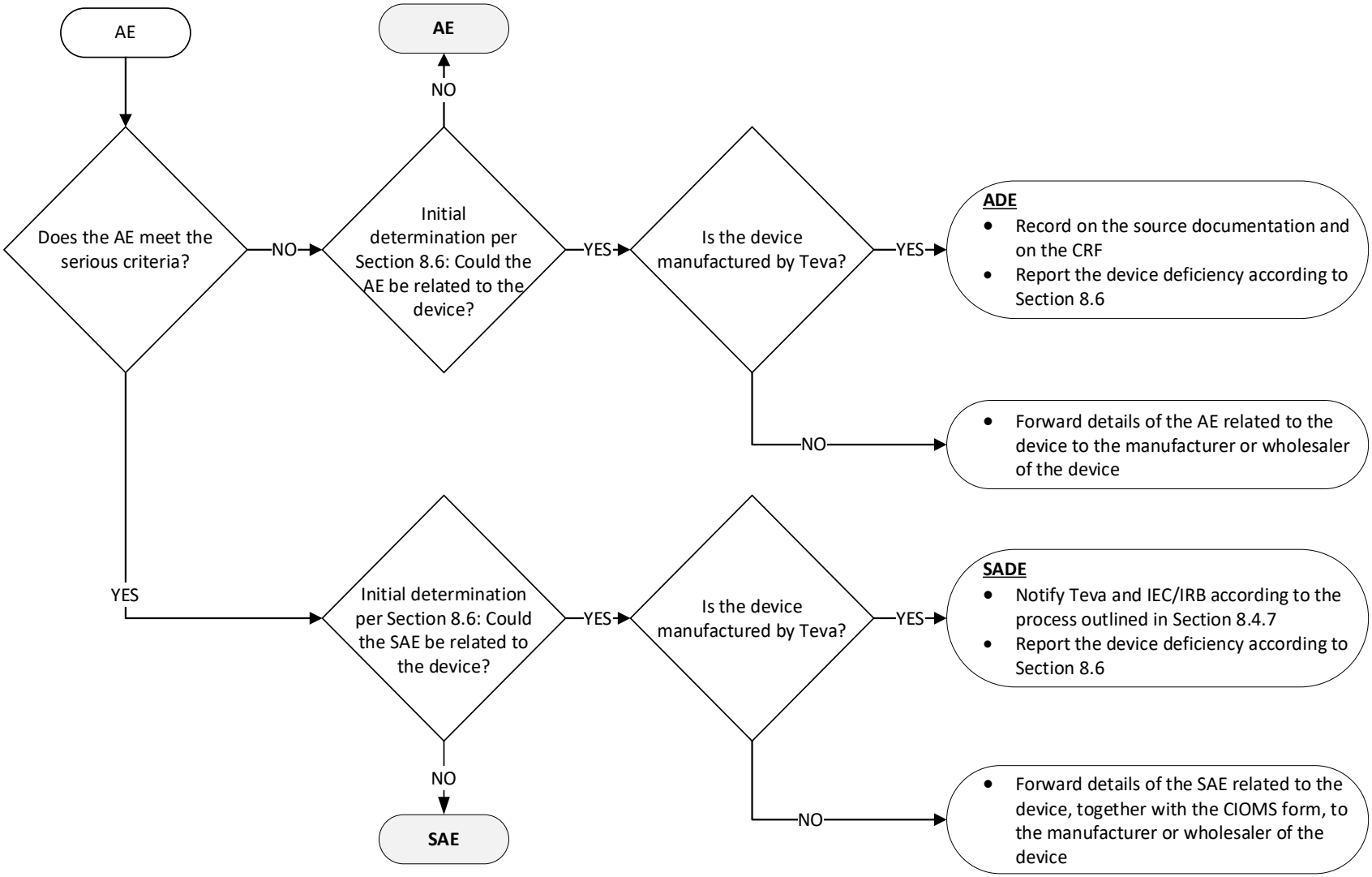
All AEs that occur during the defined trial period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP. The Investigator will record all relevant information regarding every AE/SAE and will categorize each as guided in Figure 2. For SAEs and PDAESI for expedited reporting to Global PV, the Serious Adverse Event and PDAESI Form must be completed and the SAE and the PDAESI must be reported within 24 hours (Section 8.4.6 and Section 8.4.7). The Investigator does not need to actively monitor participants for new AEs after the end of the trial.

SAEs occurring in a participant after the EOT should be reported to the Sponsor if the Investigator becomes aware of them, following the procedures described in Section 8.4.7.

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

The relationship of each AE to IMP (and relationship to the device, if applicable), and the severity and seriousness of each AE, as judged by the Investigator, must be recorded.

Figure 2: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CIOMS=Council for International Organizations of Medical Sciences; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

8.4.4.1. Severity of an Adverse Event

The severity of each AE will be graded according to the NCI CTCAE.

AEs that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local intervention or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

8.4.4.2. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

The relationship of an AE to the IMP and/or device is characterized in Table 12.

Table 12: 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 AEs 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 AE 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 participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. • 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 AEs 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 AE 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 participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE 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.

AE=adverse event; IMP=investigational medicinal product

8.4.4.3. Expectedness of Serious Adverse Events

An SAE 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 of TV-44749 sc formulations for this trial is the IB.

The RSI of ZYPREXA im in this trial to use is the prescribing information (ZYPREXA USPI 2021).

The Sponsor's Global PV will determine the expectedness for all SAEs.

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

8.4.5. Follow-up of Adverse Events and Serious Adverse Events

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

The Investigator may perform additional laboratory tests or investigations, perform histopathological examinations, or consult with other healthcare professionals to elucidate the nature and/or causality of the AE or SAE as fully as possible.

If a participant dies during participation in the trial or during a recognized follow-up period, the Investigator will provide postmortem findings including histopathology, if available, within the Serious Adverse Event Form.

New or updated information will be recorded in the originally submitted documents.

The Investigator will submit any updated data on SAEs and PDAESI for expedited reporting to Global PV within 24 hours of receipt of the information, following the process described in Section 8.4.7.

8.4.6. Reporting of Serious Adverse Events

To satisfy regulatory requirements, the Investigator must report all SAEs that occur during the trial, regardless of the judgment of relationship to administration of the IMP, to the Sponsor. The Investigator must report the event within 24 hours of learning 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 Serious Adverse Event Form should be sent to the LSO or designee (as applicable, for eg, a CRO in a country without a Sponsor LSO); the LSO will forward the report to the Sponsor's Global PV.

Each report of a SAE 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, trial procedures, and to underlying disease.

The investigational center should forward additional information (follow-up) about any SAE and PDAESI for expedited reporting unavailable at the initial reporting within 24 hours of when it becomes known, following the same process as for the initial report.

The responsibilities and procedures for reporting, receiving, processing, submission, reconciliation, and follow-up of SAEs, pregnancies, and PDAESI that require expedited reporting to Global PV are detailed in the Serious Adverse Event Management Plan (SMP). The SMP will be provided as a separate document.

Note: Although pregnancy is not an SAE, the process for reporting a pregnancy is the same as that for reporting an SAE but using the Pregnancy Form (Section 8.5).

8.4.7. Regulatory Reporting Requirements for Serious Adverse Events

If a serious unexpected adverse event (ie, the event fulfills the criteria for a SUSAR) is believed to be related to the IMP, the Sponsor will take appropriate steps to notify all Investigators

participating in sponsored clinical trials of the IMP and the appropriate regulatory authorities (and IRB/IEC, as applicable).

For all countries, the Sponsor's Global PV will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for submission to the competent authorities, IRBs/IECs, and Investigators, according to regulations. For trials in the European Economic Area (EEA), submission of SUSARs is done centrally to EMA by the Global PV. The Investigator must ensure that the IRB/IEC is also informed of the event, in accordance with national and local regulations.

In addition to notifying the Investigators and competent authorities (and IRB/IEC, if appropriate), other measures may be required, including the following:

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

8.4.8. Adverse Events of Special Interest

8.4.8.1. Protocol-defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global Pharmacovigilance

For purposes of this protocol, the following are considered protocol-defined AEs of special interest (PDAESI) to be sent to the Sponsor's Global PV for evaluation:

- PDSS events
- ISRs of pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, and atrophy

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting an SAE (Sections 8.4.6 and 8.4.7), using the same Serious Adverse Event/Protocol-Defined Adverse Events of Special Interest Form. PDAESI to be reported to Global PV can be either serious or nonserious, according to the criteria outlined in Section 8.4.1. PDAESI that occur before trial drug administration do not require reporting to Global PV.

8.4.8.2. Protocol-defined Adverse Events of Special Interest that do not Require Reporting to Sponsor's Global PV

The following are considered PDAESI that do not need to be sent to the Sponsor's Global PV and will be recorded only in the clinical database:

- ISR following sc administration, including, but not limited to, pain, bleeding, tenderness, skin induration, warmth, itching, erythema, inflammation/swelling, rash, skin irritation, dermal irritation, or bruising at the injection site

Pain at the injection site will not be recorded as an AE (but will be captured as a trial safety measure) unless it is different in character, intensity, duration, or frequency from that expected, based on Investigator judgment.

8.4.9. Protocol Deviations Because of an Adverse Event

If a participant experiences an AE or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure participant safety, after the event has stabilized or treatment has been administered (or both), the Investigator or other physician in attendance must contact the Clinical Leader as soon as possible to discuss the situation. The Investigator, in consultation with the Sponsor, will decide whether the participant should continue to participate in the trial.

8.5. Pregnancy and Postpartum Information

Any female participant becoming pregnant during the trial will discontinue and will be withdrawn from the trial.

All pregnancies of women participating in the trial and female partners of men participating in the trial, if applicable that occur during the trial or within six months from last IMP dose, whichever is longer, are to be reported within 24 hours. The completed Pregnancy Form should be sent to the LSO/CRO (as applicable, for eg, a CRO in a country without a Sponsor LSO); the LSO will forward the report to the Sponsor's Global PV. The process for reporting a pregnancy is the same as that for reporting an SAE but using the Pregnancy Form (Section 8.4.7).

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

Because this IMP(s) has suspected reproductive toxicity, female partners of men participating in the trial who become pregnant will be asked to sign an ICF. All female participants and female partners of men participating in the trial 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 trial and any complication of pregnancy that the Investigator becomes aware of after withdrawal from the trial will be reported as an AE or SAE, as appropriate.

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

- For a spontaneous abortion, report as an SAE (both Pregnancy and Serious Adverse Event Forms should be completed).
- For an elective abortion due to developmental anomalies, report as an SAE (both Pregnancy and Serious Adverse Event Forms should be completed).
- For an elective abortion **not** due to developmental anomalies, report on the Pregnancy Form; do not report as an AE.

8.6. Clinical Product Complaints

8.6.1. Definition of Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies (TV-44749 sc formulations and ZYPREXA im) and/or clinical device supplies used in a clinical research trial sponsored by Teva.

Examples of a clinical product complaint include, but are not limited to, the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling)
- 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

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

Reporting a complaint must not be delayed even if not all the required information can be immediately obtained. Known information must be immediately reported. The Sponsor will collaborate with the Investigator to obtain any outstanding information.

Once the complaint has been investigated by the Sponsor, when required, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

If the clinical product complaint is related to a device, comparator, co-medication, 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.

8.6.2. Handling the IMP/Devices at the Investigational Center

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

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

8.6.3. Product Complaint Associated with Adverse Events or Serious Adverse Events

If there is an AE or SAE due to product complaint, the protocol should be followed for recording and reporting of the AE or SAE (Section 8.4.2 to Section 8.4.7).

8.7. Pharmacokinetics

8.7.1. Timing of Pharmacokinetic Sampling

Blood samples (3 mL) will be obtained via direct venipuncture or indwelling catheter for the determination of plasma concentration of olanzapine and potentially for olanzapine metabolites at the time points detailed in Table 1 to Table 5.

Specimen collection, processing, and handling requirements are detailed in the Laboratory Manual.

Every effort must be made to obtain the PK samples within the allowed limits for sampling times, as defined in Table 6 and Table 7. The exact time of sample collection must be noted in the source documents and CRF.

When the PK blood sample collection coincides with safety assessments, PK blood samples should be collected as close to the scheduled time point as possible. Assessment of vital signs and ECGs should precede PK blood sampling.

8.7.2. Changes to Pharmacokinetic Sampling Scheme

Not applicable.

8.7.3. Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated from concentration-time data using noncompartmental methods, when possible.

The following PK parameters will be calculated following ZYPREXA im administration:

- C_{max}
- AUC_{0-t}
- λ_z over the 216-hour period following administration
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additional PK parameters for olanzapine (e.g. [redacted], $AUC_{0-\infty}$, etc) may be calculated if deemed necessary.

The following PK parameters will be calculated following sc olanzapine extended-release formulation administration:

- C_{max}
- AUC_{0-t}

- $AUC_{0-\infty}$
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Additional PK parameters for olanzapine may be calculated if deemed necessary.

8.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.9. Genetics

8.9.1. Pharmacogenomics

[redacted]

8.10. Biomarkers

[redacted]

[redacted]

8.10.1. Digital Biomarkers

Digital biomarker or outcome measures are not evaluated in this trial.

8.11. Immunogenicity Assessments

Not applicable.

8.12. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this trial.

8.13. Total Blood Volume

The total volume of blood to be collected for each participant in this trial is approximately 370 mL (at maximum). The total amount of blood will be drawn over a study duration of approximately 19 weeks.

Additional blood samples for toxicology, PK, and/or biomarkers should be collected in case of severe ISRs (Section 8.3.6); pus-containing lesion (abscess, infection, or inflammation), ulceration, necrosis, or atrophy (Section 8.3.7); or suspected PDSS (Table 8 and Section 8.3.8). Details for all blood volumes and assessments will be included in the Laboratory Manual.

8.14. Assessment of Leakage

Immediately after injection of any of the olanzapine extended-release sc formulations, qualified investigational center personnel will observe the site of injection for the incidence of leakage (ie, to inspect whether the injected suspension appears at the injection site after completion of the injection). The leakage evaluation score will be recorded in the source documents and CRF using the rating scale (0 to 4) as described in Table 13.

Continuous leakage assessment will be performed (ie, additional leakage assessment will be performed for these cohorts after the immediate assessment described above). Specifically, if leakage continues, the evaluation should be continued for up to 10 minutes and the leakage stop time should be recorded. The additional leakage score (0-4) will be recorded at the end of the leakage to capture the total volume of leakage observed post-injection. If leaked IMP is seen at the injection site 10 minutes post-injection, it should be gently wiped, while avoiding pressure or squeezing of the injection site. If leakage does not stop 10 minutes post-dose, record the re-evaluated leakage score, gently wipe the injection site and record 10 minutes for leakage reassessment time (ie, stop time). Whether or not wiping of IMP occurred at 10 minutes post-dose will be recorded on the eCRF as a Yes/No question. In case leakage continues after wiping the site (ie, after 10 minutes), this will also be recorded in the eCRF and the MM should be notified.

A recorded leakage score of 4 should be reported to the MM within 24 hours. Patients with a leakage score of 4 may be replaced.

Table 13: Leakage Evaluation

Appearance	Score
No sign of the injected suspension on the skin	0
Pinpoint to ballpoint size drop is visible on the skin	1
Only a small amount of injected suspension is visible on the skin (ie, most of the injected suspension penetrated the skin)	2
Approximately half of the injected suspension is visible on the skin (ie, approximately half of the injected suspension penetrated the skin)	3
Most of the injectable solution is visible on the skin (ie, little or no injectable solution penetrated the skin)	4

9. STATISTICAL CONSIDERATIONS

This section describes the statistical analysis as foreseen at the time of planning the trial. Changes, additions, and further details about the analyses will be described in the Statistical Analysis Plan (SAP). After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

9.1. Analysis Sets

9.1.1. Enrolled Analysis Set

The enrolled analysis set will include all participants who sign an ICF and are enrolled in the trial. This analysis set will be used for summarizing demography and baseline data.

9.1.2. Pharmacokinetics Analysis Set

The PK analysis set will include all participants who have sufficient data to calculate at least one PK parameter for any of the olanzapine formulations (IM immediate release or sc ER) and have no events of deviations that would affect the calculation of PK parameters. This analysis set will be used for all PK summaries.

A drug metabolism and PK (DMPK) scientist and a clinical pharmacologist will identify each individual participant's PK parameters to be included in the analysis. Individual PK parameters that are considered outliers (eg, parameters that were based on partial data) will be excluded from the primary analysis. Justification for exclusion of parameters will be provided in the PK parameter raw data file provided by DMPK. A Statistical Data Review meeting will be held prior to database lock of the trial (and prior to seeing any data results), and any protocol deviations that could potentially impact the PK will be identified. Data from these participants will also be excluded from the primary and secondary PK analyses. Criteria for exclusion of individual participant data will be defined in the SAP. A leakage score of 4 after TV-44749 sc administration will result in exclusion from the PK analysis set and the participant will be replaced. Data from excluded participants will be included in the relevant listing.

9.1.3. Safety Analysis Set

The safety analysis set will include all participants who receive at least 1 dose of IMP. This analysis set will be used for all safety summaries.

In the safety analysis set, cohorts will be assigned based on the formulation that the participants actually received, regardless of the cohort they were randomized to, unless otherwise specified.

9.1.4. Pharmacogenomics Analysis Set

[redacted]

9.2. Analyses Supporting Primary Objective(s)

9.2.1. Statistical Model, Hypothesis, and Method of Analysis

The PK analysis set will be used for the analysis (Section 9.1.2).

Plasma concentration data will be individually listed and summarized by treatment and cohort using descriptive statistics (n, mean, standard deviation, geometric mean [if appropriate], geometric coefficient of variation [%coefficient of variation (CV)] [if appropriate], median, minimum, and maximum).

No formal inferential statistical analyses of PK data are planned. Pharmacokinetic parameters will be individually listed and summarized for each treatment and cohort using descriptive statistics (n, mean, standard deviation, geometric mean [if appropriate], geometric coefficient of variation (%CV) [if appropriate], median, minimum, and maximum).

9.2.2. Handling of Missing Data

For all variables, only the observed data from the participants will be used in the statistical analyses, unless otherwise specified.

In general, missing data will not be imputed. Partial or missing dates of AEs and concomitant medications may be imputed and detailed in the SAP. Other specific imputations for missing safety features at baseline will also be detailed in the SAP.

9.2.3. Sensitivity Analyses

No sensitivity analyses are planned.

9.2.4. Supplementary Analyses

No supplementary analyses are planned.

9.2.5. Multiplicity Adjustment

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

9.3. Analysis Supporting Secondary Objective(s)

No formal statistical analyses are planned.

The PK parameters for ZYPREXA im and olanzapine extended-release formulations will be individually listed and summarized for each formulation and cohort using descriptive statistics (n, mean, standard deviation, geometric mean [if appropriate], geometric coefficient of variation (%CV) [if appropriate], median, minimum, and maximum). For the safety and tolerability measures/parameters, the participant counts and percentages will be provided.

9.4. Analysis of Exploratory Objective(s)

9.4.1. Pharmacogenomic Analyses

[redacted]

[redacted]

9.5. Safety Analyses

Safety analyses will be performed on the safety analysis set (Section 9.1.3). No formal statistical analyses of safety data are planned. The safety analysis will be performed by any of the IMPs (ZYPREXA im or sc olanzapine).

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error [SE], median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, participant counts and percentages will be provided.

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

Subjective overall tolerability will be assessed by calculating the number (%) of participants who failed to complete the trial, and the number (%) of participants who failed to complete the trial due to AEs.

The use of concomitant medications and rescue medications will be summarized by therapeutic class for each treatment and cohort using descriptive statistics.

The analyses will include the following data:

Adverse Events: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each participant will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all TEAEs and adverse device events (overall and by severity), including AEs determined by the Investigator to be related to IMP and/or medical device (defined as related or with missing relationship), SAEs, serious device adverse events, and AEs and adverse device events causing withdrawal from the trial. Summaries will be presented by treatment and cohort for all participants. Participant listings for TEAEs and adverse devise events that are serious and those leading to withdrawal will be presented.

PDSS events (as defined above in the stopping criteria) and ISRs of pus-containing lesions (abscess, infection, or inflammation), ulceration, necrosis, and atrophy will be subject to expedited reporting.

Local Tolerability Analysis: Injection site assessments (ie, local tolerability) will be carried out for each reported injection site AE. Injection site pain, erythema, induration/swelling, and pus-containing lesions will be assessed using standardized scales and the findings will be presented using descriptive statistics. For pain intensity, the NPRS scale will be applied. Listings and descriptive statistics will be presented.

The frequency of each score measuring local tolerability at the injection site will be determined at each time point according to treatment and cohort.

The incidence of TV-44749 leakage from the injection site post-administration, including leakage evaluation score, will be summarized descriptively.

Changes in Laboratory, ECG, and Vital Sign Measurements: All collected data will be summarized descriptively. All values will be compared with predefined criteria to identify

potentially clinically significant values or changes, as detailed in the SAP, and such values will be listed.

Actual values and changes from baseline in laboratory test results (chemistry, hematology, coagulation, and urinalysis), vital signs, and 12-lead ECG measurement data at each time point will be summarized descriptively by treatment and cohort.

Concomitant Medications: Concomitant medications will include all medications taken from first dose of ZYPREXA im through the end of follow-up (EOT/ET). Therapeutic class using descriptive statistics will summarize the use of concomitant medications. Descriptive statistics for allowed rescue medications will be presented by treatment and cohort.

Clinical Scales: Safety outcomes of the scale scores (change from baseline) including [redacted] and [redacted] from the treatment period will be presented using descriptive statistics. The [redacted] will be used to assess the risk of suicide events during the trial. Descriptive statistics will be presented by treatment and cohort.

9.6. Other Analyses

9.6.1. Population Pharmacokinetic Analysis

Pharmacokinetic parameters of olanzapine will be calculated and may be combined with data from additional clinical studies to characterize the PopPK of TV-44749.

The details of these analyses will be in a separate PopPK analysis plan for this trial. The results of this analysis will be reported separately from the main trial results.

9.6.2. Pharmacogenetic and Biomarker Analysis

[redacted]

9.7. Interim Analyses

No formal interim analysis is planned in this open-label Phase 1 trial. Review of sentinel cohort 1A data prior to dosing cohort 1B by the SRC is described in Section 4.1.2.

The Sponsor may leverage preliminary concentration data to initiate IVIVC modeling activity prior to database lock, without impacting the study conduct.

9.8. Sample Size Determination

The planned sample size for this trial is approximately 95 enrolled participants in order to achieve approximately 60 completers (approximately 20 participants per cohort). Completers are defined as participants who have completed the procedures and assessments required through

follow-up period of sc olanzapine ER (ie, the 84 days after the sc injection, up to and including day R84).

Given the descriptive and exploratory nature of the trial, which is intended to collect pharmacokinetic data for an IVIVC external analysis, no formal sample size calculation has been performed for this trial.

If a participant is enrolled but terminates the trial early (for criteria of ET, see Section 7.1), or has events that would affect the calculation of PK parameters, an additional patient may be enrolled to ensure that approximately 20 participants per group have completed the PK portion of the trial and can be considered evaluable for the primary analysis of the study (see Section 9.1.2).

9.9. Protocol Deviations

The definition of and process for reporting important protocol deviations are discussed in Section 11.2.

10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1. Regulatory and Ethical Considerations

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

Compliance Statement

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

The Investigator is responsible for performing the clinical trial 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 trial in accordance with the protocol and applicable regulations will be documented in separate clinical trial agreements with the Sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The clinical trial agreement shall outline the Investigator's and the institution's responsibilities with respect to the conduct of the clinical trial, including the Investigator's reporting obligation to the Sponsor for suspected cases of serious breach from GCP and/or protocol.

The Investigator is responsible for ensuring the privacy, health, and welfare of the participants during and after the clinical trial; and must ensure that trained personnel are immediately available in the event of a medical emergency. The Investigator and the involved clinical trial personnel must be familiar with the background and requirements of the trial and with the properties of the IMPs (TV-44749 and ZYPREXA im) 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 trial at that investigational center and for contacts with trial management, with the IRB/IEC, and with competent authorities.

See Section 10.3 for the ethics expectations of informed consent or assent, Section 10.4 for confidentiality regarding trial participants, and Section 13.7 for requirements for registration of the clinical trial.

10.2. Committees

An SRC composed of the Sponsor's clinical trial physician, clinical leader, PV physician, and other relevant experts will be summoned to review all safety data available upon completion of the first 15 days of the sentinel cohort (cohort 1A).

In the case of a suspected PDSS event, an adjudication committee composed of the Sponsor's clinical trial physician, clinical leader, PV physician, pharmacometrician, and other relevant experts, such as a statistician and a PK expert, will be summoned to review all cases of suspected PDSS to determine if each case fulfills all 5 criteria in the definition for a clinical diagnosis of PDSS (adapted from Detke et al 2010), as well as to evaluate the robustness of the available clinical evidence. An external independent physician with expertise in the relevant therapeutic area may be consulted, if needed.

10.3. Informed Consent Process

The Investigator, or a qualified person designated by the Investigator, should fully inform the participant of all pertinent aspects of the trial, including the written information approved by the IRB/IEC. All written and oral information about the trial will be provided in a language as nontechnical as practical to be understood by the participant. The participant should be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. The above should be detailed in the source documents.

If the trial is designed to treat participants in an emergency situation, specific rules for obtaining informed consent may be required to be added to the ICF, including cases where it is not possible within the therapeutic window to obtain prior informed consent from the participant or from his or her legally designated representative. Specific activities may need to be detailed in the protocol related to the unique informed consent process.

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

Adult participants with a legally acceptable representative should provide informed consent according to national and local requirements.

A separate written informed consent will be obtained from each participant before pharmacogenomics samples will be collected (Section 8.9.1).

10.4. Data Protection

Data Protection and Confidentiality

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

Teva has implemented appropriate technical, physical, organizational, and administrative information, and privacy security measures to protect the confidentiality, integrity, and availability of data in its systems. Teva's Information Security Team keeps the measures under continuous review to align with state-of-the-art standards, taking into account the nature and context of the processing. Teva systems and policies are aligned with industry-standard information security and privacy frameworks such as ISO 27001 covering categories of security controls including:

- Access Control
- Awareness and Training
- Backup and Recovery
- Change Control
- Encryption and Communication Controls
- Identity and Authentication
- Incident Response and Recovery
- Logging, Monitoring, and Alerting
- Media Protection
- Operations Control
- Personnel Security
- Physical and Environmental
- Program and Risk Management
- System and Communications Protection
- Third Party/Supplier Relationship Control

Teva employs an Information Security Team and where needed, Teva also leverages independent data security experts.

Teva employs a Cyber Defense Center to direct and coordinate all security incident activity.

Teva has implemented Incident Response and Recovery policies and processes to identify and respond to security incidents and/or data breaches both internally as well as from other involved third parties. These policies cover the full Incident Response and Recovery lifecycle from initial response/notification through triage and mitigation activities to recovery and root cause resolution. Teva also has a "Global Privacy Incident and Breach Reporting Policy" to address a privacy incident or breach (suspected or confirmed).

Where personal data are stored, transmitted, or processed externally utilizing third parties, Teva employs appropriate contractual language, and other controls requiring the third party to employ appropriate information security controls and protections to guard the confidentiality, integrity, and availability of such data.

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

Teva trains its staff regarding the handling of personal data in accordance with applicable law. This includes training on how to recognize, respond to, and mitigate a personal data breach.

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

The confidentiality of participant data is protected. Teva staff are subject to a contractual obligation of confidentiality.

The Investigator must ensure that the privacy of the participants, including their identity, and all personal medical information will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, participants will be identified not by their names, but by an identification number.

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

10.5. Early Investigational Center Closure or Trial Termination

The Sponsor or designee reserves the right to close the investigational center or terminate the trial at any time for any reason at the sole discretion of the Sponsor. An investigational center is considered closed when all required documents and trial supplies have been collected and an investigational center closure visit has been performed.

The Investigator may initiate investigational center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational center by the Sponsor or Investigator may include but are not limited to:

For trial termination:

- Discontinuation of further trial intervention development.

For investigational center termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1. Quality Tolerance Limits

Quality tolerance limits are being addressed through standard risk assessment and mitigation processes aligned with ICH guidelines and are documented in the relevant plans.

11.2. Data Quality Assurance

Refer to Section 8.6 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. Further details are given in a Pharmacy Manual.

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this trial. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this trial, along with all steps and actions taken regarding data management and data quality control, will be described in a Data Management Plan.

Data will be verified by the trial 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.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this trial. Logical checks will be implemented to ensure data quality and accuracy. 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 clinical data management system (CDMS). Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the trial, the CDMS and all other trial data will be locked to further additions or corrections. Locking the trial data represents the acknowledgment 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. An interim lock or locks may be performed during the trial, as described in Section 9.6.1 and in the SAP.

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 IRB/IEC and national and local competent authorities, as applicable, except when necessary to address immediate safety

concerns to the participants or when the change involves only non-substantial logistics or administration. The Principal Investigator at each investigational center, the Coordinating Investigator (if applicable), and the Sponsor will sign the protocol amendment.

Important Protocol Deviations

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

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

If a participant experiences an AE or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure participant safety, the Investigator or other physician in attendance must contact the Sponsor's MM as soon as possible to discuss the situation. The Investigator, in consultation with the Sponsor, will decide whether the participant should continue to participate in the trial.

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

Information to Trial Personnel

The Investigator is responsible for giving information about the trial to all personnel members involved in the trial or in any element of participant management, both before starting the trial and during the course of the trial (eg, when new personnel become involved). The Investigator must ensure that all trial personnel are qualified by education, experience, and training to perform their specific task. These trial 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 trial, as necessary.

Trial Monitoring

To ensure compliance with GCP guidelines, the trial monitor or representative is responsible for ensuring that participants have signed the ICF and the trial is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines. Details of the monitoring procedures are outlined in the trial's monitoring plan which is maintained by the Sponsor.

The trial monitor is the primary association between the Sponsor and the Investigator. The main responsibilities of the trial monitor are to explain the protocol to all trial staff including the

Investigator and to visit the Investigator before, during, and after the trial 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 participants before they participate in the trial and when changes to the consent form are warranted, in accordance with IRB/IEC approvals.

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

If electronic CRFs are used for the trial, the trial monitor will indicate verification by electronically applying source document verification flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of trial progress, other Sponsor personnel may, on request, accompany the trial monitor on visits to the investigational center. The Investigator and assisting personnel must agree to cooperate with the trial 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.

In case of an emergency situation (eg, the COVID-19 pandemic), where trial monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with global and/or local regulations.

Audit and Inspection

The Sponsor may audit the investigational center to evaluate trial conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The Sponsor's Global Clinical Quality Assurance, independent of Global Clinical 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.

In case of an emergency situation (eg, the 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 global and/or local regulations.

11.3. Source Data

Source Data

Data will be collected at the investigational center by appropriately designated and trained personnel. The Investigator must maintain the original records (ie, source documents) of each participant's data at all times. The Investigator will maintain a confidential participant identification list that allows the unambiguous identification of each participant.

Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, IMP label records, diary data, and protocol-required worksheets that are used as the source.

Data may not be recorded directly on the CRF and considered as source data unless the Sponsor provides written instructions in the trial-specific CRF Completion Guidelines specifying which data are permitted to be recorded directly to the CRF.

If data are processed by other institutions or by other means (eg, clinical laboratory, central image center, eDiary data, or devices), the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise instructed by the Sponsor. These data may also be sent electronically to the Sponsor (or organization performing data management) for direct entry into the clinical database.

The medical experts, trial monitors, auditors, IRB/IEC, and inspectors from health authorities (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 participant confidentiality is maintained in accordance with national and local requirements.

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.

Case Report Forms

CRFs that were specifically designed for this trial must be completed for each participant who provided informed consent. Participant identity should not be discernible from the data provided on the CRF. All participant data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto CRFs.

The data collected on the CRFs will be captured in a CDMS that meets the technical requirements described in 21CFR Part 11 (US) and documents of other concerned competent authorities. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the trial before it is used to capture data from this trial. Before using the CDMS, all users will receive training on the system and trial-specific training. After they are trained, users will be provided with individual system access rights.

For participants who enter a trial but do not meet entry criteria, the minimum information to be entered into the CRF includes, but is not limited to, screening failure details, demography, eligibility criteria, and AEs from the time of informed consent.

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 trial 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 ICFs

- participant identification lists
- CRFs for each participant on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, or eDiary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMP
- copies of all correspondence with Sponsor, the IRB/IEC, and any competent authority

The Investigator will retain all records related to the trial and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or Sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from trial completion, or earlier in the case of the investigational center closing or going out of business, the Investigator reasonably determines that trial 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 trial 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 trial records.

12. APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

No information is provided for this section.

13. APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1. Contraception and Pregnancy Testing

13.1.1. Definitions Related to Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with >1 FSH measurement (>35 IU/L) is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.
    - Permanent sterilization methods (for the purpose of this trial) include the following:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis), Investigator discretion should be applied to determine trial entry.
    - Note: Documentation can come from the investigational center personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IMP, additional evaluation should be considered.

Women of Nonchildbearing Potential

Women in the following categories are considered women of nonchildbearing potential:

3. Premenopausal female with permanent infertility due to one of the following (for the purpose of this trial):
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis), Investigator discretion should be applied to determine trial entry.

Note: Documentation can come from the investigational center personnel's review of the participant's medical records, medical examination, or medical history interview.

4. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with >1 FSH measurement (>35 IU/L) is required.
     - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

13.1.2. Contraception

The contraceptives allowed during the trial are listed in Table 14.

Table 14: Contraceptives Allowed During the Trial

Highly effective methods[a] that have low user dependency Failure rate of <1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] initiated at least 14 days before the first dose of IMP.
Intrauterine device in place at least 2 months before screening.
Intrauterine hormone-releasing system[b] in place at least 2 months before screening.
Bilateral tubal occlusion, except for hysteroscopic bitubal ligation (Essure®), for which a hysterosalpyngogram is required 3 months post-procedure to assess surgical success.
Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the investigational center personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[a] that are user-dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] initiated at least 14 days before the first dose of IMP • oral • intravaginal • transdermal • injectable

Table 14: Contraceptives Allowed During the Trial (Continued)

Progestogen-only hormone contraception associated with inhibition of ovulation[b] initiated at least 14 days before the first dose of IMP • oral • injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the administration of IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant. Minimum time adherence prior to first dose of IMP is 6 months.
Effective methods[c] that are not considered highly effective Failure rate of ≥1% per year when used consistently and correctly.
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Male or female condom with or without spermicide.
Cervical cap, diaphragm, or sponge with spermicide.
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[b].

[a] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
[c] Considered effective, but not highly effective – failure rate of ≥1% per year.
Notes: Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).
CTFG=Clinical Trial Facilitation Group; IMP=investigational medicinal product; WOCBP=women of childbearing potential.

13.1.3. Pregnancy Testing

HCG tests in serum or urine will be performed for all women at the time points specified in Table 1 to Table 5.

A serum pregnancy test will be performed for all women at screening on day 1 and WOCBP on day 12. A serum pregnancy test on day 12 will be performed both in central and local laboratories. Serum or urine dipstick pregnancy tests will be performed for all WOCBP on day 3. A urine dipstick pregnancy test will be administered at other time points as specified in Table 1, Table 2, Table 3, Table 4, and Table 5 (WOCBP only). A serum pregnancy test will be administered to all women, regardless of childbearing potential, on day R84: EOT).

- Refer to Section 5.3 for pregnancy testing inclusion criteria.
- Additional pregnancy tests (HCG in urine or serum) may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the trial.

13.2. Clinical Laboratory Tests

Table 15: Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis[a]
• Calcium • Phosphate • Sodium • Potassium • Chloride • Bicarbonate or carbon dioxide • Glucose • HbA1c[b] • Blood urea nitrogen • Creatinine • Cholesterol (low density lipoprotein/high density lipoprotein/total) • Triglycerides • Uric acid • Alanine aminotransferase • Aspartate aminotransferase • Lactic dehydrogenase • Gamma glutamyl transpeptidase • Alkaline phosphatase • Creatine phosphokinase • Total protein • Albumin • Total bilirubin	• Hemoglobin • Hematocrit • RBC count • Platelet count • WBC count and differential count (absolute and percentage) o Polymorphonuclear leukocytes (neutrophils) o Lymphocytes o Eosinophils o Monocytes o Basophils • Coagulation tests o INR o PT o PTT	• Protein • Glucose • Ketones • Blood (hemoglobin) • pH • Nitrates • Specific gravity • Microscopic o Bacteria o RBCs o WBCs o Casts o Crystals

[a] At each urinalysis collection, females will be asked if they are currently menstruating.
[b] HbA1c will be collected at screening and day R1 pre-dose (baseline).
HbA1c=glycated hemoglobin; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; WBC=white blood cell.

13.3. Prior Protocol Amendments

The original protocol was not submitted to the FDA. Revision 1, below, is the version that was submitted.

Original Protocol with Revision 1, 13 September 2023

The original protocol, dated 01 August 2023, was revised to address inconsistencies and correct procedural errors.

Overall Rationale for the Revision:

The original protocol required revisions due to inconsistencies between the Schedule of Activities tables and protocol body. In addition, the blood volumes table (Section 8.13, Table 13

in the original protocol), which is not required in the protocol per standard operating procedures, was removed and will be fully detailed in the Laboratory Manual. This revised protocol addresses these changes and clarifies other minor inconsistencies and typographical errors.

ADMINISTRATIVE LETTER 01

Study number: TV44749-NPC-10205

Clinical Study Protocol with Revision 01

A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three SC Olanzapine Extended-release Formulations with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder

Protocol version date: 13 September 2023

IND number: 128851

26 March 2024

Dear Investigator:

The purpose of this letter is to

1. Correct typographical errors in the protocol;
2. Clarify potentially confusing sentences in the protocol;
3. Remove irrelevant sentences from the protocol.

These changes have no impact on the safety or scientific value of the clinical trial.

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

1. Table 1, Screening, Antipsychotic Washout Period, and ZYPREXA IM Treatment Period 1: Trial Procedures and Assessments (Day -40 Through Day 4):

Footnote "r" of Table 1 will be updated to clarify that there are no specific time windows for conducting Numeric Pain Rating Scale assessments in case of injection site reaction adverse events, as follows:

> [r] On day 4, pain will be assessed 30 min after the completion of ZYPREXA im administration, and pain and injection site findings will be assessed 3 h after the completion of administration. Allowed time windows for these local tolerability assessments are ±15 min. ~~No time windows are specified for these assessments.~~ In case an adverse event associated with an ISR is reported, pain may be assessed periodically using an NPRS until resolution. No time windows are specified for NPRS assessments.

2. Section 5.4, Exclusion Criterion R:

The revision to exclusion criterion "r" clarifies that the temperature should be collected either orally or tympanic – both methods are acceptable.

r. ~~Oral body~~ Body temperature (measurement performed either orally or on both ears, recording the highest value) outside the interval of 35.4°C to 37.5°C at the screening visit.

3. Section 5.4, Exclusion Criterion S:

The total bilirubin's unit and value in the bracket in exclusion criterion "s" are incorrect and will be deleted as it was an error. Total bilirubin's remaining value and unit, 2.5 mg/dL, are correct and will remain as a part of exclusion criterion "s".

s. Clinical laboratory test abnormalities as listed below:

- Clinical laboratory values with Common Terminology Criteria for AEs (CTCAE) Grade 2 or above
- Blood urea nitrogen >31 mg/dL
- Lactate dehydrogenase ≥3 × upper limit of normal (ULN)
- Urinalysis with any clinically significant finding
- Total bilirubin >2.5 mg/dL ~~(>51 mol/L)~~

4. Section 5.4, Exclusion Criterion BB:

For exclusion criterion "bb", text will be added to align it with the relevant study population, as specified in inclusion criterion "f", the study title, and the rest of the protocol.

bb. A current clinically significant DSM-5 diagnosis other than schizophrenia or schizoaffective disorder.

5. Section 6.8.2, Permitted Concomitant Therapy

The following revision will be made to clarify that the medications that are prescribed to the patients are at the discretion of the investigator. It is highly recommended to consult the sponsor to avoid prescribing medications that could potentially affect the olanzapine pharmacokinetic levels.

Medications prescribed for the treatment of chronic medical conditions or for the treatment of acute medical conditions (such as antibiotics) may be permitted per Investigator judgment ~~after consulting with the Sponsor~~. The Sponsor may be consulted to avoid any effect on the olanzapine PK assessments. Medications required for the treatment of any AEs, and contraceptives as per Section 13.1.2 are allowed (as long as they do not interfere with the absorption, excretion, or metabolism of olanzapine).

6. Section 8.3.6, Assessment of Local Tolerability and Pain

The following sentences will be removed as there is only one (1) TV-44749 subcutaneous injection in the trial:

> Local tolerability assessments should be performed after each administration of the IMPs (olanzapine immediate-release im or any of the olanzapine for extended-release sc formulations) (Table 1 to Table 5) and should include injection site findings and pain. Injection site findings (erythema, induration/swelling, and pus-containing lesions) and pain will be assessed using the scales provided in Table 11. Pain at the injection site will be reported using a standardized 11-point NPRS for pain intensity, where 0 is "No pain" and 10 is "Worst possible pain." Participants will be asked to respond to the following question: "How much pain do you feel at the drug injection site?" ~~Where the dose is distributed across multiple injection sites, each injection site will be assessed.~~
>
> 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. Pain and injection site findings will also be assessed on the planned trial days as detailed in Table 1 to Table 5.
>
> ~~The site of the preceding IMP injection will be assessed on the day of the following IMP administration prior to administration and at the EOT visit. No time windows are specified for these assessments.~~

7. Section 8.3.7, Procedures for Injection Site Pus-containing Lesion (Abscess, Infection, or Inflammation), or Ulceration

This is the only section in the protocol where the protocol-defined adverse event of special interest (PDAESI) terms "necrosis or atrophy" were mistakenly not included. This revision will align with other locations in the protocol where these terms are listed.

> **8.3.7. Procedures for Injection Site Pus-containing Lesion (Abscess, Infection, or Inflammation), ~~or~~ Ulceration, Necrosis, or Atrophy**
>
> In case of injection site pus-containing lesion (abscess, infection, or inflammation), ~~or~~ ulceration, necrosis, or atrophy, the following procedures and assessments will be performed:
>
> - Biomarker samples will be collected at any unscheduled visits as a result of the pus-containing lesion (abscess, infection, or inflammation), ~~or~~ ulceration, necrosis, or atrophy, and for 2 consecutive visits after the event is identified (where local regulations allow, unless the participant declines to provide consent).

8. Section 9.1.2, Pharmacokinetics Analysis Set

The following revision will be applied to clarify the rout of administration and formulation:

> The PK analysis set will include all participants who have sufficient data to calculate at least one PK parameter for any of the olanzapine formulations (IM~~, IR~~ immediate release or sc ER)~~,~~ and have no events of deviations that would affect the calculation of PK parameters.

9. Section 10.5, Early Investigational Center Closure or Trial Termination

The following sentence will be deleted since it is not capturing accurately all the relevant cases stated in the paragraph, which are adequately specified in the rest of the paragraph, once this sentence is removed:

> The Sponsor or designee reserves the right to close the investigational center or terminate the trial at any time for any reason at the sole discretion of the Sponsor. ~~In such cases, investigational centers will be closed upon trial completion.~~ An investigational center is considered closed when all required documents and trial supplies have been collected and an investigational center closure visit has been performed.

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] 26-Mar-2024 | 16:37 GMT

13.4. List of Prohibited Medications

Some drugs have been reported to have a pharmacodynamic or PK drug-drug interaction with olanzapine (Table 16). Olanzapine is a CYP1A2 substrate. Thus, coadministration with inducers or inhibitors of CYP1A2 could lead to decreased or increased olanzapine concentrations, respectively. All medications that fall under prohibited medication classes should be excluded. For any questions about prohibited medications, the Sponsor or MM should be contacted.

Table 16: Partial List of Prohibited Medications

Medication class	Drug name
Enzymatic inducers	Carbamazepine, albendazole, phenytoin, phenobarbital, primidone, St. John's wort, rifampin
Anti-Parkinson agents	Dopamine agonist, agomelatine, rasagiline, ropinirole, amantadine, biperidil
Antipsychotics	Olanzapine[a]
CYP1A2 inhibitors	Fluvoxamine, ciprofloxacin, thiabendazole
Antiemetic	Metoclopramide
CYP1A2 substrates	Aminophylline, theophylline
Strong CYP2D6 inhibitors[b]	eg, quinidine, fluoxetine, paroxetine
Strong CYP3A4 inhibitors[b]	eg, itraconazole, clarithromycin, fluconazole, ketoconazole, ritonavir, mibefradil, grapefruit juice

[a] Other than provided during the trial.
[b] Partial list.

13.5. Financial Disclosure

A separate clinical trial agreement, including a trial budget, will be signed between each Principal Investigator/institution and the Sponsor (or the CRO designated by the Sponsor) before the IMP is delivered.

The participants in this clinical trial 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 participant had not taken part in the clinical trial.

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

For covered clinical trials (see 21CFR Part 54), 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 trial and for 1 year after the trial has been completed.

13.6. Recruitment Strategy

Enrollment for this clinical trial will be competitive, which means each Investigator will be given equal opportunity to enroll into an open slot. Each participating clinical site will be given an

equal number of slots, but in the event a participant cannot be identified within a specified period of recruitment time (ie, days), that slot will be opened up to another clinical site to fill.

A sufficient number of sites have been planned for this Phase 1 clinical trial, in accordance with standard industry strategy to ensure a robust recruitment rate, while also mitigating risks in data variances that can occur with too many sites in early phase trials. These risks are primarily related to variances in training and process that can affect small sample sizes to a greater degree.

One or two backup sites will also be identified for inclusion in the event some of the selected sites are unable to recruit participants to the trial. The primary tool for assisting sites with their recruitment efforts will be direct and regular engagement with the site staff to discuss participant screening, enrollment, and retention of participants once they are enrolled into the trial.

The trial team will also consider development of participant recruitment and retention materials, which will be translated to the local language(s). These tools may include, but are not limited to, the following: participant education materials for site use, direct to participant outreach materials, physician referral letters, trial landing pages, and recruitment/retention tools for site staff use.

13.7. Dissemination of Clinical Trial Data

The Sponsor is responsible for the preparation of a CSR, in cooperation with the CRO. The final report is signed by the Sponsor and Principal Investigator.

The Sponsor is responsible for ensuring that the public has access to the appropriate information about the trial according to local and regional requirements. Policies regarding the publication of the trial results are defined in the contractual agreement signed by the Sponsor and CRO.

Teva may register this Phase 1 trial.

13.8. Publication Policy

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

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

Further details pertaining to publications and review periods are described in the clinical trial agreement with the Investigator/institution.

The Sponsor will comply with the requirements for publication of trial 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 multi-center trials only in their entirety and not as individual investigational center data. In this case, a Coordinating Investigator will be designated by mutual agreement.

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

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

The publications committee established by the Sponsor will oversee this process. Additional publications may follow.

No patent applications based on the results of the trial 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.

14. APPENDIX: GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AESI	adverse event(s) of special interest
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
AUC	area under the plasma drug concentration-time curve
AUC_{0-t}	Area under the plasma drug concentration-time curve from IMP administration to last measurable concentration
$AUC_{0-\infty}$	AUC extrapolated to infinity
[redacted]	[redacted]
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
CDMS	clinical data management system
CDSS	clinical decision support system
CFR	Code of Federal Regulations (US)
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum observed plasma drug concentration
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CU	clinical unit
CV	coefficient of variation
CYP	cytochrome P450
DMPK	drug metabolism and pharmacokinetics

Abbreviation	Term
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEA	European Economic Area
ECG	electrocardiogram
EMA	European Medicines Agency
EOT	end of treatment
ER	extended-release
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin
HCG	human chorionic gonadotrophin
HEENT	head, ears, eyes, nose, throat/neck
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
im	intramuscular
IMP	investigational medicinal product
INN	international nonproprietary name
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ISR	injection site reaction
IU	international unit
IVIVC	in vitro/in vivo correlation
LSO	local safety officer
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor

Abbreviation	Term
NPRS	Numeric Pain Rating Scale
OTC	over-the-counter
[redacted]	[redacted]
PDAESI	protocol-defined adverse event(s) of special interest
PDSS	post-injection delirium/sedation syndrome
PFS	prefilled syringe
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PT	prothrombin time/preferred term
PTT	partial thromboplastin time
PV	pharmacovigilance
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
sc	subcutaneous(ly)
SD	single-dose
SMP	Serious Adverse Event Management Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization
WO	Washout
WOCBP	women of childbearing potential

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