Statistical Analysis Plan

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

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SAP Approval Date: 11 February 2025

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Trial TV44749-NPC-10205

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Pharmacokinetic Trial

Phase 1

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV44749-NPC-10205**

Study 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.

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Amendment: **NA**

Author: [redacted]

Approver: [redacted] Date

Approver: [redacted] Date

Executed signature pages are maintained separately within the Trial Master File

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
[redacted]	[redacted]
AUC	area under the plasma drug concentration-time curve
$AUC_{0-\infty}$	area under the plasma drug concentration-time curve extrapolated from time t to infinity
[redacted]	[redacted]
AUEC	area under the effect curve
[redacted]	[redacted]
BLQ	below the limit of quantitation
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
CRF	case report form
CSR	clinical study report
[redacted]	[redacted]
CU	clinical unit
CV	coefficient of variation
DBP	diastolic blood pressure
DMPK	drug metabolism and pharmacokinetics
ECG	electrocardiography, electrocardiogram
EOT	end of trial
ET	early termination
GM	geometric mean
FSH	follicle-stimulating hormone
GMR	geometric mean ratio
IA	interim analysis
IgE	immunoglobulin
IMP	investigational medicinal product
IVIVC	in vitro-in vivo correlation
MedDRA	medical dictionary for regulatory activities
NPRS	numeric pain rating scale
[redacted]	[redacted]
PDSS	post-injection delirium/sedation syndrome

Abbreviation	Term
PFS	prefilled syringe
PK	pharmacokinetics
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAP	statistical analysis plan
[redacted]	[redacted]
SBP	Systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SRC	safety review committee
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
[redacted]	[redacted]
WHO	world Health Organization
WO	washout
WOCBP	women of childbearing potential
λ_z	terminal rate constant

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study TV44749-NPC-10205, (A Multi-center, Open-label, Randomized, Parallel-group Trial to Characterize the Pharmacokinetics of Three sc Olanzapine Extended-release Formulations (TV-44749) with Different Release Rates Following Single Administration in Participants with Schizophrenia or Schizoaffective Disorder) with the purpose of establishing in vitro/in vivo correlation (IVIVC). This SAP was written in accordance with SOP GSD-SOP-702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol with amendment 01 (version date: 11 May 2024) for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

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

1. TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

1.1. 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 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) • $AUC_{0-\infty}$ 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[a]) • 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 [a])
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}) (day 4 to day 13) • Apparent plasma terminal elimination rate constant (λ_z) over the 216-hour period (9 days) following single-dose administration of ZYPREXA im (day 4 to day 13)

[a] Day R29 is considered inclusive when referencing the completion of Period 3 assessments. Thus, for the purpose of analysis, assessments associated with Period 3 are defined from Day R1 up to and including the assessments performed at Day R29 that are prior to returning a participant to antipsychotic treatment (see footnote b, Table 5 from the study protocol).

1.2. Primary Estimand

For the primary objective the estimand is described by the following attributes:

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

antipsychotic treatment (except for oral aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone), meeting all trial eligibility criteria, have received Zyprexa im during day 4, and have no intercurrent events which could adversely affect the calculation of the PK parameters over the 84-day olanzapine sc treatment and follow-up periods (day R1 to day R84).

b. Endpoints – see parameters in Section 1.1.

c. Treatment – the 3 formulations of Olanzapine 425 mg for Extended-release Injectable Suspension as follows: TV-44749 425 mg Fast-D, TV-44749 425 mg to-be-marketed formulation, TV-44749 425 mg Slow-C.

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

Rationale for estimand is to characterize the pharmacokinetics (PK) of 3 olanzapine extended-release sc formulations (TV-44749) 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.

1.3. Secondary Estimand(s)

There are no secondary estimands defined for this trial.

1.4. Exploratory Objectives and Endpoints

The exploratory objectives and measures are presented in the table below:

Exploratory Objectives	Measures/Parameters
[redacted]	[redacted]

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[a]) • Change in clinical laboratory parameters (chemistry, hematology) from baseline to the end of period 3 (day R1 to day R29[a]) • 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[a]) • 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[a]) • Number (%) of participants who reported use of concomitant medications from baseline to the end of period 3 (day R1 to day R29[a]) • Number (%) of participants who discontinued from the trial for any reason from baseline to the end of period 3 (day R1 to day R29[a]) • 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[a]) • [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 (screening to day R84) • Use of concomitant medication during trial participation (screening to day R84) • Discontinuation for any reason from enrollment until end of trial (day 1 to day R84) • Discontinuation due to an adverse event from enrollment until end of trial (day 1 to day R84)
[redacted]	[redacted]

Exploratory Objectives	Measures/Parameters
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a multi-center, open-label, randomized, parallel-group trial to characterize the pharmacokinetics (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 of the study protocol 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 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 criteria will be enrolled and 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 of the trial protocol). 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 (Table 2 of the trial protocol), 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 of the trial protocol for cohort 1A and Table 4 of the trial protocol 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.

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 first 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 of the trial protocol).

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 of the study protocol) 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.

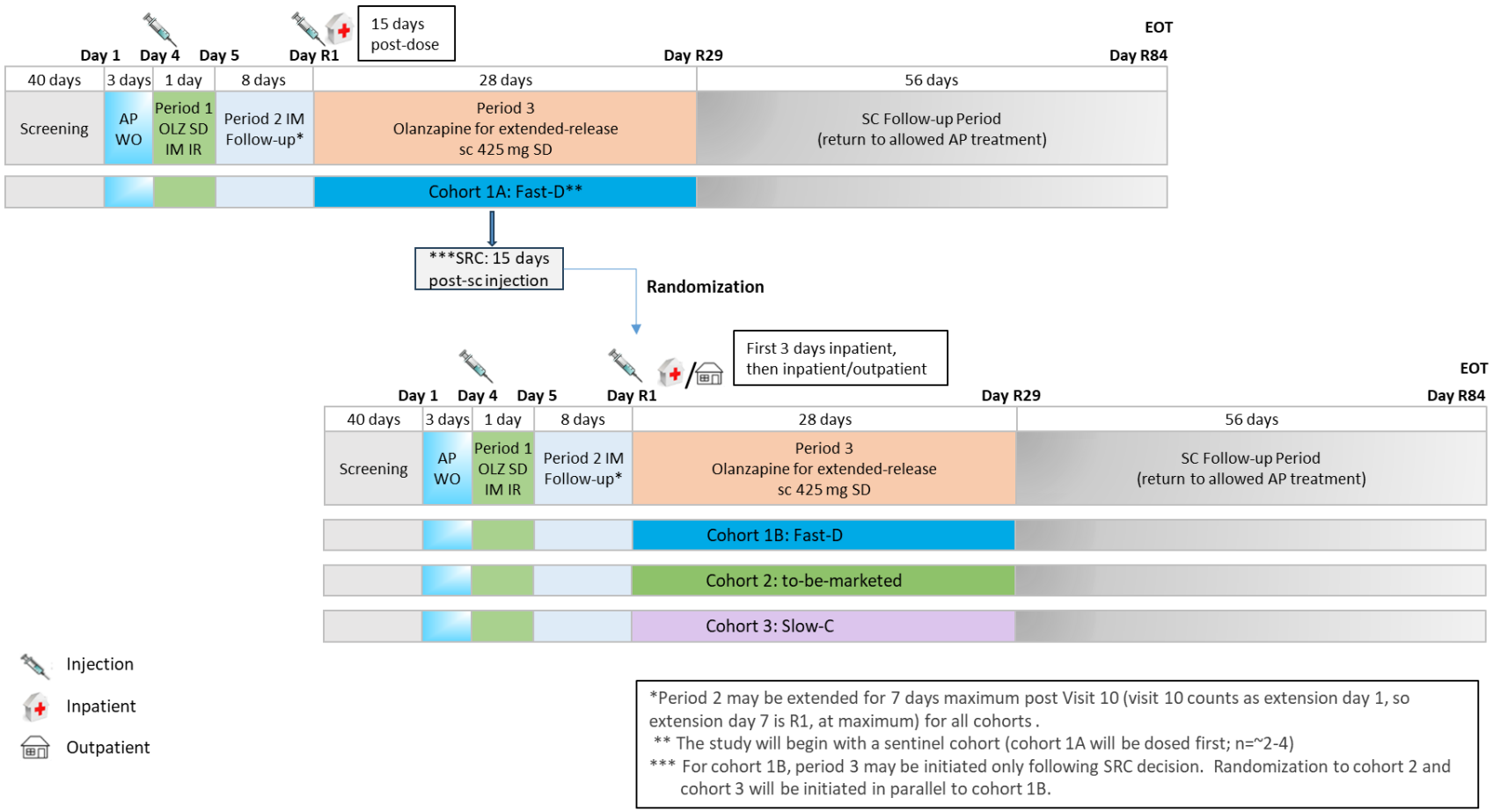
Following completion of period 3, all participants enter a 56-day follow-up period during which they will resume treatment with 1 of the allowed antipsychotics (aripiprazole, risperidone, paliperidone, quetiapine, or lurasidone) at the Investigator's discretion (day R29 to day R84).

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 of the trial protocol).

The trial schematic diagram is presented in Figure 1. Trial procedures and assessments with their time points during screening, the antipsychotic washout period and treatment period 1 are presented in Table 1 of the trial protocol. Trial procedures and assessments with their time points during period 2 are presented in Table 2 of the trial protocol. Trial procedures and assessments during treatment period (period 3) for cohort 1A (Fast-D formulation) are presented in Table 3 of the trial protocol, and for cohorts 1B (Fast-D formulation), 2 (To-be-marketed formulation), and 3 (Slow-C formulation) are presented in Table 4 of the trial protocol. Trial procedures and assessments during the follow-up period following administration of sc olanzapine for extended-release are presented in Table 5 of the trial protocol.

2.1.1. 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

2.2. Randomization and Blinding

This is an open-label, randomized, parallel-group study. Qualified subjects who meet the trial inclusion criteria and do not meet exclusion criteria are enrolled into the trial. Approximately 2-4 participants will be assigned into the sentinel cohort 1A (TV-44749 425 mg Fast-D), which will be the first cohort to proceed to Period 3, TV-44749 treatment period. Upon completion of the first 15 days in Period 3 (day R1 to day R15, inclusive) following sc administration of olanzapine Fast-D formulation to cohort 1A participants, a SRC will review all available safety and tolerability data from the beginning of the study, as described in Section 2.1. If no safety concern is raised by the SRC, randomization will be initiated to cohort 1B (TV-44749 425 mg Fast-D, n~16), cohort 2 (TV-44749 425 mg to-be-marketed, n~20) and cohort 3 (n~20) at a randomization ratio of 4:5:5.

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

2.2.1. Maintenance of Randomization

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

2.2.2. Blinding and Unblinding

This is an open-label trial. The study will be treated as open-label for all cohorts.

2.3. Data Monitoring Committee

2.3.1. Safety Review Committee

An SRC comprising the Sponsor's clinical trial physician, clinical leader, PV physician, and other relevant experts defined in the SRC Charter 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.

2.3.2. Adjudication Committee

In the case of a suspected post-injection delirium/sedation syndrome (PDSS) event, an adjudication committee will be summoned to review all cases of suspected PDSS to determine if each case fulfills all five 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.

Further details are provided in Section 10.2 of the trail protocol.

2.4. Sample Size Determination

The planned sample size for this trial is approximately 95 enrolled adult participants in order to achieve approximately 60 completers (approximately 20 participants per each single-dose Olanzapine extended-release 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 concentration/pharmacokinetic data for an IVIVC analysis and modelling to be carried out by an external service provider, 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 of the trial protocol), or has events that would affect the calculation of PK parameters, an additional patient may be enrolled to ensure that at least 20 participants per group have completed the PK portion of the trial and can be considered evaluable for the primary analysis of the trial (see Section 3.2).

2.5. Sequence of Planned Analyses

2.5.1. Planned 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 2.3.1.

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

2.5.2. Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of trial as defined in the trial protocol.

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

3. ANALYSIS SETS

3.1. 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.

3.2. 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 intercurrent events or deviations that would affect the calculation of PK parameters. This analysis set will be used for all PK summaries. In the PK 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.

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 (e.g. parameters that were based on partial data) will be excluded from the primary analysis. Any exclusion of PK parameters will be justified in the PK parameter raw data file provided by the DMPK. A Data Review meeting will be held prior to database lock of the trial, and any protocol deviations that could potentially impact the PK will be identified. In case intercurrent events which could adversely affect the calculation of the PK parameters for any of the participants are identified, the participant may be excluded from the primary and secondary PK analyses. A leakage score of 4 after TV-44749 sc administration will result in exclusion from the PK analysis set. Data from excluded participants will be included in the relevant listing.

3.3. Safety Analysis Set

The safety analysis set will include all participants who receive at least 1 dose of IMP (ZYPREXA im or one of the Olanzapine sc extended-release formulations). 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.

3.4. Pharmacogenomics Analysis Set

[redacted]

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. For pharmacokinetic data, descriptive statistics will also include geometric mean (GM) and % geometric CV. Descriptive statistics for categorical variables include number of subjects (n) and percentages, missing category will be displayed as appropriate.

4.2. Specification of Baseline Values

Baseline values are defined as the last observed data before the first dose of the trial drug, i.e. Zyprexa im or one of the sc Olanzapine extended-release formulations. For Zyprexa im, the assessments which will serve as baseline values will be based on samples collected up to and including Day 4, as long as the samples are collected prior to dosing of ZYPREXA im. For Olanzapine extended-release formulations, Day R1 (pre-dose of the sc Olanzapine extended-release formulations) assessments will serve as baseline values, except for clinical scales ([redacted], [redacted], [redacted] and [redacted]) to which day 12 will serve as baseline.

4.3. Handling Withdrawals and Missing Data

Missing data will not be imputed. In general, for all variables only the observed data from the patients will be used in the statistical analyses.

4.4. Trial Days and Visits

The trial will consist of a screening period (up to 40 days), a 3-day AP 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) with an optional extension of additional maximum 7 days, 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).

Trial days will be numbered relative to the WO period on day 1 (ie, ..., –2, –1, 1, 2, ...; with day 1 of the washout period of antipsychotics and day –1 being the day before the first day of washout) and the end of the screening period. The trial days will be numbered relative to the TV-44749 administration on day R1 in Period 3 (ie, R1, R2, ...; with day R1 of the TV-44749 administration period and day R29 to day R84 of the follow-up period).

For by visit (time point) summaries, if there are multiple assessments at a post-baseline visit (time point), then the last non-missing assessment at that visit (time point) will be used for the summary (this includes both scheduled and unscheduled assessments). In general, for the by-visit summaries, Early-Termination (ET) visit will be presented as a separate visit, per study periods as follows; if the ET visit occurred between Day 4 to Day R1 (prior to the administration of TV44749) it will be mapped to "ET visit prior to TV44749 administration", if it has occurred between day R1 to day R29 it will be mapped to "ET visit during TV44749 treatment" and in case ET visit has occurred between Day R30 to Day R84 it will be mapped to "ET visit during TV44749 follow-up period". For the 'at any time' summary statistics in the shift tables and in the

presentation of Potentially Clinically Significant (PCS) summaries, all visits will be used (including unscheduled visits).

5. STUDY POPULATION

5.1. General

The enrolled analysis set will be used for all study population summaries unless otherwise noted. Summaries will be presented by cohort and overall, as appropriate.

5.2. Patient Disposition

Data from patients screened and screened but not enrolled (with reason for no enrollment) will be summarized overall using patient counts only. Participants who were enrolled in Period 1, patients who continued to Period 2, patients who are randomized in Period 3, patients randomized but not treated in Period 3, pharmacokinetic, pharmacogenomics and safety analysis sets, treatment completers (patients who have completed the procedures and assessments required in period 3, i.e 28 days after TV44749 administration), patients who complete the trial (patients who have completed the procedures and assessments requires through treatment and follow-up period), patients who withdraw from the study, patients who discontinue the trial prior to TV44749 formulation administration, patients who discontinue the trial during Period 3 (day R1 to day R29) and patients who discontinue the trial during the Follow-up period (day R30 to day R84) will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics. The summary will be based on all patients.

5.3. Demographics and Baseline Characteristics

The continuous variables of patient age, weight, height, and body mass index (BMI) will be summarized using descriptive statistics. The categorical variables of patient sex, race, ethnicity, and smoking status will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each preferred term and SOC category. Summaries will be presented by cohort and for all patients.

5.5. Prior Therapy and Medication

Any prior therapy, medication, or procedure a patient has had within 30 days before study drug administration will be recorded on the CRF. Trade name or INN, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

5.6. Electrocardiography

Electrocardiogram findings (normal, abnormal not clinically significant, abnormal clinically significant, and missing) in screening period, AP WO period (day 3) and on day R1 in period 3 will be summarized using descriptive statistics.

5.7. Childbearing Potential and Methods of Contraception

For female patients, information related to childbearing potential, and menopause will be collected at the time points specified in Table 1 to Table 5 of the trial protocol. Data will be listed.

For female and male patients, methods of contraception will be collected at the screening period. Data will be listed.

5.8. Trial Protocol Deviations

Data from patients with any important protocol deviations during the trial will be summarized for overall and each category using descriptive statistics. All protocol deviations will be listed.

6. PHARMACOKINETIC ANALYSIS

6.1. General

The pharmacokinetic analysis set will be used for all plasma concentration descriptive summaries, graphs, and listings and for PK parameter listings, unless otherwise stated. The pharmacokinetic analysis set will be used for parameter descriptive summaries, graphs, and statistical analyses, unless otherwise stated. No formal inferential statistical analyses of PK data are planned.

6.2. Values below the Limit Quantification or Missing

The lower limit of quantitation (LLOQ) is 10 pg/mL for the olanzapine formulations (ZYPREXA IM or sc extended-release formulations).

For summary displays of pharmacokinetic concentration data, values below the limit of quantitation (BLQ) will be imputed as ½*lower limit of quantitation (LLOQ). If the mean concentration at a timepoint is less than LLOQ, then "BLQ" will be reported in place of summary statistics. In addition, BLQ values will be treated as 0 in plasma concentration data figures (individual subject plot and mean concentration plots).

For calculating PK parameters, a BLQ value at time 0, at a sampling time before the 1st quantifiable plasma drug concentration, or at a sampling time between 2 quantifiable concentrations will be treated as 0. All other BLQ values (ie, those occurring at the end of the profile) will be treated as missing for the computation of pharmacokinetic parameters.

In data listings, the data will be reported as is (ie, no imputation).

6.3. Pharmacokinetic Concentrations

Plasma concentration data will be individually listed and summarized by nominal time point 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).

6.4. Graphical Summaries

Linear and semi-logarithmic plots of mean (± SD) plasma concentration by scheduled sampling time will be provided. Plots will show time in hours for ZYPREXA IM and time in days for olanzapine sc extended-release formulations. Plots will be presented separately for ZYPREXA IM, and for olanzapine sc extended-release formulations by cohort (including a separate plot up until day R29).

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by patient (one patient per page). For each patient, there will be a separate plot for ZYPREXA IM and olanzapine extended-release formulation. Plots will show time in hours for ZYPREXA IM (starting with day 4) and days for olanzapine extended-release formulations (starting with R1).

6.5. Pharmacokinetic parameters

Pharmacokinetic parameters will be calculated from individual olanzapine plasma concentrations, actual elapsed time profiles by non-compartmental methods, when possible. The PK parameters detailed in Table 1 will be calculated following ZYPREXA im administration. Additional PK parameters may be calculated if deemed necessary.

Table 1: Description of Pharmacokinetic Parameters Following Zyprexa IM Administration

Pharmacokinetic Parameter	Description
C_{max}	Maximum observed plasma drug concentration (Cmax) over the 24-hour period following single-dose administration of ZYPREXA im (day 4), obtained directly from the observed concentration time data
AUC_{0-t}	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); calculated by lin- up log down trapezoidal method
λ_z	apparent plasma terminal elimination rate constant (λ_z), estimated by linear regression of the terminal portion of the log-concentration by time curve;
[redacted]	[redacted]
[redacted]	[redacted]
$AUC_{0-\infty}$	AUC extrapolated to infinity ($AUC_{0-\infty}$) calculated from last measurable plasma concentration following single dose administration of ZYPREXA im (pre-dose ZYPREXA im to 216 hours post im administration); calculated by linear-up log-down method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The PK parameters detailed in Table 2 will be calculated following sc olanzapine extended -release formulation administration. Additional PK parameters for olanzapine extended -release formulation may be calculated if deemed necessary.

Table 2: Description Of Pharmacokinetic Parameters Following sc Olanzapine Extended-Release Formulation Administration

Pharmacokinetic Parameter	Description
C_{max}	Maximum observed plasma drug concentration (Cmax) over the 84 day period following single-dose administration of 1 of the sc formulations to EOT (day R1 to day R84)
[redacted]	[redacted]
AUC_{0-t}	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); calculated by lin- up log down trapezoidal method.
$AUC_{0-\infty}$	AUC extrapolated to infinity ($AUC_{0-\infty}$) calculated from last measurable olanzapine plasma concentration following singledose administration of 1 of the sc formulations from time 0 to EOT (day R1 to day R84); calculated by lin- up log down trapezoidal method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Pharmacokinetic parameters will be individually listed and summarized for each treatment and cohort (ZYPREXA im, and Olanzapine sc extended-release formulations) using descriptive statistics (n, mean, standard deviation, geometric mean [if appropriate], geometric coefficient of variation (%CV) [if appropriate], median, minimum, and maximum).

7. SAFETY ANALYSIS

7.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented by cohort and treatment (including any of the IMPs; ZYPREXA im or Olanzapine sc extended-release formulations) and overall, unless otherwise stated.

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.

7.2. Adverse Events

Adverse events will be collected and recorded from the time a patient signs the informed consent to the end of follow-up period (day R84).

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be presented for all adverse events occurring after the first dose of IMP (ZYPREXA im and/or Olanzapine extended-released formulation), as overall and by Common Terminology Criteria for Adverse Events [CTCAE] grade, including AEs determined by the investigator to be related to IMP and/or medical device (defined as related or with missing relationship),serious adverse events and injection site adverse events. Adverse events missing relationship to study drug will be included in the study drug related summary. A summary of occurrence of adverse events, serious adverse events and injection site adverse events will be presented separately for period 1 + 2 (from the administration timepoint of Zyprexa IM until and not including the administration timepoint of Olanzapine extended-release formulation), for period 3 (day R1 to day R29) and for the follow up period (day R30 to day R84). The occurrence of adverse events, serious adverse events and injection site adverse events will also be listed for the Wash-Out period (from day 1 to the administration of Zyprexa im). The incidence of adverse events will be summarized using descriptive statistics by SOC and PT. For the incidence of adverse events, patients are counted only once in each SOC category, and only once in each PT category. For the summary by grade, patients are counted at the worst grade.

Protocol defined adverse event of special interest (PDAESI) (section 8.4.8 of the study protocol) will also be summarized and presented by cohort separately for period 1 + 2 (from the administration timepoint of Zyprexa IM until and not including the administration timepoint of Olanzapine extended-release formulation), for period 3 (day R1 to day R29) and for the follow-up period (day R30 to day R84). PDAESI that required reporting to Sponsor's Global PV for evaluation may be presented in a separate summary table.

7.3. Deaths

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

7.4. Clinical Laboratory Tests

Laboratory test results will be presented in standard international (SI) units.

Clinical laboratory tests will include chemistry, hematology, coagulation, and urinalysis.

Summary statistics for chemistry, hematology and coagulation laboratory tests will be presented at baseline and each visit that it is measured. Laboratory values and changes from baseline to each visit will be summarized using descriptive statistics.

For chemistry, hematology, coagulation and urinalysis, shifts (below, within, and above the normal range) from baseline to each visit that is measured will be summarized using subject counts.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics with the criteria specified in Table 3.

Table 3: Criteria for Potentially Clinically Significant Laboratory Values

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

7.4.1. 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, will be included in adverse events reporting as a 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 <2 × ULN of alkaline phosphatase).

All incidences will be listed.

7.4.2. Other Clinical Laboratory Tests

7.4.2.1. 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. Results will be presented in the data listings.

7.4.2.2. 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]). Results will be presented in the data listings.

For pregnancy testing, see Section 5.7.

7.4.2.3. 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 of the trial protocol. Any participant who becomes pregnant during the trial will be withdrawn. Procedures for reporting the pregnancy are provided in Section 8.5 of the trial protocol. Results will be presented in the data listings.

7.4.2.4. Alcohol and Drug Screen

A serum and urine drug screen and a serum and breathalyzer alcohol screen results will be presented in the data listings.

7.5. Neurological and Clinical Symptoms Measures

The following neurological and clinical symptoms measures ([redacted] SAS, [redacted] CGI-S, and [redacted]) will be administered by a qualified rater at the time points specified in Table 1 to Table 5 of the trial protocol.

7.5.1. [redacted]

[redacted]

[redacted]

[redacted]

7.5.2. [redacted]

[redacted]

[redacted]

7.5.3. [redacted]

[redacted]

[redacted]

7.5.4. [redacted]

[redacted]

[redacted]

7.5.5. [redacted]

[redacted]

7.5.6. [redacted]

[redacted]

7.6. Assessment of Local Tolerability and Pain

Local tolerability assessments should be performed after each administration of the IMPs (ZYPREXA im or any of the Olanzapine extended-release sc formulations) (Table 1 to Table 5 of the trial protocol) 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 4 below. 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?".

Injection site reactions 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 of the trial protocol.

The local tolerability (injection site findings and pain) will be summarized at each timepoint and visit, when applicable, for each IMP (ZYPREXA im and Olanzapine extended-release formulations) separately, using descriptive statistics as categorical data.

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

Test	Response
Erythema[a]	Absent Surface diameter 5 mm to ≤50 mm Surface diameter >50 to ≤100 mm Surface diameter >100 mm
Induration/swelling[a]	Absent Surface diameter 5 mm 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 diameter should be recorded.	Yes/No <5 mm 5 to 15 mm >15 mm

[a] The decision on whether any of the above meet adverse event criteria and as such should be recorded as an adverse event is per the investigator's clinical judgment.
AESI=adverse event of special interest; NPRS=numeric pain rating scale.

7.6.1. Overall Tolerability

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 will be provided. A summary will be provided as part of the AEs and disposition summaries, separately for period 1+2 up until the Olanzapine extended-release formulation administration, for period 3 (day R1 to day R29), and for the Follow-up period (day R30 to day R84).

7.7. Leakage Assessment

Immediately after injection 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 5.

Table 5: 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

Leakage will be summarized using descriptive statistics of the rating scale (0 to 4).

7.8. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 1 to Table 5 of the trial protocol.

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 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 judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 8.4.4 of the trial protocol.

7.9. Vital Signs

Summary statistics for vital signs including physical measurements (height, weight, and calculation of BMI), body temperature, respiratory rate, supine or semi-supine pulse rate and blood pressure (systolic and diastolic), and their orthostatic changes will be presented at the time points detailed in Table 1 to Table 5 of the trial protocol. Vital signs values and changes from baseline to the end of period 3 will be summarized using descriptive statistics.

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 of the trial protocol.

Summaries of potentially clinically significant abnormal values will include all post baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal values for vital signs variables will be summarized using descriptive statistics with the criteria specified in Table 6 below.

Table 6: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value
Systolic blood pressure (SBP)	≥180 mm Hg
	≤90 mm Hg
Diastolic blood pressure (DBP)	≥105 mm Hg
	≤50 mm Hg
Pulse (HR)	≥120 bpm
	≤50 bpm
Orthostatic Change –decrease in systolic blood pressure between sitting/supine measurement to 2 to 5 minutes of standing measurement	A decline of ≥ 20 mm Hg in systolic blood pressure
Orthostatic Change – change in diastolic blood pressure between sitting/supine measurement to 2 to 5 minutes of standing measurement	A decline of ≥ 10 mm Hg in diastolic blood pressure
Body temperature	≥38.3°C

bpm = beats per minute; mm Hg = millimeters of mercury.

7.10. Electrocardiography

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

Shifts (normal and abnormal) from baseline to each visit that it is measured will be summarized using patient counts. For overall finding, the summary will use the worst post-baseline finding for the patient (the abnormal finding if there are both normal and abnormal findings). Summary statistics for ECG variables will be presented at baseline and each visit. Actual values and changes from baseline to each visit will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values for ECG variables will be summarized using descriptive statistics with the criteria specified below.

- QT interval corrected using Fridericia's formula (QTcF) values >450 msec, or >480 msec, or >500 msec.
- QTcF change from baseline values >30, or >60.
- PR change from baseline ≥25% and value >200.
- QRS change from baseline ≥25% and value >110.
- Heart rate value <60 bpm or >100 bpm.

The number (%) of participants with QTcF change from baseline values >30, or >60, will be also presented separately for Period 3 (day R1 to day R29)

7.11. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. All concomitant medications will be coded using the WHO Drug.

The incidence of concomitant medications and therapies will be summarized using descriptive statistics by therapeutic class category and PT. Patients are counted only once in each therapeutic class, and only once in each PT category. A separate summary will be provided for the screening period, for period 1 and period 2 (day 4 up until day R1), for period 3 (day R1 to day R29) and for the Follow-up period (day R29 to day 84).

8. PHARMACOGENETIC AND BIOMARKER ANALYSIS

[redacted]

9. PLANNED INTERIM ANALYSIS

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 2.3.1.

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

10. STATISTICAL SOFTWARE

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

11. REFERENCES

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