STATISTICAL ANALYSIS PLAN

PROTOCOL INDV-7000-401

An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of 180mg Risperidone Subcutaneous Injection (PERSERIS™) Following a Switch from 6 mg Oral Risperidone in Patients with Clinically Stable Schizophrenia

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1 LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AIMS	abnormal involuntary movement scale
ATC	anatomical therapeutic chemical
BARS	Barnes Akathisia rating scale
BLQ	below the limit of quantification
bpm	beats per minute
CGI-S	clinical global impression scale
CSR	clinical study report
C-SSRS	Columbia-suicide severity rating scale
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
FSH	follicle stimulating hormone
GPSS	general psychopathology scale score
HbA1c	haemoglobin A1c
ICF	informed consent form
ISGS	injection site grading scale
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
mg	Milligram
mm	Millimeter
n	number of non-missing observations
NSS	negative scale score
PANSS	positive and negative syndrome scale
PK	pharmacokinetic/pharmacokinetics
PSS	positive scale score
PT	preferred term
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus scale

SC	Subcutaneous
SD	standard deviation
SI	Système International
SOC	system organ class
TEAE	treatment emergent adverse event
VAS	visual analog scale
WHO-Drug	world health organization drug classification

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods, including pharmacokinetic (PK) analyses, to be used during the analysis and reporting of data collected under Protocol INDV-7000-401. This version of the SAP is developed using the protocol Version 1.0, dated 14Mar2019, the corresponding protocol administrative letters, dated 01Jul2019 and 30Aug2019, and the electronic case report form (eCRF).

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Post-hoc or unplanned analyses performed and not planned in the SAP will be documented in the clinical study report (CSR).

2.1 Study Design

This is an open-label study designed to assess the safety, tolerability, PK, and efficacy of 180 mg of PERSERIS in subjects with clinically stable schizophrenia (as determined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria).

Approximately 65 subjects will be screened with 25 eligible subjects receiving study treatment, in order to have 15 evaluable subjects for the PK analyses.

The study will enroll subjects who are currently on a stable dose of 5 mg or 6 mg of oral risperidone daily. Any daily or twice daily dosing combination will be acceptable (i.e. 4/2, 3/2). Subjects will provide written informed consent before any protocol related procedures commence (i.e., before screening procedures). Potential subjects will be screened considering the inclusion and exclusion criteria, and those who have been successfully screened will be enrolled in the study. Only extensive CYP2D6 metabolisers will be included in the study. Poor, intermediate and ultra-rapid CYP2D6 metabolisers will be excluded from the study based on CYP2D6 genotyping results from blood sampling at Screening.

All subjects will be stabilized on 6 mg daily (3 mg risperidone will be administered twice a day approximately 12 hours (±30 minutes) apart) for 5 days. After 5 days, oral risperidone dosing will be stopped and PERSERIS treatment will be initiated.

After completion of the stabilization period, all subjects will receive 1 dose of 180 mg PERSERIS (each 180-mg dose will be administered as two 90-mg subcutaneous [SC] injections) every 28 days in the abdominal region over 3 months. The 2 injections of 90 mg will be administered in different quadrants of the abdomen at the same clinic visit. Injection sites will be rotated to minimize irritation. An additional monthly dose of 180 mg (given as two 90-mg SC injections) will be administered at an alternate site (back of upper arm) as a 4th dose; subjects will receive 1 injection of 90 mg in each arm at the same clinical visit.

Dosing will be split into 2 sub-groups: 5 sentinel subjects and 20 remainder subjects. A safety and tolerability review of the data from the first 5 subjects from Day 1 to Day 15 (after receiving the 1st dose of 180 mg) will be conducted. If no limiting safety concerns are found, then the first 5 subjects will continue with the study and the remaining 20 subjects will be enrolled into the study.

Subjects will attend the clinical unit on separate occasions: one initial screening visit, an initial inpatient stay of 8 days [5-day stabilization period, plus 1st PERSERIS injection], three 4-day inpatient stays [for 2nd, 3rd and 4th PERSERIS injections] and a total of 33 outpatient visits followed by a final study follow-up phone call.

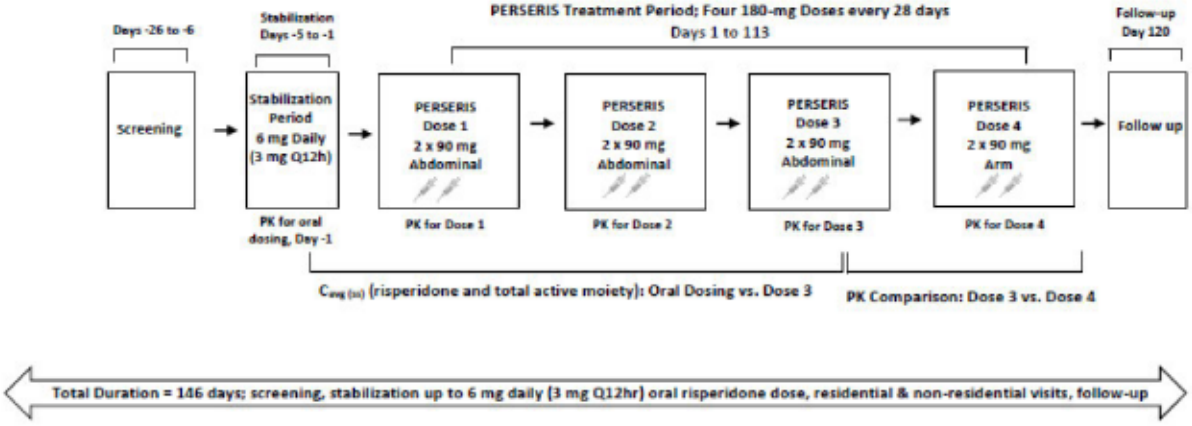
Subjects will report to the clinic on the non-residential days at approximately the same time in the morning, with an allowed ±1 day visit window.

At the end of the study, subjects will be evaluated and prescribed an appropriate maintenance antipsychotic. The appropriate maintenance dose will be determined by the physician's clinical judgment.

The total duration of the study for each subject, including Screening, Treatment, and Follow-up, will be approximately 146 days, divided as follows:

- Screening: up to 21 days (Days -26 to -6).
- Treatment:
  - Stabilization with 6 mg oral risperidone daily: 5 days (Days -5 to -1); 3 mg risperidone will be administered twice a day approximately 12 hours apart; will be stopped prior to initiating PERSERIS treatment.
  - PERSERIS treatment period, dosed every 28 (+/- 1) days: Days 1 to 113, 4 doses of 180 mg PERSERIS, each administered as two 90-mg SC injections.
- Follow-up: 7 days (Days 114 to 120).

The overall study schema is shown in the diagram below:



Please refer to Appendix 1 to Appendix 5 for schedules of events for screening and oral risperidone dosing, and PERSERIS Doses 1, 2, 3, and 4.

3 STUDY OBJECTIVE

The primary study objective is:

- To evaluate the PK profiles of risperidone, 9-hydroxyrisperidone and total active moiety after 3 monthly 180-mg doses (each 180-mg dose will be administered as two 90-mg SC injections) of PERSERIS in subjects with clinically stable schizophrenia after switching treatment from an oral risperidone dose of 6 mg/ day.

The secondary study objectives are:

- To evaluate efficacy and the maintenance of stability following a switch from daily 6 mg oral risperidone to monthly 180 mg (2 x 90 mg) PERSERIS SC injections,

- To evaluate the safety and tolerability of PERSERIS SC injections,

- To evaluate whether administration of PERSERIS at an alternate injection site (back of upper arm) provides an adequate exposure to total active moiety throughout the 28-day dosing interval and determine the PK, efficacy, safety and tolerability of administering PERSERIS at an alternate site (back of upper arm) compared with the abdominal region.

4 STUDY VARIABLES

4.1 Primary Endpoint

- Cavg(ss) for risperidone and total active moiety after oral and SC administration.

4.2 Secondary Endpoints

- All other PK parameters including the PK parameters derived after the 4th dose (at an alternate site) will be considered as secondary endpoints.

- Adverse events (AEs), local injection-site tolerability (i.e., injection-site reactions), concomitant medications, changes in clinical laboratory results, vital sign measurements, 12 lead electrocardiographic (ECG), body weight and monitoring of extrapyramidal symptoms (EPS) using neurological and clinical symptom assessments (Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], Barnes Akathisia Rating Scale [BARS], and the Columbia-Suicide Severity Rating Scale [C-SSRS]).

- Clinical Outcome Measurements: Change from baseline in Positive and Negative Syndrome Scale (PANSS) scores (including the total score, the Positive sub-scale score, the Negative sub-scale score and the General Psychopathology scale score) and Clinical Global Impression Scale for Severity of Illness (CGI-S) scores.

5 STUDY POPULATIONS

5.1 Enrolled Population

The enrolled population includes subjects who sign the informed consent form (ICF) and are assigned a subject number.

5.2 Safety Population

The safety population includes subjects who receive at least one PERSERIS injection.

5.3 Pharmacokinetic Population

The PK Population includes subjects who receive oral risperidone or at least one dose (i.e., 2 injections of 90 mg) of PERSERIS and provide an adequate number of blood samples (as determined by a pharmacokineticist) for determination of risperidone, 9-hydroxyrisperidone and total active moiety (risperidone + 9-hydroxyrisperidone) PK parameters.

The primary endpoint for the study will be the measurement of Cavg (ss) for risperidone and total active moiety after oral and SC administration. For the primary analysis, only the data from those subjects who receive 3 doses of PERSERIS and provide an adequate number of blood samples for determination of Cavg (ss) for risperidone and total active moiety will be considered.

5.4 Efficacy Population

The efficacy population consists of subjects who receive at least one PERSERIS injection and have at least one post-dose efficacy observation.

6 General Considerations and Data Handling Rule

PK listings will be based on the PK population. The listing of PERSERIS exposure will be based on the safety population. All other listings will be based on the enrolled population.

Unless otherwise specified, descriptive statistics will include the number of non-missing observations (n), mean, standard deviation (SD), median, and minimum and maximum values for continuous/quantitative data, or frequency counts and percentages for categorical/qualitative data. Unless otherwise noted, denominators used in the calculations of percentages will be defined according to the analysis population used.

6.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date (i.e., Day 1) is defined as the day of the first PERSERIS dosing. Study day for any assessment or event will be calculated as below:

- If the date of the event is on or after the reference start date then: Study Day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date then: Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings and study day will not be calculated.

6.2 Baseline

Baseline is defined as the last non-missing value prior to the first PERSERIS dosing, including unscheduled and repeated assessments. If the last non-missing measurement and the first PERSERIS dosing were done on the same date, time of day of the assessment will be compared to time of PERSERIS dosing to determine the baseline status of the measurement; if time of the measurement was not collected, measurements done on the same date as the first PERSERIS dosing will be considered pre-dose. Since start and end times were not collected for AEs and medications, AEs and medications commencing on the first PERSERIS dosing date will be considered post-dose.

6.3 Windowing Conventions

No windowing will be used for summaries or analyses. All data will be summarized and analyzed according to the visit denoted on the eCRF.

6.4 Repeated or Unscheduled Measurements, and Early Termination Data

For summaries and analyses, multiple observations within visits for a given parameter will be handled as follows:

- For the baseline visit, all collected data (scheduled, unscheduled, retest) will be considered and the last observation before first PERSERIS dosing will be flagged as the baseline observation.
- For post-baseline visits, the latest available observation will be used, either from the originally scheduled testing or retesting. Data from unscheduled visits will not be considered.

- If multiple observations for a given visit have the same date/time, the mean (arithmetic or geometric, as appropriate) of the observations will be used.

Data recorded on the Early Termination eCRF will be mapped to the nominal visit that corresponds to the study day of the early termination; if no such visit exists, the visit mapping will be "unscheduled."

Listings will include all scheduled, unscheduled, retesting, and early termination data.

6.5 Missing Data

Missing safety or efficacy data will not be imputed. When calculating a total score or sub-scale score for any assessment with more than one item, if one or more items are missing at a visit, then the associated total score will be set to missing.

6.6 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a summary table due to the fact, for example, that a character string is reported for a parameter of numerical type, an imputed value will be used. For example, '< a numeric value' or '<= a numeric value' will be treated as half of that value, and '> a numeric value' or '>= a numeric value' will be treated as the value itself.

7 SUBJECT DISPOSITION

Subject disposition will include the number of subjects in the enrolled population; the number and percentage of subjects who were screen failures; who were in the safety, PK, and efficacy populations; and number and percentage of subjects completing the study (i.e., completing all phases of the study, including the follow-up phone call) and discontinuing the study. For percentages, the number of subjects in the enrolled population will be the denominator for screen failures and the safety population, and the number of subjects in the safety population will be the denominator for the PK and efficacy populations and for subjects completing and discontinuing the study.

Reason for study discontinuation will also be summarized by number and percentage of subjects for each reason reported; for the percentage, the number of subjects who discontinued will be the denominator.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the safety population. The same summary will be repeated for the PK population. Parameters to be included are age, sex, child-bearing potential, race, ethnicity, CYP2D6 genotypes, haemoglobin A1c [HbA1c] at screening (> 8.0%, <= 8.0%), and baseline weight/ height/ body mass index [BMI]. BMI will be calculated as [weight (kg)] ÷ [height (m)]^2.

8.2 Relevant Medical, Surgical, and Psychiatric History

Relevant medical, surgical, and psychiatric history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0, and will be summarized for the safety population.

8.3 Prior and Concomitant Medications

Prior and concomitant medications used within 30 days prior to screening and during the study will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug dictionary (WHO-Drug), Version Global-B3-201903. Prior and concomitant medications will be summarized separately for the safety population. The summary of incidence (number and percentage of subjects reporting the medication at least once) will be sorted alphabetically by medication class (i.e., ATC level 2) and standardized medication name.

Medications that stopped prior to the start of PERSERIS or were taken by subjects who did not start PERSERIS will be considered prior medications. All other medications are defined as concomitant medications.

The below algorithm will be used to decide whether a medication is prior or concomitant in case the end date is missing or incomplete:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of PERSERIS, the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of PERSERIS, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications.

8.4 Protocol Deviations

Protocol deviations identified and recorded will be listed.

9 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 Extent of Exposure

Administration of oral risperidone (including fasting condition 1 hour before and 1 hour after dosing) and PERSERIS will be listed separately. Exposure will be summarized for both treatments separately based on the safety population.

For oral risperidone, total dose, dose duration, average daily dose, and frequency and percentage of subjects with any violation of fasting will be summarized. Oral dose duration (day) will be calculated as date of last dose of oral risperidone - date of first dose of oral risperidone +1. Average daily oral dose (mg/day) will be calculated as total risperidone taken orally (mg)/oral dose duration, where total risperidone taken orally (mg) = 3 * number of morning and evening doses with dose time available. Number and percentage of subject with average daily dose less than 80% (4.8 mg) of expected will be summarized.

For PERSERIS, each dose of 180 mg PERSERIS is administered as two 90-mg SC injections in different locations, and "any issues with study drug administration" is evaluated for each of the two injections. If both injections are administered, a full dose of 180 mg is considered administered. Extent of exposure will be assessed by number of full doses administered (i.e., 1, 2, 3, and 4), summarized as a categorical variable. Number and percentage of subject with number of full doses less than 80% (3.2 doses) of expected will be summarized. Number and percentage of subjects with IMP administration "issues" will be summarized, both overall and by number of issues as a categorical variable.

9.2 Measurement of Treatment Compliance

Treatment compliance is not relevant for this study as all study medication is administered by study personnel.

10 EFFICACY ANALYSES

The efficacy variables are change from baseline in PANSS total score, PANSS subscale scores (i.e., Positive, Negative, and General Psychopathology scale score), and CGI-S score and will be summarized for the efficacy population.

The PANSS total score is the sum of all 30 PANSS items recorded on the eCRF form of PANSS. Scores for each individual item range from 1 to 7; therefore, the range of the PANSS total score is 30 to 210.

The Positive scale score (PSS) is the sum of the 7 items associated with the Positive scale of the PANSS instrument; the range is 7 to 49. The PSS is defined as:

PSS = P1+P2+P3+P4+P5+P6+P7

The Negative scale score (NSS) is the sum of the 7 items associated with the Negative scale of the PANSS instrument; the range is 7 to 49. The NSS is defined as:

NSS = N1+N2+N3+N4+N5+N6+N7

The General Psychopathology scale score (GPSS) is the sum of the 16 items associated with the General Psychopathology scale of the PANSS instrument; the range is 16 to 112. The GPS is defined as:

GPSS = G1+G2+G3+G4+G5+G6+G7+G8+G9+G10+G11+G12+G13+G14+G15+G16

For the PANSS total score and all subscale scores, change from baseline for each score will be summarized by visit (i.e., Day x / Dose x). For all scores, if any item is missing, the score is set to missing.

The CGI-S score, ranging from 1 to 7, is recorded on the eCRF form of CGI-S. Change from baseline will be summarized by visit.

Mean [+/- standard error (SE)] change from baseline along time for all the above efficacy variables will be plotted.

11 SAFETY ANALYSES

The safety analysis will be performed using the safety population. Safety variables include treatment-emergent adverse events (TEAEs), local injection tolerability, clinical laboratory parameters, vital signs, ECG parameters, physical examination, AIMS, SAS, BARS, and C-SSRS.

11.1 Treatment Emergent Adverse Events

All AEs will be coded using MedDRA, Version 22.0.

A TEAE is an AE that starts or worsens in frequency or severity on or after initiation of the first dose of PERSERIS and no later than 5 days after study completion (follow-up phone call or early termination date). All other reported AEs are non-TEAEs.

For TEAEs, the injection number of the most recent PERSERIS SC administration (i.e., 1, 2, 3, or 4) at the time of event onset, including an SC administration that occurred on the same day, will be assigned to the event. Injection number will be presented in AE listings and will be used in the summaries of TEAEs evaluated as injection site reactions.

All AEs will be listed for individual subjects, including information regarding onset and end dates, duration, number of the most recent PERSERIS administration at onset, severity, seriousness and seriousness criteria, relationship to study treatment, action taken with study treatment, and outcome. Duration (days) is calculated as the AE end date – the AE onset date +1; for ongoing AEs, the date of end of study participation will be used as the end date. Duration will be missing if either the start or end date is partially or completely missing. Serious AEs and AEs resulting in death will be listed separately.

The incidence and number of TEAEs [all TEAEs, treatment-emergent serious AEs (TESAEs), TEAEs related to study treatment, TESAEs related to study treatment, severe TEAEs, injection site reaction TEAEs, TEAEs resulting in study treatment withdrawal or interruption, TEAEs resulting in death] and TEAEs by severity will be summarized by system organ class (SOC) and preferred term (PT). If an AE is reported more than once by a subject within a SOC and/or PT, the maximum reported level of severity will be used at each level of summation in the severity summary table. AEs with missing severity will be considered severe, and AEs with missing relationship to study treatment will be considered related for summary tables.

The incidence of common (i.e., occurring in ≥ 5% of subjects in the safety population) TEAEs will be summarized by PT and sorted by decreasing frequency.

Customized MedDRA Queries will be used to classify TEAEs as injection site reactions and these will be summarized by SOC/PT both overall and by PERSERIS administration at onset (i.e., PERSERIS Injections 1, 2, 3, and 4).

Non-TEAEs will be summarized by SOC and PT for the enrolled population.

The below algorithm will be used to flag TEAEs. The imputed dates will not be presented in data listings.

Start Date	**Stop Date**	**Action**
Known		If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date		Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (e.g. last day of month if day unknown or 31st December if day

		and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

11.2 Local Injection Tolerability

11.2.1 Injection Site Grading using Injection Site Grading Scale (ISGS)

Local injection site grading is assessed by appropriately trained site personnel on the injection days using ISGS and recorded on the eCRF form of Injection Site Grading. Observations will be listed and summarized by category (pain, tenderness, erythema/redness, and induration/swelling), visit/corresponding injection number, time point (within 10 minutes post-injection and at 3 hours post-injection), and severity (none [Grade 0], mild [Grade 1], moderate [Grade 2], severe [Grade 3], and potentially life threatening [Grade 4]). At each time point, the more severe grade from the 2 injection sites will be used for summary.

In addition, the maximum severity following each injection will be summarized by category and injection number.

11.2.2 Injection Site Pain using Visual Analogue Scale (VAS)

Local injection site pain is assessed using subject-reported VAS on the injection days and recorded on the eCRF form of injection site pain VAS. The score ranges from 0 to 100 millimeter (mm), with 0 and 100 indicating no pain and unbearably painful, respectively. The VAS scores will be listed and summarized descriptively by visit/corresponding injection number and time point (i.e., 1, 5, 30, and 60 minutes post injection completion). The mean (+/- SE) injection site pain VAS scores for each injection will be plotted over time. For each visit and time point, the bigger VAS score from the 2 injection sites will be used for summary.

Number and percentage of subjects experiencing burning or stinging at the injection site will be summarized by visit and time point. For each visit and time point, the more severe result (i.e., experiencing burning /stinging) from the 2 injection sites will be used for summary.

11.2.3 Injection Site Evaluation

The injection site is evaluated for size by the appropriate trained personnel by observation and examination. The injection-site depot is evaluated for size (length, breadth and depth of the depot using a tape measure), position (quadrant of the abdomen and back of arm) and consistency (soft, firm, hard). The results are recorded on the eCRF form of injection site evaluation and will be listed.

11.2.4 Early Removal of PERSERIS Depot

In the event of an emergency, or if a subject withdraws or is withdrawn within the first 14 days of being injected with PERSERIS, an attempt to surgically remove the depot may be made by a physician identified to perform surgery at the discretion of the PI. The primary reason for depot removal must be entered in the eCRF. If a subject elects not to have PERSERIS removed, the reason for refusal should be fully documented. All data entered in eCRF will be presented in a listing.

11.3 Clinical Laboratory Parameters

A complete list of laboratory tests is provided in Table 1 of the protocol, which includes haematology, chemistry, urinalysis (dipstick and microscopic), serology, urine drug screen, pregnancy test (urine and serum), follicle stimulating hormone [FSH], CYP2D6 genotypes, and HbA1c.

All test results will be provided in data listings using Système International (SI) units.

The following summaries will be provided for haematology, chemistry, and urinalysis by parameter and visit:

- Observed values and, for quantitative measurements, changes from baseline (i.e., last non-missing value prior to the first PERSERIS dosing) to each scheduled post-baseline visit (i.e., prior to 2nd, 3rd, and 4th PERSERIS dosing, and at ET/EOS)

- Shift from baseline according to reference range criteria (for quantitative measurements and categorical measurements) at each scheduled post-baseline visit.

11.4 Vital Signs

All vital sign results from supine and standing systolic blood pressure [SBP], supine and standing dystopic blood pressure [DBP], supine and standing pulse rate, oral temperature, respiratory rate, weight, and BMI will be listed. BMI will be calculated as shown in Section 8.1. Standing measurements are taken for a subset of time points for orthostatic evaluation after PERSERIS administration. Summaries of observed values and changes from baseline by parameter, visit, and time point will be provided. There will be no summaries of changes from baseline for standing measurements since there are no baseline values.

When the orthostatic measurements are taken (e.g., at 6 hours post-injection on the injection days), vital signs are taken after a 5-minute rest in the supine position, then the subjects are asked to stand and blood pressure and pulse are repeated at 1 minute and 3 minutes.

Orthostatic change (from supine to standing position) will be calculated, listed, and summarized at 1 minute and 3 minutes by parameter and visit.

In addition, the number and percentage of subjects meeting each criterion below will be summarized at 1 minute and 3 minutes by visit:

- SBP orthostatic decrease >20 mmHg;
- DBP orthostatic decrease >10 mmHg;
- SBP orthostatic decrease >20 mmHg or DBP orthostatic decrease >10 mmHg;
- Pulse rate orthostatic increase >10 beats per minute (bpm);
- SBP orthostatic decrease >20 mmHg or DBP orthostatic decrease >10 mmHg or Pulse rate orthostatic increase >10 beats per minute (bpm).

11.5 Electrocardiogram

The ECG parameters include QT interval, Fridericia's corrected QT interval (QTcF), PR interval, QRS interval, and heart rate. Summaries of observed values and changes from baseline by parameter, visit, and time point will be provided.

At each time point, the investigator's overall ECG interpretation is recorded on the eCRF as normal, abnormal - not clinically significant, or abnormal - clinically significant. Number and percentage of subjects with clinically significant abnormal ECG will be summarized by visit and time point.

11.6 Abnormal Involuntary Movement Scale (AIMS) for Tardive Dyskinesia

The AIMS is a clinician rated assessment of abnormal movements recorded on the eCRF form of AIMS. Facial and oral movements (Items 1-4), extremity movements (Items 5-6), and trunk movements (Item 7) are evaluated on a scale from 0 to 4, representing increasing symptom level, in which 0=none, 1=minimal, maybe extreme normal, 2=mild, 3=moderate and 4=severe. In addition, global judgments (Items 8-10 on a scale from 0 to 4 representing increasing symptom level) and dental status (Items 11-12, with 1=Yes, 0=No) are documented. The total AIMS score is a sum of all 12 items with values ranging from 0 to 42. The total non-global and non-dental AIMS score is the sum of Items 1 through 7 with values ranging from 0 to 28. Higher values of the total non-global and non-dental AIMS score indicate increased severity in abnormal movement. If one or more items are missing at a visit, the impacted total AIMS score will be set to missing.

Individual items, the two total scores, and "abnormal" assessment will be provided in a data listing. Abnormal assessment within visit is designated if two AIMS items have a response of 'Mild' or higher or if at least one item has a response of 'Moderate' or higher among Items 1-7. Abnormal assessment is missing if neither condition is met and any of Items 1-7 are missing.

The observed values and changes from baseline for the two total scores will be summarized by visit.

11.7 Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced parkinsonism consisting of 10 items. Items are anchor-based, rated on a 5-point scale and address rigidity, gait (bradykinesia), tremor, glabellar tap, salivation, and akathisia. Each individual item on the SAS ranges from 0 for normal to 4 for extreme symptoms. The total SAS score is defined as the sum of all 10 items and ranges from 0 to 40. The mean SAS score is defined as the mean of all 10 items. Lower values of the total SAS score indicate milder symptoms. If one or more items are missing at a visit, the total SAS score will be set to missing and the mean score will

be based on non-missing items.

Individual items, total score, mean score, and "abnormal" assessment will be provided in a data listing. Abnormal assessment within visit is designated if the mean score exceeds 3.

The observed total and mean scores and changes from baseline will be summarized by visit.

11.8 Barnes Akathisia Rating Scale (BARS)

The BARS is a rating scale that measures the observable restless movements that characterize akathisia. It consists of 4 items: objective restlessness, awareness of restlessness, distress related to restlessness, and global clinical assessment of akathisia. Each item is on a 0 to 3-point scale, except for the global clinical assessment which is on a 0 to 5-point scale, both using low values to represent absence of akathisia and high values to represent severe akathisia. The total BARS score is the sum of all 4 items and the possible range of values is 0 to 14. The total non-global BARS score is the sum of Items 1 through 3 and ranges from 0 to 9. Higher values of the total BARS score indicate higher severity of akathisia. If one or more items are missing at a visit, the impacted total BARS score will be set to missing.

Individual items and the two total scores will be provided in a data listing. The observed values and changes from baseline for the two total scores will be summarized by visit.

11.9 Columbia-Suicide Severity Rating Scale (C-SSRS)

Responses to all C-SSRS items at each visit will be listed.

A composite endpoint of Suicidal Ideation and Suicidal Behavior will be derived from the following binary (Yes/No) C-SSRS categories, re-ordered from the actual scale to facilitate the definition of the composite endpoint:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide: if the subject has an AE with a PT of completed suicide

Categories 1-5 are from the suicidal ideation portion of the C-SSRS and Categories 6-10 are from the suicidal behavior portion of the C-SSRS, with Category 10 verified from the AE form of the eCRF.

The parameters below will be summarized by visit, with "lifetime" and "past 6 months" from the screening/baseline C-SSRS presented separately. Observed values and changes from baseline will be provided for continuous variables, and frequencies and percentages will be provided for categorical variables. "Past 6 months" observations will be used as baseline for "since last visit" observations that are not available.

- Suicidal Ideation (binary): Yes if the answer is Yes to any of Categories 1 to 5, otherwise No if none are missing but expected to be non-missing.
- Suicidal Behavior (binary): Yes if the answer is Yes to any of Categories 6 to 10, otherwise No if none are missing but expected to be non-missing.
- Suicidal Ideation or Behavior (binary): Yes if the answer is Yes to any of Categories 1 to 10, otherwise No if none are missing but expected to be non-missing.
- Maximum Suicidal Ideation Severity Score (range 0-5): the maximum suicidal ideation category among Categories 1-5 with an answer of Yes. If none of the answers are Yes and none are missing but expected to be non-missing, the score is equal to 0.
- Suicidal Ideation Intensity Score (range 0-25): the sum of the 5 intensity scores (frequency, duration, controllability, deterrents, and reason for ideation) recorded within the Intensity of Ideation section of the C-SSRS. Set to 0 if the Maximum Suicidal Ideation Severity Score is 0. Set to missing if Maximum Suicidal Ideation Severity Score > 0 and at least one of the 5 intensity scores is missing but expected to be non-missing.
- Maximum Suicidal Behavior Score (range 0-5): the maximum suicidal behavior category among Categories 6-10 with an answer of Yes. If none of the answers are Yes and none are missing but expected to be non-missing, the score is equal to 0.

12 PHARMACOKINETIC ANALYSES

All PK analyses will be performed on the PK population. The descriptive statistics of n, arithmetic mean and SD, minimum, median, maximum, geometric mean, coefficient of variation (%CV) will be presented for all three analytes (risperidone, 9-OH and total active moiety). Total active moiety plasma concentration will be determined by adding risperidone concentration to 9-hydroxyrisperidone concentration after correction for their molecular weights (410 for risperidone and 426 for 9-hydroxyrisperidone), according to the following equation:

[Total Active Moiety] = [Risperidone] + (410/426) * [9-hydroxyrisperidone]

Here [Risperidone] and [9-hydroxyrisperidone] are the reported concentrations for the separate analytes. Concentration data for risperidone and 9-hydroxyrisperidone that are below the limit of quantification (BLQ) will be treated as zero in the calculation of total active moiety concentration.

Summary tables will be provided by dosing (i.e., oral risperidone, SC injections 1 to 4) and time point for all three analytes (i.e., risperidone, 9-hydroxyrisperidone, and total active moiety).

12.1 Plasma Concentration

Individual plasma samples are collected for oral risperidone and all 4 SC doses of PERSERIS according to the schedule outlined in Appendix 6 of the protocol.

Dosing route (oral, SC) and number (1-4), nominal time point (e.g., "Pre-Dose"), sampling date and time, relative day to each injection, time since dosing, deviation from scheduled sampling time, and concentrations will be listed.

Relative day to each injection is derived as:

- = date of sampling – date of first PERSERIS dosing, for oral risperidone samplings with date of sampling < date of first PERSERIS dosing;
- = date of sampling – date of first PERSERIS dosing +1, for oral risperidone samplings with date of sampling = date of first PERSERIS dosing;
- = date of sampling – date of the corresponding PERSERIS dosing + 1, for PERSERIS samplings.

Time since dosing (hour) will be calculated as the sampling date and time – date and time of the last corresponding dose.

Time deviation (minute) will be calculated as sampling date and time – (date and time of the last corresponding dose + nominal sampling time).

Individual and mean (+/-SD) plasma concentration versus time plots will be presented on linear and semi-logarithmic scales, by dosing, for all three analytes, as appropriate. Mean (+/-SD) C_{trough} plots on a linear scale will be derived using concentration data. Actual sampling time and nominal scheduled sampling time will be used to present results in the individual and mean figures, respectively, where actual sampling time (hour) = sampling date and time – date and time of the last injection of the corresponding dose.

The concentration of BLQ will be presented as "BLQ" in the data listing and treated as zero for the summary statistics. They will be presented as 0 in linear-scale figures and will not be presented in semi-logarithmic-scale figures.

12.2 Pharmacokinetic parameters

The below PK parameters will be calculated using WinNonlin Phoenix version 6.3 or higher for risperidone, 9-hydroxyrisperidone, and total active moiety, by non-compartmental analysis. Actual sampling times are used in the calculation. Additional PK parameters may be calculated if required. No PK parameters will be derived for the 2nd dose of PERSERIS.

All plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The measurable concentrations between 2 BLQ values will be set to missing. If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. If a BLQ concentration is followed by a quantifiable concentration, and the quantifiable concentration is then followed by two or more consecutive BLQ concentrations, the quantifiable concentration will be set to missing. The BLQ values following the last quantifiable time points will be set to missing. No concentration estimates will be imputed for missing sample values.

Pharmacokinetic Parameters:

Oral Risperidone Administration (Day -1; 0 to 12 Hours) Note: The PK analysis will include data from all subjects who receive oral risperidone and provide an adequate number of blood samples to derive the following parameters:	
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
$C_{avg\ (ss)}$	Average plasma concentration from time 0 to 12 hours post-dose at Day -1
C_{min}	Minimum observed plasma concentration

percent fluctuation	= 100*(C_{max}-C_{min})/ $C_{avg\ (ss)}$
AUC_{0-12}	Area under the plasma concentration-time curve from Time 0 to 12 hours post-dose at Day -1; calculated using the linear trapezoidal rule
C_{trough}	Trough plasma concentration (measured pre-dose concentration during oral administration period; directly before oral administration)
Subcutaneous Administration (1st, 3rd, and 4th doses of 180 mg PERSERIS) Note: The PK analysis will include data from all subjects who receive at least one dose of PERSERIS and provide an adequate number of blood samples to derive the following parameters:	
Initial Peak Parameters (approximately 0-24 hours post-dose)	
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
Secondary Peak Parameters (approximately 24-672 hours [28 days])	
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
Overall PK Profile	
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
C_{avg}	Average plasma concentration from Time 0 to 672 hours post-dose (1st SC injection); total exposure over the dosing interval divided by the time of the dosing interval
$C_{avg\ (ss)}$	Average plasma concentration at steady-state from Time 0 to 672 hours post-dose (3rd and 4th SC injection); total exposure over the dosing interval divided by the time of the dosing interval
t_{max}	Time of maximum observed plasma concentration
AUC_{τ}	Area under the plasma concentration-time curve from Time 0 to 672 hours post-dose; calculated using the linear trapezoidal rule
percent fluctuation	= 100*(C_{max}-C_{min})/ $C_{avg\ (ss)}$
C_{trough}	Trough plasma concentration (measured pre-dose concentration during the SC administration period; directly before next dose administration)
Partial PK Profile (0 to 336 hours [0 to 14 days])	
$C_{max14days}$	Maximum observed plasma concentration
$C_{min14days}$	Minimum observed plasma concentration
$C_{avg14days}$	Cavg14days Average plasma concentration from Time 0 to 336 hours post-dose; partial area under the curve over the 0-336 hours ($PAUC_{14days}$) divided by 336 hours
$PAUC_{14days}$	Area under the plasma concentration-time curve from Time 0 to 336 hours post-dose; calculated using the linear trapezoidal rule
Partial PK Profile (336 to 672 hours [14 to 28 days])	
$C_{max28days}$	Maximum observed plasma concentration
$C_{min28days}$	Minimum observed plasma concentration
$C_{avg28days}$	Average plasma concentration from Time 336 to 672 hours post-dose; partial area under the curve over the 336-672 hours ($PAUC_{28days}$) divided by 336 hours
$PAUC_{28days}$	Area under the plasma concentration-time curve from Time 336 to 672 hours post-dose; calculated using the linear trapezoidal rule

Summary of all PK parameters will be done for the PK population by dosing for all three analytes.

In addition, the primary PK analysis of the primary endpoint of $C_{avg\ (ss)}$ after oral and SC administrations will also be performed on those subjects who receive at least 3 doses of PERSERIS and provide an adequate number of blood samples for the determination of $C_{avg\ (ss)}$ for risperidone and total active moiety.

Steady-state attainment after oral dosing and SC dosing will be evaluated based on descriptive-statistic summaries of plasma concentrations and PK parameters.

The following PK parameters from the 4th SC dose (an alternate site, arm) will be descriptively compared against those from the 3rd SC dose (the abdominal site) to evaluate the administration of PERSERIS at an alternative injection site:

- Initial peak parameters: Cmax, tmax
- Secondary peak parameters (if applicable): Cmax, tmax,
- Overall parameters: Cmax, Cmin, Cavg (ss), tmax, AUCτ, percent fluctuation, Ctrough

- PK parameters over partial interval (0 to 14 days): Cmax14days, PAUC14days, Cmin14days, Cavg14days
- PK parameters over partial interval (14 to 28 days): Cmax28days, PAUC28days, Cmin28days, Cavg28days

13 INTERIM ANALYSIS

An interim PK analysis will be performed by the pharmacokineticist after the first fifteen subjects complete the first injection phase of PERSERIS SC injection. The purpose of the interim analysis is to preliminarily assess the adequacy of exposure from 2 X 90 mg injections. The results of the interim analysis will be shared internally with the study team only and will have no impact on the conduct of trial or the ability to fulfill all objectives of the trial. The analysis will focus on C_{avg} for oral risperidone administration, the first dose of subcutaneous PERSERIS, and the overall PK profile.

14 DETERMINATION OF SAMPLE SIZE

No formal statistical justification was performed to determine the sample size. The sample size of 25 subjects was selected to be consistent with the sample size used in an earlier clinical trial. This sample size is expected to provide an adequate number of subjects (at least 15 evaluable) to assess PK parameters of PERSERIS.

15 COMPUTER METHODS

All statistical analyses and reporting will be performed using the validated software SAS® for Windows version 9.4 or higher (SAS Institute, Inc., Cary, NC, USA).

WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation) will be used for PK parameter calculation.

16 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the planned analyses defined in the protocol.

17 REFERENCE

Nilsson ME, Suryawanshi S, Gassmann-Mayer C, Dubrava S, McSorley P, Jiang K. Columbia-Suicide Severity Rating Scale Scoring and Data Analysis Guide, Version 2.0, Feb2013.

18 APPENDICES

18.1 Appendix 1:Data Presentation Plan