Clinical Study Protocol: INDV-7000-401

Protocol Title:	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
Protocol Number:	INDV-7000-401
Product Name:	PERSERIS™
Development Phase:	Phase IV
IND Number:	105,623
Indivior Legal Registered Address:	Indivior Inc. 10710 Midlothian Turnpike, Suite 430 Richmond, VA 23235 USA
Original Protocol Date:	14 Mar 2019
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CLINICAL PROTOCOL SIGNATURE PAGE

Protocol Title:	An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of 180-mg Risperidone Subcutaneous Injection (PERSERIS™) Following a Switch from 6 mg Oral Risperidone in Patients with Clinically Stable Schizophrenia
Protocol Number:	INDV-7000-401
Original Protocol Version Number & Date:	Version 1.0 (14 March 2019)

This clinical study protocol was subject to critical review and has been approved by the appropriate protocol review committee of Indivior. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational medicinal product.
- The moral, ethical and scientific principles governing clinical research as set out in the principles of International Council on Harmonisation (ICH) E6 (Good Clinical Practice) and according to applicable local laws and regulations.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational medicinal product.

Signed: [redacted] Date: _____
DD-MMM-YYYY
Indivior Medical Monitor, Global Medicines Development

Signed: [redacted] Date: _____
DD-MMM-YYYY
Senior Vice President, Global Medicines Development
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INDV-7000-401

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

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to this investigational medicinal product (IMP) is the confidential and proprietary information of Indivior, and except as may be required by local laws or regulation, may not be disclosed to others without prior written permission of Indivior.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. My staff and/or I will conduct this study as outlined herein, in accordance with the regulations stated in the International Council on Harmonisation E6 / Good Clinical Practice (ICH/GCP) guidelines and will make a reasonable effort to complete the study within the time designated.

I agree to ensure all associates, colleagues and employees delegated to assist with the conduct of the study are trained on this study protocol and amendments, other study-related materials and are qualified to perform their delegated tasks. I will provide all study personnel copies of the protocol and any amendments and grant access to all information provided by Indivior or specified designees. I will discuss the material with them to ensure that they are fully informed about the IMP and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Signed:_____ Date:_____

Printed Name and Credentials:	
Title:	
Site Name:	
Telephone:	
Address:	

SYNOPSIS

Protocol Title:

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

Protocol Number:

INDV-7000-401

Rationale:

Risperidone is an atypical antipsychotic medication with potent antagonist effects at the dopamine type-2 (D_2) and type 2A serotonin ($5\text{-}HT_{2A}$) receptors. The clinical effect of risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (i.e., total active moiety). PERSERIS™ was developed to address the compliance issues associated with oral risperidone treatment.

Recently, US Food and Drug Administration (FDA) approved PERSERIS (risperidone) for extended-release injectable suspension, the first once-monthly subcutaneous (SC) risperidone-containing long-acting injectable (LAI) at 90-mg and 120-mg doses for the treatment of schizophrenia in adults. PERSERIS is risperidone in an extended-release delivery system that is comprised of a sterile, polymeric solution of a biodegradable poly DL-lactide-co-glycolide (PLGH) polymer and N-methyl-2-pyrrolidone (NMP), a water-miscible, biocompatible solvent. The delivery system provides the monthly extended-release delivery of risperidone.

The pharmacokinetic (PK) profile of risperidone and total active moiety following SC injection of PERSERIS has been evaluated in subjects with clinically stable schizophrenia after single doses (60 mg, 90 mg and 120 mg) and after repeated doses (60 mg, 90 mg and 120 mg); injections were separated by 28 days for up to 3 injections following oral risperidone. Based on average plasma concentrations at steady-state [$C_{avg\ (ss)}$] of risperidone and total active moiety, 90 mg PERSERIS corresponds to 3 mg oral risperidone and 120 mg PERSERIS corresponds to 4 mg oral risperidone.

Pursuant to approval of the PERSERIS NDA, a post marketing commitment was made to conduct a PK study to evaluate exposure of PERSERIS that approximates a daily administration of 6 mg oral risperidone. This protocol will evaluate the PK of risperidone, 9-hydroxyrisperidone and total active moiety after three 180-mg doses (each 180-mg dose will be administered as two 90-mg SC injections) in subjects and after switching treatment from a stable oral risperidone daily dose of 6 mg (3 mg risperidone will be administered twice a day approximately 12 hours apart). The dose(s) of PERSERIS 180 mg will be administered subcutaneously in the abdominal region (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. This study will also evaluate whether injection of PERSERIS (180 mg) at an alternate injection site (back of upper arm) is well tolerated and provides similar exposure (total active moiety throughout the 28 day dosing interval) to that obtained after injection of PERSERIS (180 mg) in the abdominal region. Therefore, a 4th dose of 180 mg PERSERIS

will be administered at an alternate site (SC tissue in the back of each upper arm) as two 90-mg SC injections given at the same visit clinic.

Target Population:

Adult subjects with clinically stable schizophrenia as assessed by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) currently taking 5 mg or 6 mg oral risperidone daily. 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.

Number of Subjects:

Twenty-five subjects are planned to receive study drug treatment. No formal calculation of study sample power was performed for the sample size for this study. This sample size is based on earlier clinical experience and expected to provide an adequate number of subjects (at least 15 evaluable subjects) to assess the PK parameters of PERSERIS as well as oral risperidone.

Duration of Treatment:

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 screening period (Days -26 to -6)
- Stabilization with 6 mg oral risperidone daily (for all subjects): 5 days (Days -5 to -1); Oral risperidone 6 mg daily (3 mg risperidone will be administered twice a day approximately 12 hours apart); oral risperidone dosing will be stopped prior to initiating PERSERIS treatment
- PERSERIS treatment period: 4 doses of 180 mg PERSERIS (each 180-mg dose will be administered as two 90-mg SC injections on Days 1 to 113); each dose of 180 mg will be administered every 28 (+2) days
- Follow-up: 7 days (Day 120)

Objective(s):

The primary objective of this study 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 objectives of this study 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
Study Design: This open-label study will assess the safety, tolerability, pharmacokinetics and efficacy of 180 mg of PERSERIS in subjects with clinically stable schizophrenia (as determined by the DSM-5 criteria). The study will enrol 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. All subjects will be stabilized on 6 mg daily [3 mg risperidone will be administered twice a day approximately 12 hours (±30 mins) 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 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. Adverse event (AE) assessments will be made until Day 120, and PK assessments will be conducted through Day 113. 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. **Study Population:** The study population consists of subjects who are assessed with clinically stable schizophrenia and who are already stabilized on oral risperidone (stable dose of 5 mg or 6 mg oral risperidone daily dose via any regimen). 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.

Inclusion criteria

Only subjects who meet all the following conditions will be included in the study:

Sex: male and female, Age: ≥ 18 to ≤ 65 years

1. Diagnosis of schizophrenia as defined by DSM-5 criteria
2. Status: clinically stable subjects defined as subjects with no hospitalizations for acute exacerbations within 3 months of screening and screening Positive and Negative Syndrome Scale (PANSS) total score ≤ 70
3. Subjects with a body mass index (BMI) between 18.0 and 35.0 kg/m^2 and who weigh at least 49.9 kg
4. Subjects who have given written informed consent

Primary Endpoint(s)

- The primary endpoint for the study will be $C_{avg\ (ss)}$ for risperidone and total active moiety after oral and SC administration

Secondary Endpoint(s):

The following safety endpoints will be analysed:

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

- AEs, local injection-site tolerability (i.e., injection-site reactions), concomitant medications, changes in clinical laboratory results, vital sign measurements, 12 lead electrocardiograms (ECGs), body weights 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 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 – Severity of Illness Scale (CGI-S) scores

Pharmacokinetic Assessments:

The PK analyses will include data from all subjects who receive oral risperidone or at least one dose 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. Individual plasma concentrations will be summarized using descriptive statistics and will be used to compute PK parameters. The PK parameters will be listed and summarized using descriptive statistics.

The primary endpoint for the study will be the measurement of $C_{avg\ (ss)}$ for risperidone and total active moiety after oral and SC administration. For primary PK analysis, only the data from those subjects who receive 3 doses of PERSERIS and provide an adequate number of blood

samples for determination of $C_{avg\ (ss)}$ for risperidone and total active moiety (evaluable population) will be considered.

In addition, the following secondary PK parameters for risperidone, 9 hydroxyrisperidone and total active moiety will be derived. These PK parameters will be derived after oral risperidone and 1st, 3rd and 4th doses of 180 mg of PERSERIS as follows:

Oral Administration:

C_{trough} (trough plasma concentration), C_{max} (maximum plasma concentration), t_{max} (time of occurrence of C_{max}), C_{min} (minimum observed plasma concentration), AUC_{0-12} (area under the plasma concentration versus time curve from time zero to 12 hours post-dose) and percent fluctuation

SC Administration (Doses 1, 3):

- Initial peak parameters: C_{max}, t_{max}
- Secondary peak parameters (if applicable): C_{max}, t_{max}
- Overall parameters (over 28 days): C_{max}, C_{min}, average plasma concentration (C_{avg})(after 1st injection only), t_{max}, AUC_{τ} (area under the plasma concentration versus time curve from time zero to the time of dosing interval), percent fluctuation, C_{trough}
- PK parameters over partial interval (0 to 14 days): $C_{max14days}$ (maximum plasma concentration over 0 to 14 days), $PAUC_{14days}$ (area under the plasma concentration versus time curve from time zero to 14 days), $C_{min14days}$ (minimum plasma concentration over 0 to 14 days), $C_{avg14days}$ (average plasma concentration over 0 to 14 days)
- PK parameters over partial interval (14 to 28 days): $C_{max28days}$ (maximum plasma concentration over 14 to 28 days), $PAUC_{28days}$ (area under the plasma concentration versus time curve from time 14 days to 28 days), $C_{min28days}$ (minimum plasma concentration over 14 to 28 days), $C_{avg28days}$ (average plasma concentration over 14 to 28 days)

Steady-state attainment after oral dosing and SC dosing will be evaluated.

Alternate Injection Site SC Administration (Dose 4):

The following PK data collected after 4th PERSERIS dose (an alternate site, back of arm) will be compared against PK data collected after 3rd dose (the abdominal site):

- Initial peak parameters: C_{max}, t_{max}
- Secondary peak parameters (if applicable): C_{max}, t_{max}
- Overall Parameters: C_{max}, C_{min}, $C_{avg\ (ss)}$, t_{max}, AUC_{τ}, percent fluctuation, C_{trough}
- PK parameters over partial interval (0 to 14 days): $C_{max14days}$, $PAUC_{14days}$, $C_{min14days}$, $C_{avg14days}$
- PK parameters over partial interval (14 to 28 days): $C_{max28days}$, $PAUC_{28days}$, $C_{min28days}$, $C_{avg28days}$

A more complete description of the PK analyses will be provided in the Statistical Analysis Plan (SAP).

Pharmacogenomic Assessments:

PERSERIS is metabolised to its active metabolite, 9-hydroxyrisperidone, by the enzyme cytochrome CYP2D6, with minor contribution by CYP3A4. CYP2D6 is subject to genetic polymorphism, which influences the rapidity of risperidone metabolism. Extensive CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolisers convert much more slowly. Approximately 6 to 8% of Caucasians and a very low percentage of Asians have little or no activity and are "poor metabolisers". In order to control variability of risperidone PK parameters, only extensive CYP2D6 metabolisers will be included in the study; low, intermediate and ultra-rapid CYP2D6 metabolisers will be excluded from the study.

Blood samples will be collected during the screening period for DNA analysis to evaluate genetic polymorphism (CYP2D6 genotype) status. The results of the biomarkers will be reported in the data listings.

Statistical Methods:

Demographic and baseline characteristics, (e.g., gender, race, age, weight, height) will be summarized for all subjects using descriptive statistics for the Safety Analysis Set.

Observed, change from baseline and percent change from baseline in PANSS total score, PANSS positive scale score, PANSS negative scale score, PANSS general psychopathology scale score and CGI-S score will be summarized by visit using the efficacy analysis population.

Individual plasma concentrations will be summarized using descriptive statistics and will be used to compute PK parameters. The PK parameters will be listed and summarized using descriptive statistics.

Safety parameters comprise AEs and serious adverse events (SAEs), local injection-site tolerability (i.e., injection-site reactions), concomitant medications, changes in clinical laboratory results, vital sign measurements, 12 lead ECGs, physical examination and neurological examination results, body weights and monitoring of EPS using neurological, clinical symptom assessments (AIMS, SAS, BARS and the C-SSRS), Injection-Site Grading Scale (ISGS) and Visual Analog Scale (VAS).

A treatment-emergent adverse event (TEAE) is an AE that either commenced following initiation of PERSERIS or was present prior to the initiation of PERSERIS dosing but increased in frequency or severity following initiation of PERSERIS, regardless of causality. The incidence of treatment-emergent AEs (TEAEs) during the study period will be tabulated by system organ class, preferred term and treatment visit number (Day 1, Day 29, Day 57 and Day 85). The incidence of TEAEs (any TEAE, serious TEAEs, related TEAEs, serious related TEAEs, TEAEs leading to treatment discontinuation or death) and TEAEs by severity will be summarized. If a TEAE is reported more than once by a subject within a system organ class and/or preferred term, the maximum level of severity will be used in the severity summary

tables. All AEs will be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, injection number and action taken.

Vital signs, body weight and 12-lead ECG will be summarized by timepoint for all subjects using descriptive statistics at baseline and at each post-baseline assessment (along with change from baseline). Clinical laboratory data (haematology and serum chemistry, urinalysis) will be summarized using descriptive statistics. For each parameter with numeric results, values at baseline and at end of treatment, together with changes from baseline, will be summarized.

The observed and change from baseline values of AIMS, SAS, BARS and C-SSRS (Suicidal Ideation and Suicidal Behaviour) will be summarized by timepoint.

The results ISGS, VAS and the number of subjects that experience burning or stinging at the injection site will be summarized by timepoint.

More details about safety and efficacy analyses will be provided in the SAP.

STUDY SCHEMATIC

Figure 1 Study Schematic

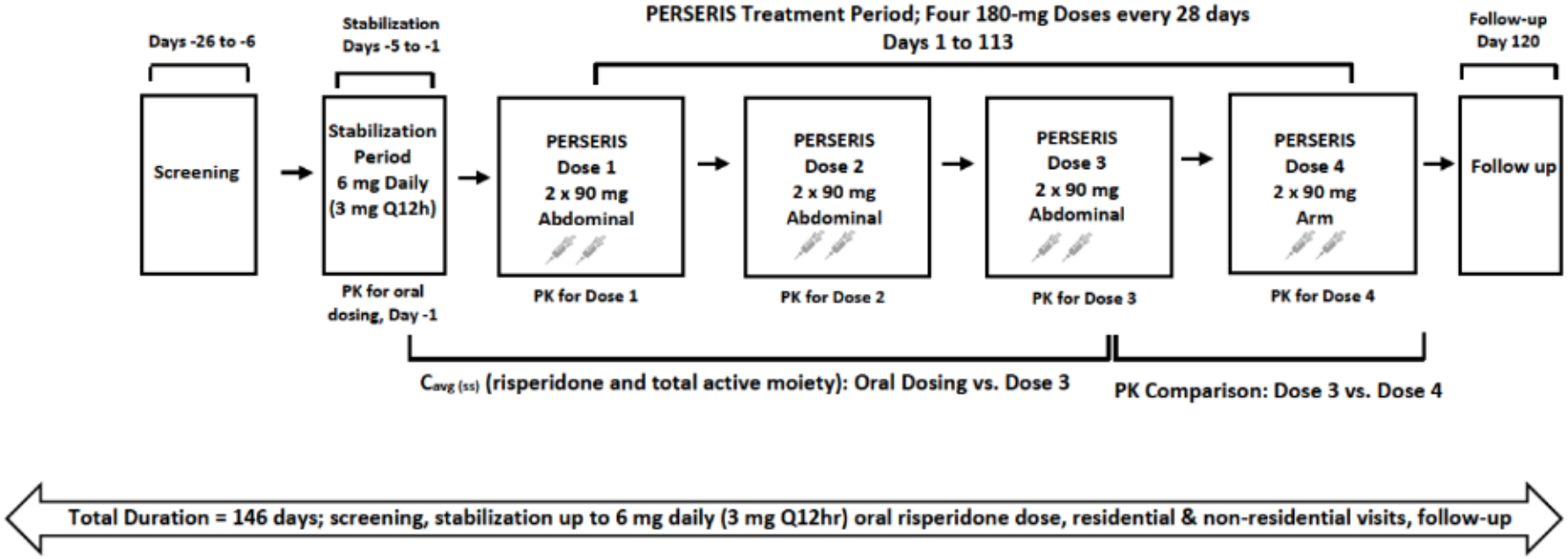


Table of Contents

List of In-Text Tables

List of In-Text Figures

List of Abbreviations

AE	adverse event
AIDS	acquired immunodeficiency syndrome
AIMS	Abnormal Involuntary Movement Scale
ALB	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BUN	blood urea nitrogen
C_{avg}	average plasma concentration
$C_{avg\ (ss)}$	average plasma concentrations at steady-state
$C_{avg14days}$	average plasma concentration over 0 to 14 days
$C_{avg28days}$	average plasma concentration over 14 to 28 days
CGI-S	Clinical Global Impression Scale for Severity of Illness
C_{max}	maximum plasma concentration
$C_{max14days}$	maximum plasma concentration over 0 to 14 days
$C_{max28days}$	maximum plasma concentration over 14 to 28 days
C_{min}	minimum plasma concentration
$C_{min14days}$	minimum plasma concentration over 0 to 14 days
$C_{min28days}$	minimum plasma concentration over 14 to 28 days
CPK	creatine phosphokinase
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	trough plasma concentration
D_2	dopamine type-2 receptor
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
EDC	electronic data capture

EOS	end-of-study
EPS	extrapyramidal symptoms
ET	Early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HbA1c	haemoglobin A1c
HBsAg	hepatitis b surface antigen
Hct	Haematocrit
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	Haemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
5-HT_{2A}	serotonin type-2A receptor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgM anti-HBc	anti-Hepatitis B IgM core antibody
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
ISGS	Injection Site Grading Scale
LAI	long-acting injectable
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities

NMP	N-methyl-2-pyrrolidone
OTC	over-the-counter
$PAUC_{14days}$	Area under the plasma concentration versus time curve from time zero to 14 days
$PAUC_{28days}$	Area under the plasma concentration versus time curve from time 14 days to 28 days
PANSS	Positive and Negative Syndrome Scale
PGx	Pharmacogenomics
PD	Pharmacodynamics
PI	principal investigator
PK	Pharmacokinetics
PLGH	poly (DL-lactide-co-glycolide) with a carboxylic acid end group
PO	*per os* (oral administration)
QA	quality assurance
QTc/QTcF	corrected QT interval/heart rate-corrected QT interval/ Fridericia's corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SC	Subcutaneous
SD	standard deviation
SOE	Schedule of Events
SOP	Standard Operating Procedure
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TG	Triglycerides
t_{max}	time of occurrence of C_{max}
ULN	upper limit of normal
UDS	urine drug screen

VAS	Visual Analog Scale
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background and Introduction

Schizophrenia is a severe, chronic and disabling mental disorder affecting an estimated 0.5% to 1% - roughly 23 million adults - worldwide (Lieberman 2012). For most patients who have schizophrenia, maintenance treatment with antipsychotic drugs is necessary to reduce the risk or relapse or recurrence of an acute exacerbation (Kane 1999).

Risperidone is an atypical antipsychotic medication with potent antagonist effects at the dopamine type-2 (D_2) and type 2A serotonin (5-HT_{2A}) receptors. The clinical effect of risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (i.e., total active moiety). Patients switching from shorter-acting oral medications to longer-acting injectables experience significantly reduced hospitalization rates (Chue 2005, Crivera 2011) and improved health-related quality of life (MacFadden 2011, Nasrallah 2004).

PERSERIS™ (risperidone) is an extended-release subcutaneous (SC) injectable suspension administered once-monthly for the treatment of schizophrenia in adults. PERSERIS uses the extended-release delivery system which is comprised of a sterile, polymeric solution of a biodegradable poly DL lactide-co-glycolide (PLGH) and N-methyl-2-pyrrolidone (NMP) polymer. The delivery system forms a subcutaneous depot that provides sustained levels of risperidone over one month.

Initial peak risperidone plasma concentrations occur within 4 to 6 hours of dosing and are due to an initial release of the drug during the depot formation process. Clinically relevant concentrations are reached after the 1st injection of PERSERIS without the use of a loading dose or any supplemental oral risperidone. Based on average plasma concentration at steady-state ($C_{avg\ (ss)}$) of risperidone and total active moiety, 90 mg PERSERIS corresponds to 3 mg oral risperidone and 120 mg PERSERIS corresponds to 4 mg oral risperidone.

PERSERIS is metabolised to its active metabolite, 9-hydroxyrisperidone, by the enzyme cytochrome CYP2D6, with minor contribution by CYP3A4. CYP2D6 is subject to genetic polymorphism, which influences the rapidity of risperidone metabolism. Extensive CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolisers convert much more slowly. Approximately 6 to 8% of Caucasians and a very low percentage of Asians have little or no activity and are “poor metabolisers”. In order to control variability of risperidone pharmacokinetic (PK) parameters, only extensive CYP2D6 metabolisers will be included in the study; low, intermediate and ultra-rapid CYP2D6 metabolisers will be excluded from the study.

Current labelling for oral risperidone products specifies a target daily dose of 4 to 8 mg and an effective daily dose of 4 to 16 mg for the treatment of schizophrenia in adults. Literature suggests that the dose response plateaus at around 4 mg per day for most patients and that the optimal daily oral dose of risperidone in adults with schizophrenia is 4 to 6 mg per day (Davis 2004). Approximately 18% of adults with schizophrenia being treated with oral risperidone receive dosages of 6 mg/day, and 5% receive dosages greater than 6 mg/day. Because patients

who are prescribed long-acting injectable (LAI) antipsychotics generally have greater illness severity than those prescribed oral antipsychotics (Kishimoto 2018), it is anticipated that there will be a significant number of patients who would benefit from a PERSERIS dose that approximates 6 mg/day oral risperidone.

This study will be carried out in accordance with the protocol and with local legal and regulatory requirements, International Council on Harmonisation/Good Clinical Practice (ICH/GCP) and all applicable subject privacy requirements.

1.2 Study Rationale

This study is designed to evaluate the safety, tolerability, pharmacokinetics 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 [DSM-5] criteria). The study will enrol subjects who are currently on a stable dose of 5 mg or 6 mg of oral risperidone daily via any regimen. Current clinical practice suggests that oral risperidone doses 5mg/day and higher are generally administered in divided doses twice daily (i.e., 3/3, 4/2, 3/2). Therefore, in this study, all subjects will be stabilized to receive 3 mg risperidone twice a day approximately 12 hours (±30 mins) apart (i.e., 6 mg oral risperidone daily) prior to administration of PERSERIS. Any prior daily or twice daily dosing combination (i.e., 3/3, 4/2, 3/2) will be acceptable. 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. 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 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 dose of 180 mg (administered 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.

1.2.1 Rationale for Dose and Alternate injection site

The PK profile of risperidone and total active moiety following SC injection of PERSERIS has been evaluated in subjects with clinically stable schizophrenia after single doses (60 mg, 90 mg and 120 mg) and repeated doses (60 mg, 90 mg and 120 mg); injections were separated by 28 days for up to 3 injections following oral risperidone. Based on $C_{avg\ (ss)}$of risperidone and total active moiety, 90 mg PERSERIS corresponds to 3 mg oral risperidone and 120 mg PERSERIS corresponds to 4 mg oral risperidone.

It is anticipated that $C_{avg\ (ss)}$ of risperidone and total active moiety obtained after 180 mg PERSERIS will approximate to that obtained after 6 mg oral risperidone.

Data cited from literature suggests that the upper arm is a viable injection site for SC administration delivering similar PK and pharmacodynamic (PD) properties. Steady-state plasma concentrations were reached by the end of the second injections for both risperidone, 9-hydroxyrisperidone and total active moiety and were maintained for 4 weeks after the last injection. Therefore, both the 3rd and 4th injections of PERSERIS will be at steady-state allowing a like-for-like comparison of SC administration in the abdomen and upper arm. Having an alternate injection site is important in this patient population who may be taking this medication indefinitely, based upon clinical response. may also benefit patients with schizophrenia receiving treatment in a community mental health setting.

1.2.2 Potential for Drug-Drug Interactions

No specific drug interaction studies have been performed with PERSERIS. The drug interaction data provided in this section is based on studies with oral risperidone. Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), potent CYP2D6 inhibitors, have been shown to increase the plasma concentration of risperidone by 2.5- to 2.8-fold and 3- to 9-fold, respectively. Co-administration of known CYP3A4 enzyme inducers (e.g., carbamazepine, phenytoin, rifampin and phenobarbital) with risperidone may cause decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of PERSERIS.

1.2.3 Clinical Adverse Event Profile

The safety of PERSERIS was evaluated in a total of 814 adult subjects with schizophrenia who received at least 1 dose of PERSERIS during the clinical development program. A total of 322 subjects were exposed to PERSERIS for at least 6 months, 234 of which were exposed to PERSERIS for at least 12 months; 281 and 176 of these, respectively, received the 120-mg dose. Adverse drug reactions in adult subjects with schizophrenia (≥5% in any PERSERIS-treated group and greater than placebo) during the 8-week double-blind, placebo-controlled study) were weight increased, constipation, sedation/somnolence, pain in extremity, back pain, akathisia, anxiety and musculoskeletal pain. In addition, the frequency of reported injection-site reactions was similar across treatment groups with both PERSERIS and placebo; the most common (≥ 5%) of which were injection-site pain and erythema. During the 52-week open-label long-term safety study, no new safety signals were observed compared with the primary double-blind study or the known safety profile or risperidone. The overall systemic safety profile for PERSERIS was consistent with the known safety profile of oral risperidone, with the exception of the expected injection-site reactions.

1.2.4 Changes in Body Weight

In the 8-week double-blind study, an increase in mean weight was observed for all treatment groups, including the placebo group, which may be related to changes in dietary habits in this exclusively inpatient study. There was a dose-dependent increase in mean change in weight from baseline to post-dose assessments in the PERSERIS 90-mg and 120-mg groups when compared to the placebo group. Overall mean weight gain from baseline to end-of-study (EOS) was 4.4 kg in the 90-mg group, 5.3 kg in the 120-mg group and 2.6 kg in the placebo group. In the 52-week open-label long-term safety study, mean weight increased by approximately 2 kg from baseline

to Day 85 then remained stable for the remainder of the study. There was a mean weight gain increase during the first 3 months of treatment, but then weight was stable over the remaining 9 months of treatment. Data from the supportive safety studies did not reveal any new safety concerns relative to weight gain.

1.2.5 Increased Prolactin

In the 8-week double-blind, placebo-controlled study, a typical increase in mean prolactin levels was observed in blood samples of fasting subjects from baseline to the EOS assessments in both the PERSERIS 90-mg and 120-mg groups, while mean prolactin for the placebo group remained stable during the study. Changes in mean prolactin were dose-dependent and more pronounced in female subjects than male subjects This finding was not unexpected as increases in prolactin are known to occur with risperidone administration. In the 52-week open-label long-term safety study, both male and female subjects who had not received antipsychotic medications for the 8 weeks prior to participation in the open-label study (i.e., placebo rollovers) had mean increases from baseline in prolactin values, consistent with the expected effect with oral risperidone. For the other enrolment groups, there were no clinically relevant changes in mean values from baseline to post-dose assessments for prolactin.

1.2.6 Extrapyramidal Symptoms (EPS)

Methods to measure EPS included: (1) the Barnes Akathisia Rating Scale (BARS) global clinical rating score that evaluates akathisia, (2) the Abnormal Involuntary Movement Scale (AIMS) scores that evaluates dyskinesia, (3) the Simpson-Angus Scale (SAS) global score that broadly evaluates Parkinsonism and (4) the incidence of spontaneous reports of EPS-related adverse reactions.

In the 8-week double-blind, placebo-controlled study, the mean changes from baseline in BARS, AIMS and SAS total scores were comparable between PERSERIS- and placebo-treated patients. At all post-baseline assessments, mean changes from baseline were between -0.1 and 0.2 (inclusive) for the BARS, between 0 and 0.2 (inclusive) for the AIMS and between -0.1 and 0.2 (inclusive) for the SAS.

A higher incidence of akathisia was observed in the PERSERIS 120-mg (6.8%) group compared with the PERSERIS 90-mg (2.6%) and placebo group (4.2%); reports of extrapyramidal disorders were higher in the PERSERIS 90-mg group (4.3%) compared with the PERSERIS 120-mg (1.7%) and placebo group (0.8%).

In the 52-week open-label long-term safety study, there were no clinically relevant differences in the mean BARS, AIMS or SAS total scores within any treatment group during the study or across the treatment groups. At all post-baseline assessments, mean changes from baseline were between -0.2 and 0.3 (inclusive) for the BARS, between 0.1 and 0.5 (inclusive) for the AIMS and the SAS. The most commonly occurring EPS-related treatment-emergent adverse events (TEAEs) were akathisia (6.0%), tremor (2.0%) and extrapyramidal disorder (1.8%).

The incidence of treatment-emergent akathisia and other EPS symptoms was consistent with the established safety profile of risperidone.

1.2.7 Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the 1st few days of treatment. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. In the 8-week double-blind, placebo-controlled study, there was a higher incidence of dystonia in the placebo group (2.5%) compared with the PERSERIS groups (0 and 0.9%, respectively). In the 52-week open-label long-term safety study, there was a low incidence of dystonia in the de novo group (subjects diagnosed with schizophrenia) (0.7%) and none reported in the rollover treatment group (subjects who have completed a minimum of 56 days of double-blind placebo-controlled study).

1.2.8 Changes in Electrocardiograms

In the 8-week, double-blind, placebo-controlled study, there were no clinically relevant differences in mean changes from baseline to EOS in electrocardiogram (ECG) parameters, including QTcF (Fridericia's corrected QT interval), QRS and PR intervals, and heart rate, in subjects in either PERSERIS treatment group (90 mg and 120 mg) compared with placebo. Similarly, in the 12-month, open-label long-term safety study, there were no clinically relevant changes in mean ECG interval values from baseline to post-dose assessments.

1.2.9 Pain Assessment and Local Injection-Site Reactions

Local injection-site pain was assessed using subject-reported Visual Analog Scales (VAS) (0-100 mm; 0 = no pain to 100 = unbearably painful). In the 8-week, double-blind placebo-controlled study, the mean subject-reported Injection-Site Pain VAS scores were similar for all treatment groups following both injections. Pain scores decreased from a mean of 27 (VAS score) 1 minute after the 1st dose to a range of 3 to 7 (VAS score) 30 to 60 minutes post-dose. In the 12-month, long-term safety study, the 1-minute post-dose Injection-Site Pain VAS scores were highest on Day 1 (mean of 25) and decreased over time with subsequent injections (14 to 16 following last injection).

Throughout the clinical development program, the maximum reported intensity at any time point for each injection-site assessment (pain, tenderness, inflammation/swelling and erythema) was none or mild for most subjects receiving PERSERIS. Most subjects (≥ 79%) reported no tenderness and most who had tenderness reported mild severity. Less than 1% of subjects had moderate tenderness at any time point and 1 subject at Injections 1, 2 and 5 had severe tenderness. At each time point, most subjects (≥ 75%) reported no pain on injection. Of subjects who did have pain on injection, almost all of these were mild at each time point; only 1 or 2 subjects at Injections 1, 2, 7 and 12 had moderate pain on injection. At least 92% of subjects reported no erythema on each injection. All reports of erythema were of mild severity except for 2 cases of moderate erythema on Injection 1. Inflammation/swelling had a similar profile, with at least 88% of subjects reporting no inflammation/swelling and only mild symptoms except for 1 case of moderate severity on Injection 1.

1.3 Risk-Benefit Assessment

The risks associated with PERSERIS monthly SC injectable are indistinguishable from oral risperidone-containing products except for local injection-site reactions that are generally mild-to-moderate and self-limiting. The benefits of oral risperidone have been well established (NDA 210655, Section 2.7.3), as has the efficacy of PERSERIS (Nasser 2016, PERSERIS™ Prescribing Information 2018).

Over 4700 PERSERIS injections were administered across the clinical development program; all TEAEs pertaining to injection-site reactions were of mild-to-moderate severity. None of the injection-site reactions were assessed as serious by the Investigator. Injection-site reaction TEAEs (injection-site pain and injection-site nodule) resulted in study treatment discontinuation in only 2 subjects across the program.

The clinical benefits of PERSERIS include achievement of rapid results following a single treatment intervention and the delivery of continuous medication therapy via monthly SC injections. No loading dose or supplemental dosing is required at initiation of treatment since clinically relevant plasma concentrations of risperidone total active moiety are achieved during the 1st day of administration. The onset of action is rapid and persists with continued treatment, allowing for a simpler and more consistent treatment regimen for both patients and clinicians.

The benefits and safety of a 6-mg oral dose of risperidone have also been established (Risperdal® 2018). The expectation is that the 180-mg dose of PERSERIS will approximate both the benefit and the risk of 6 mg oral risperidone.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this study 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

2.2 Secondary

The secondary objectives of this study 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

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint for the study will be the measurement of $C_{avg\ (ss)}$ for risperidone and total active moiety after oral and SC administration.

3.2 Secondary

The following PK endpoints and safety assessments will be analysed:

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

- AEs, local injection-site tolerability (i.e., injection-site reactions), concomitant medications, changes in clinical laboratory results, vital sign measurements, 12 lead ECGs, body weight and monitoring of EPS using neurological and clinical symptom assessments (AIMS, SAS, 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

4 STUDY PLAN

4.1 Study Design

This Phase IV, open-label study will assess the safety, tolerability, pharmacokinetics and efficacy of 180 mg of PERSERIS in subjects with clinically stable schizophrenia (as determined by the DSM-5 criteria).

The study will enrol subjects who are currently on a stable dose of 5 mg or 6 mg of oral risperidone daily via any regimen. Any daily or twice daily dosing combination will be acceptable (i.e. 3/3, 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. All subjects will be stabilized on 6 mg daily [3 mg oral risperidone will be administered twice a day approximately 12 hours (±30 mins) apart] for 5 days. 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 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 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. Adverse event assessments will be made until Day 120, and PK assessments will be conducted through Day 113.

Dosing will be split into 2 sub-groups: 5 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.

At the EOS visit, subjects will be evaluated and prescribed an appropriate maintenance antipsychotic at a dosage determined by the physician.

A schematic of the study design is shown in Figure 1.

4.2 Schedule of Events

A complete list of procedures and assessments is included in the Schedule of Events (SOE), Appendix 1 through Appendix 5.

4.3 Duration of Treatment

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 for a total duration of 146 days.

5 STUDY POPULATION SELECTION

5.1 Number of Subjects

Approximately 65 subjects will be screened to enrol 25 eligible subjects, with an expected study completion of 15 evaluable subjects for the analyses.

Eligible subjects will be those who are assessed with clinically stable schizophrenia and who are already stabilized on oral risperidone (stable dose of 5 mg or 6 mg oral risperidone daily via any regimen). Any daily or twice daily dosing combination will be acceptable (i.e. 3/3, 4/2, 3/2). 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.

5.2 Inclusion Criteria

Subjects must meet **all** the following criteria:

1. Sex: male and female, Age: ≥ 18 to ≤ 65 years.

2. Diagnosis of schizophrenia as defined by DSM-5 criteria.

3. Status: clinically stable subjects defined as subjects with no hospitalizations for acute exacerbations within 3 months of Screening and Screening total PANSS score ≤ 70.

4. Subjects with a body mass index (BMI) between 18.0 and 35.0 kg/m^2 and who weigh at least 49.9 kg.

5. Subjects who have given written informed consent.

5.3 Exclusion Criteria

Subjects who meet any of the following conditions must be excluded from the study:

1. Subjects who have received a once-monthly LAI antipsychotic within 60 days of screening and a once-every-3-month LAI antipsychotic within 120 days of screening.

2. Subjects taking the following concurrent medication/over-the-counter (OTC) products:

    a. Inducers or inhibitors of CYP2D6 (See Appendix 7) within 14 days or 5 half-lives whichever is greater prior to study screening

    b. Bupropion, chlorpheniramine, cimetidine, clomipramine, doxepin or quinidine within 30 days prior to study screening

    c. Clozapine, phenothiazines, aripiprazole, haloperidol or any other antipsychotic other than oral risperidone within 14 days prior to study screening

d. Selective serotonin reuptake inhibitors (SSRIs) (See Appendix 7) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (See Appendix 7) within 30 days prior to study screening

e. Opioids or opioid-containing analgesics within 14 days prior to study screening

f. Medications, in the addition to those listed above which in the opinion of the Investigator in conjunction with the medical monitor, may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone, that may be associated with a significant drug interaction with risperidone, or that may pose a significant risk to subjects' participation in the study. The medical monitor should be contacted with any questions regarding the use of CYP2D6 or 3A4 inducers or inhibitors in particular.

3. Subjects with a history of cancer (with the exception of resected basal cell or squamous cell carcinoma of the skin) unless they have been disease free for ≥5 years.

4. Subjects with another active medical condition or organ disease that may either compromise subject safety or interfere with the safety and/or outcome evaluation of the study drug.

5. Subjects with evidence or history of a significant hepatic disorder that may either compromise subject safety or interfere with the safety and/or outcome evaluation of the study drug. Individuals with acute or chronic hepatitis (including but not limited to hepatitis B or C); or individuals with 1) total bilirubin >1.5x the upper limit of normal (ULN) and/or 2) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN will be excluded.

6. Subjects with a history of renal disease, or a creatinine clearance of less than 60 mL/min (as determined by the Cockcroft-Gault formula).

7. Subjects with a history of orthostatic hypotension, syncope, significant low white blood cell (WBC) count (i.e., absolute neutrophil count < 1.5 x 10^9/L), or drug-induced leukopenia or other medical conditions including, but not limited to, history of heart attack (i.e., myocardial infarction) or brain injury (i.e., traumatic with loss of consciousness and/or cardiovascular accident) within a year of Screening and clinically significant low blood pressure or arrhythmias as interpreted by the principal investigator (PI).

8. Subjects with corrected QT interval [Fridericia's calculation (QTcF)] >450 msec (male) or >470 msec (female) at Screening or prior to administration of the 1st dose of PERSERIS, or with a known history of Torsades de Points, or family member with sudden unexplained cardiac death.

9. Subjects who are known to have AIDS (acquired immunodeficiency syndrome) or to be HIV (human immunodeficiency virus) positive.

10. Subjects with suicidal ideation with intent and plan (C-SSRS affirmative answers to questions 4 and 5 of the ideation section) or suicide attempts within the last 6 months, as

noted on the C-SSRS, or subjects with uncontrolled depression in the opinion of the Investigator.

11. Subjects with a known diagnosis of type 1 diabetes or subjects with Haemoglobin A1c (HbA1c) >8.0% at Screening.

12. Subjects who have participated in a clinical trial within 30 days prior to study screening.

13. Subjects with significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.

14. Subjects who meet the criteria for the diagnosis of current moderate or severe substance use disorder, by DSM-5 criteria.

15. Subjects with prior allergic reactions, sensitivities, or other known contraindications to any component of PERSERIS (i.e., risperidone, PLG, PLGH or NMP).

16. Women of childbearing potential who are pregnant or breastfeeding, seeking pregnancy or failing to use adequate contraceptive methods during the study.

    a. Acceptable forms of contraception for female subjects include: oral, transdermal, injectable or implanted contraceptives, intrauterine device, or double barrier method (e.g., condom, diaphragm, cervical cap) with spermicide. Abstinence (defined abstaining from heterosexual intercourse for the duration of the study) is an acceptable form of contraception only if it is the subject's pre-existing method of contraception.

    b. A woman of childbearing potential is defined as any female who is less than 2 years postmenopausal or has not undergone a hysterectomy or surgical sterilization (e.g., bilateral tubal ligation, bilateral ovariectomy [oophorectomy]). Postmenopausal status will be confirmed by follicle stimulating hormone (FSH) test at initial screening.

    c. Male subjects with partners of childbearing potential should utilize a double barrier contraceptive method with spermicide to prevent pregnancy.

       Note: Following study termination or completion, it is recommended that all subjects maintain their current form of contraception for at least 30 days after the last dose of PERSERIS.

17. Subjects with a positive urine drug screen (UDS) anytime through Day -1 for opioids, cocaine, amphetamines, methadone, cannabinoids, barbiturates, benzodiazepines, methamphetamine and phencyclidine, unless the positive screen is determined to be secondary to an allowable concomitant medication. If a positive UDS is possibly the result of a subject's use of OTC or prescription medications, a repeat urine drug screen may be permissible. Study site personnel should contact the medical monitor for approval to retest.

18. Subjects with tardive dyskinesia as assessed by a score of ≥2 on Item 8 of the AIMS at Screening.

19. Subjects with epilepsy or other seizure disorders, Parkinson's disease or dementia.

20. Subjects with a history of neuroleptic malignant syndrome

21. Subjects who have been previously injected with PERSERIS within 6 months prior to Screening.

22. Subjects who are unable, in the opinion of the PI, to comply fully with the study requirements.

23. Subjects who are determined to be poor metabolisers, intermediate metabolisers or ultra-rapid metabolisers for CYP2D6 genotype

5.4 Deviation from Inclusion/Exclusion Criteria

This study is intended to be conducted as described in this protocol. Waivers from inclusion and exclusion criteria are not allowed because they have the potential to jeopardize subject safety, the scientific integrity of the study or regulatory acceptability of the data. Indivior does not grant waivers to the protocol-defined inclusion and exclusion criteria, and strict adherence to these criteria as outlined in the protocol is essential. The PI, sub-Investigator or suitably qualified designee will be responsible for identifying, documenting and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. In the event of a major deviation from the protocol due to an emergency, accident or mistake (e.g., eligibility or PERSERIS dosing errors), the PI, sub-Investigator or suitably qualified designee must contact the Indivior medical monitor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the PI and the Sponsor and reviewed by the study monitor. Deviations will be reviewed at the Medical Monitor Meetings. Deviations will be reported as required to the Institutional Review Board (IRB) and in the final study report.

Protocol deviations will be identified and documented through programmatic checks of study data, as well as through review of selected subject data listings prior to database lock.

6 STUDY CONDUCT

6.1 Subject Enrolment

After the informed consent form (ICF) has been signed and initial screening assessments completed and reviewed by the Investigator, eligible subjects who are currently on a stable dose of 5 mg or 6 mg of oral risperidone daily via any regimen will be admitted into the clinical unit. All subjects will be stabilized on 6 mg daily [3 mg risperidone will be administered twice a day approximately 12 hours (±30 mins) apart] for 5 days. After 5 days, oral risperidone dosing will be stopped and PERSERIS treatment will be initiated.

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 as indicated in the SOE (Appendix 1).

Study participation begins once written informed consent is obtained; a subject ID is then assigned. The subject ID will be used to identify the subject during the screening process and throughout study participation.

The Investigator is responsible for maintaining a master list (i.e., a subject identification list) of all consented subjects and will document all subjects that did not meet study eligibility criteria (i.e., screen failures), including reason(s) for ineligibility (i.e., a subject screening and enrolment log). This document will be reviewed by Indivior or designated representative for accuracy and completeness. Ineligible subjects, as defined by the protocol-specific inclusion and exclusion criteria, should not receive PERSERIS and should be documented as screen failures.

6.2 Oral Risperidone

Indivior will supply oral risperidone as Risperdal® to the study site as 3-mg tablets. The oral risperidone will be dispensed to eligible subjects at the study site by qualified study personnel and administered only during the inpatient stabilization period. Oral risperidone dosing will occur under fasted conditions (minimum fasting 1-hour pre-dose and 1hour post-dose). Water is allowed. The 6-mg oral risperidone daily dose will be administered as 3 mg two times a day approximately 12 hours (±30 mins) apart.

6.3 Screen Failure

A subject will be considered a screen failure if written informed consent is obtained but the subject did not meet inclusion or exclusion criteria. The study site will keep a Screening Log documenting subjects who have signed an informed consent. Screen failure reasons will be documented on the Screening Log.

6.4 Subject Completion

A completed subject is one that has completed all phases of the study, including the follow-up phone call. The end of the study is defined as the last subject's last visit.

6.5 Withdrawal Criteria

6.5.1 Subject Withdrawal from Treatment

A subject will be considered withdrawn from treatment if the subject has permanently discontinued study treatment. The primary reason for withdrawal from treatment must be entered into the electronic case report form (eCRF) (e.g., death, adverse event (AE), protocol non-compliance, Investigator decision, termination of the study by Indivior, or as requested by the subject for another or unknown reason). If a subject is withdrawn or withdraws prematurely from the study after receiving PERSERIS or oral risperidone, the reason for withdrawal is to be documented in the source documents and in the eCRF. At the time of withdrawal, the EOS procedures will be performed as the early termination (ET) assessments and captured in the withdrawn subject's source documents and eCRF. Subjects who are withdrawn from the study for any reason after treatment will not be replaced.

6.5.2 Subject Withdrawal of Consent

If a subject withdraws consent during study treatment, the subject will be evaluated and prescribed an appropriate maintenance antipsychotic. The maintenance dose will be determined by the physician's clinical judgment. The subject may be offered additional tests as-needed to monitor their safety (e.g., EOS safety assessments or procedures).

6.5.3 Subjects Lost to Follow-up

In cases of a missed visit, the Investigator or designee must attempt to contact the subject and re-schedule as soon as possible. The Investigator or designee must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

In the event a subject is lost to follow-up, the Investigator or designee must make a reasonable effort to contact the subject. Two documented attempts (e.g., phone, email, etc.) to contact the subject followed by a certified mailed letter is considered reasonable.

For documenting the date of discontinuation for a subject confirmed to be lost to follow-up, the date of discontinuation should be the date of last contact with the subject.

- In the case where a certified letter is sent but not confirmed as received by the subject, the date of discontinuation is the date the certified letter was sent.

- In the case where a certified letter is sent and has been confirmed as received by the subject, the date of discontinuation is the date of the confirmed subject receipt.

If neither of the above cases applies (which should be explained in the source documents), the date of discontinuation is the date of the subject's last study visit.

7 STUDY SUSPENSION OR TERMINATION

Indivior reserves the right to temporarily suspend and/or permanently discontinue the study at any time and for any reason, including safety or ethical concerns or severe non-compliance. If such action is taken, Indivior will discuss the rationale for the decision with the PI. In cases where a trial is suspended or terminated for safety reasons, Indivior will promptly inform Investigators and the Regulatory Authorities of this action and the reason(s) for the suspension or termination.

If required by applicable regulations, the PI must inform the IRB/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and study drug remaining on-site must be returned to Indivior or its designated representative.

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarized in Appendix 1 through Appendix 5 Further details on safety and efficacy assessments are provided in Section 8.10 and Section 8.11, respectively.

8.1 Informed Consent

A signed written ICF must be obtained from the subject or a legal representative before any study assessments or procedures may be performed. The potential subject will be given the IRB-approved ICF to review and the opportunity to ask questions concerning the study until he or she is satisfied. The potential subject should be able to answer simple questions about the study after the ICF has been reviewed and explained. After this explanation, the potential subject will be asked to sign and date the written ICF. The PI or designee obtaining informed consent from the subject will also sign the ICF to confirm that consent has been obtained as required. A copy of the signed ICF will be given to the subject.

If an assessment or procedure has already been performed as part of routine standard of care and was completed within the protocol-designated Screening window, the assessment or procedure does not need to be repeated unless clinically indicated.

8.2 Demographics and Medical History

A detailed medical history will be obtained by the PI or medically qualified designee during the Screening Visit. This will include information regarding the subject's full medical history including tobacco, alcohol and caffeine use, and psychiatric conditions, diagnoses, procedures, surgery, treatments, concomitant medications, demographic information (sex, race, date of birth, ethnicity) and any other noteworthy medical information, including suicidal ideation and behaviour measured using the C-SSRS. Any updates to medical history information that the PI or medically qualified designee becomes aware of will be captured throughout the study. If applicable, the subject's primary care physician will be notified of their involvement (with the subject's agreement) and request of medical records be provided upfront (to verify eligibility) and concomitant medication.

8.3 Physical Examination

The PI or a medically qualified designee will perform the physical examinations at the time points indicated in the SOEs (Appendix 1 and Appendix 5). A complete physical examination will include assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities and general appearance. The physical examination will not include a pelvic, breast or rectal examination. Additional unscheduled symptom-directed physical examinations may be conducted at any time at the PI's or medically qualified designee's discretion.

If any clinically significant change from Screening is noted, it will be reported as an AE and followed up to resolution or until reaching a stable endpoint.

8.4 Vital Signs

Evaluation of vital signs will be performed by qualified site personnel after the subject has been supine for 5 minutes and will include a measurement of systolic and diastolic blood pressure, pulse rate, oral temperature and respiratory rate. Vital sign measurements including orthostatic measurements of blood pressure and pulse will be obtained at the time points indicated in the SOE (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5) and following the supine ECG assessments, if taken at the same time. Blood pressure should be taken on the same arm throughout the study and will be taken with either a completely automated device consisting of an inflatable cuff and an oscillatory detection system or a non-automated device. Body temperature will be measured with an oral thermometer.

Weight (in kg) will be assessed in ordinary indoor clothing with shoes off and will be recorded at the time points indicated in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5). Height (in cm) will be recorded at the Screening visit. BMI will be calculated at Screening and at the EOS visit. BMI is defined as the subject's weight (in kg) divided by the square of the subject's height in metres (kg/m^2).

If the PI or medically qualified designee determines that clinically significant changes have occurred in any vital sign measurement, that measurement will be captured as an AE and repeated at medically appropriate intervals until the value returns to an acceptable range wherein the subject is clinically stable, a specific diagnosis is established, or the condition is otherwise explained.

8.5 12-Lead Electrocardiograms

A 12-lead ECG will be conducted at the time points indicated in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5) following a supine rest for 5 minutes. ECG parameters including the QT interval, QTcF, PR interval and QRS intervals, and heart rate will be recorded. The ECG measurements will be reviewed during the visits by the PI or medically qualified designee to assess any immediate abnormalities. Findings of the ECGs will be marked by the PI or medically qualified designee as normal, abnormal–not clinically significant or abnormal–clinically significant.
ECG parameters, including the QT interval, QTcF, PR, QRS intervals and heart rate will be recorded on the tracing and in the eCRF. The formula for QTcF are as follows:

$$QTcF = QT/\sqrt[3]{RR \text{ (time between QRS complexes)}}$$

8.6 Local Tolerability

8.6.1 Injection-Site Grading

Local injection-site grading will be assessed by appropriately trained personnel by observation and subject questioning, according to the SOEs (Appendix 2, Appendix 3, Appendix 4 and Appendix 5), for pain, tenderness, erythema/redness and induration/swelling. Severity will be assigned as none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3) or potentially life-threatening (grade 4) utilizing the Injection-Site Grading Scale (ISGS) (Appendix 9). The

local injection-site grading assessment will be completed on injection day within 10 minutes post-injection and at 3 hours (± 30 minutes).

8.6.2 Injection-Site Pain Visual Analog Scale (VAS)

The Injection Site Pain Visual Analog Scale (VAS) (see Appendix 10) 100 will be completed by the subject after each PERSERIS injection, commencing at 1 minute (± 15 seconds), 5 (± 2 minutes), 30 (± 2 minutes) and 60 minutes (± 2 minutes), according to the SOEs (Appendix 2, Appendix 3, Appendix 4 and Appendix 5). The timing of the VAS should be measured after the completion of the injection. This VAS is used to measure injection site pain as rated by the subject. For example, the amount of injection site pain that a subject has at each time point can be marked on paper along a continuum from "no injection site pain" to "worst imaginable injection site pain." Operationally, the VAS is a horizontal line 100 mm in length anchored by word descriptors at each end as illustrated in Appendix 10. The sites will use the injection site pain VAS scale that is provided and will not make any copies of the scale. The subject marks on the line the point that he/she feels represents their perception of their current state. The VAS score is determined by measuring (mm) from the left hand end of the line to the point that the subject marks. A specific ruler will be provided to the sites to be used for the measurement of the VAS score.

8.6.3 Injection-Site Evaluation

The injection site will be evaluated for the size by the appropriate trained personnel by observation and examination, according to SOE (Appendix 2, Appendix 3, Appendix 4 and Appendix 5). The injection-site depot will be evaluated for size (using a tape measure the length, breadth and depth of the depot), position (quadrant of the abdomen and back of arm) and consistency (soft, firm, hard). Previously injected site will be inspected for all the above as well.

8.6.4 Early Removal of PERSERIS

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 surgical procedure requires a small incision at the injection site with a sterile scalpel where the depot was placed, removal of the depot with forceps and irrigation of the incision with sterile normal saline. To close the incision, suturing may be required. The primary reason for depot removal must be entered into the electronic eCRF (e.g., death, AE, protocol non-compliance, Investigator decision, termination of the study by Indivior, or as requested by the subject for another or unknown reason). If a subject elect not to have PERSERIS removed, the reason for refusal should be fully documented. Subjects who have PERSERIS removed should undergo all EOS assessments and follow-up visit assessments according to the procedures described in SOE (Appendix 5) at the time of PERSERIS removal or study withdrawal. These subjects should have an unscheduled follow-up visit within 7 days after removal.

8.7 Clinical Laboratory Tests

With the exception of the Screening visit, subjects should fast for a minimum of 8 hours prior to blood draws for all laboratory assessments. If screening random glucose is abnormal, a fasted retest is allowed. A fasting sample will be required to measure glucose and/or cholesterol (high-density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides [TG]). Subjects with clinically significant abnormal laboratory test results at Screening may enter the treatment period only after laboratory test(s) are repeated once and the results are received and determined by the Investigator prior to treatment to have no abnormality(ies) that is/are clinically significant. Subjects will be in a seated or supine position during blood collection. Clinical laboratory assessments will be performed by the local clinical laboratory accredited by the College of American Pathologists or a certificate of compliance issued by the Center for Medicare & Medicaid Services, Clinical Laboratory Improvement Amendments. PK and pharmacogenomics (PGx) samples will be processed by the site and sent to a designated central laboratory. The laboratory assessments will include routine and screening laboratory tests and are performed at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

Any abnormal haematology, serum chemistry or urinalysis test result after study drug intake that is deemed clinically significant by the PI or medically qualified designee will be reported as an AE and repeated, including test results obtained on the final study day. For any test abnormality deemed erroneous or clinically significant, repeat analysis will be performed until resolution or until the PI or medically qualified designee determines that resolution of the laboratory abnormality is not expected.

The following clinical laboratory (Table 1) tests will be performed according to the SOE in Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

Table 1 List of Laboratory Tests

Haematology	**Serum Chemistry:**
Haematocrit (Hct)	Albumin (ALB)
Haemoglobin (Hgb)	Alkaline phosphatase (ALP)
Platelet count	Alanine aminotransferase (ALT)
Red blood cell count (RBC)	Aspartate aminotransferase (AST)
WBC count with differential (absolute neutrophil count, lymphocytes, monocytes, basophils, eosinophils)	Blood urea nitrogen (BUN)
	Calcium
	Carbon dioxide
Urinalysis:	Chloride
Appearance	Creatinine
Bilirubin	Creatinine Clearance (Cockcroft-Gault creatinine clearance (mL/min) = [140 – age] x [body weight (kg)] x [0.85 *if female*]/[serum creatinine (mg/dL)] x 72)
Colour	
Glucose	
Ketones	

Leucocyte esterase	Creatine phosphokinase (CPK)
Microscopic examination of sediment[a]	Gamma-glutamyl transferase (GGT)
Nitrite	Glucose
Occult blood	HDL
pH	LDL
Protein	Lipase
Specific gravity	Magnesium
Urobilinogen	Phosphorus
	Potassium
Serology:	Prolactin
Anti-Hepatitis B IgM core antibody (IgM anti-HBc)	Sodium
Hepatitis B surface antigen (HBsAg)	Total bilirubin
Hepatitis C virus (HCV) antibody	Direct bilirubin
HIV-1 and -2 antibodies	Total cholesterol
	Total protein
Pregnancy:	Triglycerides
FSH for postmenopausal female subjects (screening only)	Uric acid
Urine Pregnancy (only for females not postmenopausal or surgically sterile for at least 1 year), Serum pregnancy test for female subjects of childbearing potential (screening only)	**Urine Drug Screen (UDS):**
	Opioids[b]
Screening Only:	Cocaine
Haemoglobin A1c	Amphetamines
PGx sample for CYP2D6 genotyping	Methadone
	Cannabinoids
	Barbiturates
	Benzodiazepines
	Methamphetamine
	Phencyclidine

[a] Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive (microscopic examination may include but is not limited to WBC count, RBC count, casts and crystals).

[b] Oxycodone may not show up in all opiate assays and should be assessed separately.

8.7.1 Sample Collection, Storage and Shipping

All blood sampling will be drawn by individual venipuncture or saline lock . Blood sample collection and processing procedures will be outlined in a separate reference manual to be provided to the clinical facility.

8.8 Pharmacokinetic Assessments

The PK analyses will include data from all subjects who receive oral risperidone or at least one dose 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 $C_{avg\ (ss)}$ for risperidone and total active moiety after oral and SC administration. For primary analysis, only the data from those subjects will be considered who receive 3 doses of PERSERIS and provide an adequate number of blood samples for determination of $C_{avg\ (ss)}$ for risperidone and total active moiety.

Individual plasma concentrations will be collected according to the schedule outlined in Appendix 6. 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 will be treated as zero in the calculation of total active moiety concentration.

Individual and mean plasma concentration versus time plots will be presented on linear and semi-logarithmic scales, by treatment, for risperidone, 9-hydroxyrisperidone and total active moiety, as appropriate.

Pharmacokinetic parameters will be calculated for risperidone, 9-hydroxyrisperidone and total active moiety (risperidone + 9-hydroxyrisperidone), by non-compartmental analysis.

The PK parameters calculated after the 4th dose of 180 mg PERSERIS will be considered a secondary endpoint.

Table 2 Pharmacokinetic Parameters

Oral Risperidone Administration (Day -1; 0 to 12 Hours) Note: The PK analysis will include data from all subject 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)	
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)	
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 (2nd and 3rd 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
$C_{avg14days}$	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

Analysis may include calculation of other PK parameters as applicable. Pharmacokinetic calculations will be performed using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation). Summary statistics (number of observations, arithmetic mean, median, standard deviation, minimum, maximum, geometric mean and coefficient of variation) for all relevant PK parameters of risperidone, 9-hydroxyrisperidone and total active moiety will be presented after oral and subcutaneous administration.

Steady-state attainment after oral dosing and SC dosing will be evaluated.

The following PK data collected after 4th dose (an alternate site, arm) will be compared against PK data collected after 3rd dose (the abdominal site):

- Initial peak parameters: C_{max}, t_{max}
- Secondary peak parameters (if applicable): C_{max}, t_{max}
- Overall Parameters: C_{max}, $C_{avg\,(ss)}$, t_{max}, AUC_{τ}
- PK parameters over partial interval (0 to 14 days): $C_{max14days}$, $PAUC_{14days}$, $C_{min14days}$, $C_{avg14days}$
- PK parameters over partial interval (14 to 28 days): $C_{max28days}$, $PAUC_{28days}$, $C_{min28days}$, $C_{avg28days}$

A more complete description of the PK analyses will be provided in the Statistical Analysis Plan (SAP).

8.8.1 Plasma Samples for Pharmacokinetic Analysis

Blood samples will be collected for PK analysis according to the SOE (Appendix 6). Additional PK samples will be collected should injection related issues (i.e., obstruction or leaking) occur

on the day of injection. Any additional PK samples taken on injection days will be collected within one hour of injection.

Blood samples will be collected in pre-labelled vacutainer tubes containing K_2-EDTA (ethylenediaminetetraacetic acid) as a preservative. Blood sampling will be performed by appropriately qualified and trained study personnel, by individual venipuncture, or, if necessary, through an inserted indwelling catheter with a saline lock in the subject's forearm to minimize subject risk and discomfort. Heparin flushing is not permitted. The indwelling catheter will only be flushed with saline. Each blood sample by venipuncture will be approximately 6.0 mL. In the event an indwelling venous catheter is used during PK sampling, this will result in approximately an additional 3.0 mL of blood per sample for the initial drawback, which will be discarded prior to obtaining the 6.0 mL blood sample for analysis.

The exact times (to the minute) and date of collection of each sample will be recorded in the source documents.

All PK blood samples must be placed immediately into an ice bath after collection.

PK blood samples will be centrifuged at approximately 3000 rpm for 10 minutes at 4ºC. The resulting plasma samples will be harvested, divided into approximately equal aliquots of 1.5 mL each and transferred into appropriately labelled polypropylene screw-cap tubes. Thus, one half of each processed blood sample (i.e., plasma) will be the primary sample, and the other will be the backup sample. The samples will be shipped to the bioanalytical lab for analysis, as requested by the Sponsor. The backup samples should be transferred to the bioanalytical lab only after the clinical site has received a confirmation notice from the bioanalytical lab that the original samples have been received.

All PK plasma samples will be placed in a storage freezer at -20ºC within 60 minutes of blood draw. Samples will remain frozen until assayed. A more detailed description of plasma sample preparation requirements and shipment of samples will be provided in the laboratory manual. Appropriate documentation shall be placed in the trial master file.

8.8.2 Sample Analysis

Plasma samples will be analysed for risperidone and 9-hydroxyrisperidone concentrations using a validated method of liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation is 0.1 ng/mL for risperidone and 0.1 ng/mL for 9-hydroxyrisperidone. Raw data will be archived at the bioanalytical site.

8.9 Biomarkers and Pharmacodynamic Markers

8.9.1 CYP2D6 Genotyping

Approximately 5 to 10 mL of whole blood in purple top polypropylene Vacutainers® containing K_2-EDTA will be collected at screening. The blood sample will be de-identified (i.e., labelled with a study number and subject number) and submitted to a central laboratory for analysis. The blood should not be frozen prior to shipping but immediately refrigerated following collection. No genetic investigations other than CYP2D6 genotyping are planned, and none will be done on subject blood samples without IRB approval and specific, written informed consent of the subject.

The normal (wild-type) allele is designated as CYP2D6*1. Null (loss of function) alleles that are associated with the poor metaboliser phenotype: CYP2D6*3, CYP2D6*4, CYP2D6*5 (gene deletion), CYP2D6*6, CYP2D6*7 and will be analysed. Reduced activity alleles that are associated with the intermediate metaboliser phenotype: CYP2D6*9, CYP2D6*10, CYP2D6*17 and CYP2D6*41 will be analysed. CYP2D6 phenotypes will be classified based on the publication 'Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants' by Hicks et al (2013).

Results for genotyping may take 1 to 2 weeks to be received from the date of receipt at the testing facility.

The PGx samples are for the purpose of assessing genetic variation in enzymes that may affect the PK of PERSERIS. PGx sample collection, handling and storage are explained in greater detail in the laboratory manual.

8.10 Safety Assessments

8.10.1 Abnormal Involuntary Movement Scale (AIMS) for Tardive Dyskinesia

The AIMS is a tool that aids in early detection and ongoing monitoring of tardive dyskinesia, a movement disorder that can result from long-term treatment with antipsychotic medication. By assessing the subject's body movement in specific positions requiring rotation, a psychiatrist is able to determine whether abnormal facial or body movements exist (Keith 2009). Facial, oral, extremity and trunk degree of involuntary movement is 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, a global assessment of the subject is made, which includes overall level of involuntary movement severity (based on the highest single movement score recorded), incapacitation due to involuntary movement, self-awareness of involuntary movement and dental status. This scale is presented in Appendix 12 and is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

8.10.2 Simpson-Angus Scale (SAS)

The SAS is a 10-item scale used to detect the presence of drug-induced Parkinsonism and extrapyramidal side effects and evaluates symptom severity (Keith 2009). The 10 items focus on

rigidity rather than bradykinesia and do not assess subjective rigidity or slowness. Items are rated for severity on a 0–4 scale, with definitions given for each anchor point. The SAS is presented in Appendix 13 and is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

8.10.3 Barnes Akathisia Rating Scale (BARS)

The BARS is a 4-item scale that detects the presence and severity of any drug-induced akathisia. The scale measures objective and subjective effects such as restlessness and awareness of restlessness, respectively (Keith 2009, Riezen 1988). Subjects are observed while seated, then while standing and engaged in neutral conversation, for a minimum of 2 minutes in each position. Symptoms observed during additional situations, such as subject behaviour on the ward, may also be rated. Subjective phenomena should be elicited through direct questioning of the subject. Global assessment is made on a scale of 0 to 5, with comprehensive definitions provided for each anchor point on a scale in which 0=absent, 1=questionable, 2=mild akathisia, 3=moderate akathisia, 4=marked akathisia and 5=severe akathisia. The BARS is presented in Appendix 15 and is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

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

The C-SSRS is a scale developed by the National Institute of Mental Health trial group as a counterpart to the Food and Drug Administration's (FDA) categorization of suicidal events (Möller 2007, Posner 2007). It is based on a categorization of thoughts and behaviour that are statistically identified as significantly related to suicidal behaviour. The scale captures the occurrence, severity and frequency of suicide-related thoughts and behaviours throughout lifetime at Screening and for the time interval since last administration for repeat administrations during a study. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behaviour occurred (baseline/screening and since-last-visit versions of the C-SSRS are presented in Appendix 16). For the baseline/screening version, the subsection "Suicidal Ideation" should reflect responses from the past 6 months of the subject's life, and the subsection "Suicidal Behaviour" should reflect responses from the past year of the subject's life. The C-SSRS is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

8.11 Clinical Assessments

8.11.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a medical scale designed to measure symptom severity among subjects with schizophrenia, utilizing a 30-item, 7-point rating scheme comprising adaptations of 18 items from the Brief Psychiatric Rating Scale and 12 items from the Psychopathology Rating Schedule (Kane 2003, Risperdal® 2018, Risperdal Consta® 2018, Kay 1987, Peralta 1994). Each item on the PANSS is accompanied by a complete definition as well as detailed anchoring criteria for all 7 rating points, which represent increasing levels of psychopathology: 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe and 7= extreme. The PANSS is scored by

summation of ratings across items such that the potential ranges are 7 to 49 for the Positive and Negative Scales and 16 to 112 for the General Psychopathology Scale. The PANSS is presented in Appendix 11 is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

8.11.2 Clinical Global Impression – Severity of Illness Scale (CGI-S)

The overall clinical severity of illness for each subject will be rated using the Clinical Global Impression – Severity of Illness scale (CGI-S). To perform this assessment, the rater will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time"? Response choices include: 0 = not assessed; 1 = normal, not ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. This scale is presented in Appendix 14 and is administered at the visits listed in the SOEs (Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5).

8.12 Appropriateness of Measurements

The clinical data measures to be employed in this study are standard, generally accepted clinical assessment scales. The PANSS is a medical scale designed to measure symptom severity among subjects with schizophrenia. The CGI-S is a conventional tool for determining the subject's severity of illness, clinical status and change from baseline over time.

The conventional safety assessments that will be used in this study are suitable, standard and widely used measures for evaluating the safety of the study drug. Measurement of drug levels in plasma over time is a standard evaluation of pharmacokinetic parameters.

Secondary safety evaluations will include 4 scales: the AIMS, the SAS and BARS, which are standard neurological and clinical symptom assessments of EPS; and the C-SSRS, a validated screening measure for detecting suicide risk.

8.13 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or ICH/GCP requirements. The non-compliance may be either on the part of the subject, the Investigator or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly and in accordance with ICH E6. It is the responsibility of the Investigator and study site staff to use continuous vigilance to identify and report deviations to Indivior or specified designee. All deviations must be addressed in the study source documents. Protocol deviations must be sent to the local IRB/IEC as required. The Investigator and study site staff are responsible for knowing and adhering to the IRB/IEC's requirements.

9 STUDY DRUG MANAGEMENT

9.1 Description

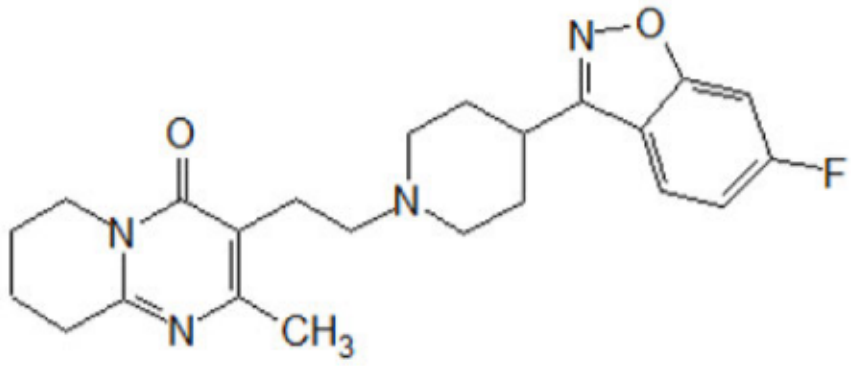
The term 'study treatment' is used throughout the protocol to describe any combination of product received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

9.1.1 Study Treatment

PERSERIS

PERSERIS injection contains risperidone, an atypical antipsychotic. Risperidone belongs to the chemical class of benzisoxazole derivatives. The chemical designation 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl) piperidin-1-yl] ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a] pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.5 g/mol.

The structural formula is:



Risperidone is a white to off-white powder. It is practically insoluble in water and soluble in methanol and 0.1 N HCl.

PERSERIS is available as a sterile 2-syringe mixing system; a liquid syringe pre-filled with the delivery system, a colourless to yellow solution. The delivery system provides the monthly extended-release delivery of risperidone in PERSERIS. It is comprised of poly (DL-lactide-co-glycolide) polymer and *N*-methyl-2-pyrrolidone. The powder syringe is pre-filled with risperidone (white to yellow). Prior to use, the product is constituted by coupling the liquid and powder syringes and passing the contents back-and-forth between the syringes. On completion of the mixing cycles, the combined mixture resides in the liquid syringe. A sterile, safety needle is affixed to the liquid syringe and the expressible syringe contents are injected subcutaneously into the abdomen or back of upper arm. The product should be prepared immediately prior to use for

subcutaneous injection. See Appendix 8 for Investigational Product Preparation and Dispensing Instructions.

After mixing, PERSERIS is available as an extended-release injectable suspension, for subcutaneous use, in the following strengths of risperidone: 90 mg and 120 mg.

Reference:

Manufactured for: Indivior Inc., North Chesterfield, VA 23235.

Powder syringe manufactured by Patheon Manufacturing Services, Greenville, NC 27834.

Liquid syringe manufactured by AMRI Global, Burlington, MA 01803.

Risperdal® (risperidone) Tablets for oral use, 3mg

Risperdal® contains risperidone. Risperdal® tablets are for oral administration and the 3mg tablet is a yellow, capsule-shaped tablet in bottles of 60 count.

Reference:

Active Ingredient is made in Ireland

Finished Product is manufactured by:

Janssen Ortho, LLC

Gurabo, Puerto Rico 00778

9.2 Packaging and Storage

9.2.1 PERSERIS

PERSERIS labels will be developed in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements.

PERSERIS inner packaging (pouches) must remain with the outer product carton until the time of administration.

How Supplied

PERSERIS (risperidone) for extended-release injectable suspension, for subcutaneous use is, when fully mixed, a viscous suspension that varies from white to yellow-green and is commercially available in dosage strengths of 90 mg and 120 mg.

PERSERIS 90 mg will be supplied for this study as a single-dose kit, packaged in a carton (NDC 12496-0090-1), containing the following:

- One pouch with a sterile syringe (labelled P'for powder) pre-filled with risperidone powder
- One pouch with a sterile syringe (labelled 'L'for liquid) pre-filled with the delivery system and desiccant.
- One 18-gauge, 5/8-inch sterile safety needle.

Storage and Handling

Store in refrigerator at 2° to 8°C (36° to 46°F). Allow PERSERIS kit to come to room temperature, 20°C to 25°C (68°F to 77°F), for at least 15 minutes prior to mixing.

PERSERIS may be stored in its unopened original packaging at room temperature, 20°C to 25°C (68°F to 77°F), for up to 7 days prior to administration. After removal from the refrigerator, use PERSERIS within 7 days or discard.

9.2.2 Risperidal®

Risperdal® clinical identifier label will be developed in accordance with GMP and local regulatory requirements.

How Supplied

Risperdal® (risperidone) tablets, for oral use will be supplied in bottles of 60 count, 3mg tablets (NDC- 50458-0330-06). Each bottle will have a clinical trial identifier label applied.

Storage and Handling

Risperdal® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

9.3 Drug Administration

Study drug must be administered under the supervision of the PI or a medically qualified designee. Study drug will be administered only to subjects participating in the study. The Investigator or designee agrees to neither administer the study drug from - nor store it at - any location other than the study site agreed upon with Indivior.

The PI is responsible for ensuring proper and accurate documentation of the administration of investigational product.

See Appendix 8 for additional instructions on preparing the study drug for dispensing and administering.

9.3.1 Drug Preparation, Inspection and Administration

Drug preparation, inspection and dispensing instructions are presented in Appendix 8.

9.4 Accountability

The Investigator is responsible for ensuring that all study drug received at the site is inventoried, accounted for and documented in accurate study drug accountability records. Upon completion of the study and/or as requested by Indivior, copies of study drug accountability records will be provided to Indivior. Upon completion of the study and following Indivior approval, all unused study treatment will be disposed of by the study site or specified designee. Study drug must be handled strictly in accordance with the protocol, handling guidelines and the label; it must be stored in a locked, limited-access area under appropriate environmental conditions.

The dispensing of all study treatments (PERSERIS and Risperdal®) to the subject must be documented on the drug dispensing form. All study drug dispensation will be performed by a pharmacist or designee, checked by a study site staff member and documented on a drug dispensation form.

Unused study treatment must be available for verification by the site monitor during on-site monitoring visits.

9.5 Reporting Product Complaints

The Investigator and study site staff are responsible for prompt recognition and reporting of product quality complaints to Indivior. A product complaint is any concern pertaining to the manufacturing or quality control of the study drug and includes, but is not limited to, short counts/empty pouches, broken needles, labelling defects, missing inserts, packaging defects or difficult to open packaging, study drug that is thought to be ineffective, or has an appearance, taste or odour that is outside of what is expected.

All product complaints should be reported to Indivior in a timely manner and the following information provided:

- Site Number
- Site contact/reported by
- Subject Number (if already assigned to a subject)
- Description of issue
- Picture, if available (photographs should be taken only if safe to do so/within site policy or practice to take photograph)

If the product has not yet been opened (i.e. product does not pose any hazard), retain the product and packaging in a quarantined space until further instruction is provided by Indivior. If the product is potentially hazardous, dispose per site process and document in the source.

9.6 Permitted and Prohibited Concomitant Therapies

Concomitant medications will be collected 30 days prior to screening until EOS visit at the time points listed in Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5. Any concomitant medications (including health, herbal and dietary supplements) taken during the study will be recorded in the source documents and in the eCRF. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy and dose changes.

The best medical interests of the subject should guide the Investigator in the management of conditions that are pre-existing or that develop during the study (intercurrent illness or AEs). All study personnel should be familiar with the content of the Investigator's Brochure (IB) in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed. The PI or medically qualified sub-Investigator should carefully assess the potential for interaction with risperidone before prescribing any concomitant medications.

Concomitant use of benzodiazepines, propranolol and anti-parkinsonian medication may be required to treat and alleviate side effects during the study treatment period.

9.6.1 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications deemed necessary to the subject, with the exception of those medications defined in Appendix 7 of the protocol.

Treatment of Agitation and Anxiety

Concomitant use of the following oral (PO) benzodiazepines for treatment of agitation and/or anxiety is allowed, at the Investigator's discretion, as-needed, in divided doses.

- lorazepam 3 mg/24 hours (PO)
- alprazolam 1.5 mg/24 hours (PO)
- clonazepam 1.5 mg/24 hours (PO)
- diazepam 15 mg/24 hours (PO)

If a subject requires more than the dose(s) of benzodiazepine(s) listed above or requires benzodiazepine treatment for more than 5 days, the site should contact the medical monitor to discuss suitability of the subject to continue in the study.

Benzodiazepines should not be administered within the 12-hour period prior to assessment with the CGI-S, or EPS scales.

Treatment of Insomnia

Only 1 sleep aid may be used per night.

Concomitant use of oral zolpidem should not exceed 10 mg/night total dose.

Lorazepam can be used to treat insomnia if used as outlined above.

Eszopiclone (up to 3 mg) or zaleplon (up to 20 mg) may be used in place of zolpidem.

Sleep aids for insomnia should not be used within 12 hours prior to rating symptoms with the CGI-S, or EPS scales.

Treatment of Extrapyramidal Symptoms (EPS)

In the event of newly emergent EPS during the treatment period, oral propranolol (for akathisia) up to 60 mg/day and/or concomitant use of anti-parkinsonian medications is allowed on an as-needed basis only. Every effort should be made to rate on neurological motor scales (SAS, BARS and AIMS) prior to initiation of anti-parkinsonian medications. Concomitant use of oral anticholinergic medications should not exceed an equivalent of benztropine 4 mg/24 hours given in 1 to 2-mg doses. The PI should make every effort to minimize and taper anti-parkinsonian use as clinically indicated and appropriate.

These medications should not be used within 12 hours prior to assessment with the CGI-S, or EPS scales.

Non-Therapy Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the Investigator. Any elective procedures (e.g., minor surgery, dental surgery, orthopaedic surgery, etc.) that might require hospitalization or general anaesthesia should be evaluated by the PI before the subject is enrolled in this study.

Short Term Opioid Use for Acute Pain

Short term use of opioid analgesics for acute pain during open-label treatment may be permitted with approval of the medical monitor. In case of emergency, the Investigator may administer necessary medication, but should inform the medical monitor as soon as possible.

9.6.2 Prohibited Concomitant Therapies

Subjects should be instructed not to take any medications, including OTC products, without first discussing with the Investigator.

The use of the following treatments will not be permitted from Screening to EOS visit:

- Clinically relevant inducers or inhibitors of cytochrome P450 CYP2D6, or CYP3A4, within the required washout period of a minimum of 5 half- lives prior to Day 1 and for

the duration of the study. A list of prohibited CYP450 inducers or inhibitors is presented in Appendix 7. The medical monitor should be contacted with any questions regarding the use of CYP2D6 or CYP3A4 inducers or inhibitors.

- Benzodiazepines within the 12-hour period prior to administration of CGI-S and EPS scales (SAS, BARS and AIMS).
- Non-benzodiazepine sleep aids within 12 hours prior to administration of CGI-S and EPS scales (SAS, BARS and AIMS).
- Propranolol within 12 hours prior to administration of CGI-S and EPS scales (SAS, BARS and AIMS).
- Anti-parkinsonian medications within the 12-hour period prior to administration of CGI-S and EPS scales (SAS, BARS and AIMS).
- Any antipsychotic medication for the duration of the study with the exception of protocol dictated oral risperidone and PERSERIS treatment.
- Medications, in addition to those listed in Section 9.6.1 and Appendix 7, which, in the opinion of the PI in conjunction with the medical monitor, may be expected to significantly interfere with the metabolism or excretion of risperidone and/or 9-hydroxyrisperidone, may be associated with a significant drug interaction with risperidone, or that may pose a significant risk to subjects' participation in the study are also prohibited.

9.6.3 Lifestyle Restrictions

Urine Drug Screen Substances

If a subject has a positive UDS for opioids, cocaine, amphetamines, methadone, barbiturates, benzodiazepines, methamphetamine, cannabinoids or phencyclidine, the Investigator or designee will solicit additional information from the subject regarding the use of illicit substance(s) as well as frequency of use. Based on this information, the Investigator will consult with the medical monitor to determine whether continued participation in the study would impact the safety of the subject.

9.7 Compliance

This study involves the administration of oral risperidone and 4 doses of 180 mg of PERSERIS (each 180-mg dose will be administered as two 90-mg SC injections). The PI or sub-Investigator may terminate a subject based on the subject's ability to comply with the protocol requirements.

Study drug will be administered by designated qualified study personnel at the clinical facility. The PI or sub-Investigator will be present during the administration of study drug. The time and duration, the dose delivered and any dosing observations will be recorded in source documentation. The PI, sub-Investigator or designated individual will maintain a log of all study

drugs dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study.

10 ADVERSE EVENTS

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an AE.

An AE is any untoward medical occurrence in a subject associated with the use of PERSERIS regardless of the presence of a causal relationship to the study drug. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with PERSERIS, whether or not considered related to the study drug.

Events meeting the definition of an AE include:

- New condition detected after PERSERIS administration even though the AE may have been present prior to receiving the study drug.
- Exacerbation of a pre-existing condition (including intensification of a condition and/or an increase in frequency).
- Any abnormal laboratory test results or other safety assessments felt to be clinically significant in the opinion of the Investigator (including those that worsen from baseline).
- Symptoms and/or the clinical sequelae of a suspected interaction or an overdose of either PERSERIS or a concomitant medication
- Signs, symptoms or clinical sequelae resulting from special interest conditions (e.g., PERSERIS misuse, medication error, leaking from the injection site, PERSERIS withdrawal, PERSERIS depot removal etc). Overdose per se will not be reported as an AE/serious adverse event (SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.
- Symptoms of dose-dumping or any obstructions/issues with PERSERIS injection based on the clinical judgment of the investigator.
- Symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE.
- Symptoms and/or clinical sequelae that resulted in intervention.

Events that do not meet the definition of an AE include:

- The disease/disorder being studied, or expected progression, signs, or symptoms or the disease being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedures; the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, hospitalization for elective surgery, hospitalization for observation in the absence of an AE).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1 Assessment of Adverse Events

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment and reporting of AEs may be delegated to a medically qualified sub-Investigator, trained on this study protocol, who is listed on the delegation of authority log. All AEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described in this protocol.

Adverse events should be volunteered by the subject or solicited from the subject using a standard statement, obtained from examination of the subject at a site visit, or from observations of clinically significant laboratory values or special examination abnormal values. If an event assessed by one of the study scales requires intervention, or if in the opinion of the Investigator, it is clinically significant, then it will be reported as an AE.

All AEs are to be assessed and recorded in a timely manner and followed to resolution or until the Investigator determines that there is not an anticipated resolution. Each AE is to be documented with reference to severity, date of occurrence, duration, treatment and outcome. Furthermore, each AE is to be classified as being serious or non-serious. In addition, the Investigator must assess whether the AE is study drug-related or not.

10.1.1 Time Period for Collecting Adverse Events

Adverse event monitoring and reporting will begin after the subjects sign the ICF, continue throughout the study and include EOS/ET/Follow-up. Subjects will be monitored by the study site staff for untoward effects and will be released from the study after the last procedure is completed and confirmed that the subject has no residual untoward effects from the study drug that may affect safety.

Surgical procedures, planned before enrolment of the subject in the study, are not considered AEs if the condition was known before study inclusion. In this case the medical condition should be reported in the subject's medical history.

Any clinically significant symptoms will be reported as AEs. All AEs and corresponding treatment will be recorded in the eCRFs and a summary of all the safety data will be presented in the final Clinical Study Report (CSR). Any ongoing AEs will be appropriately followed up until resolution or 7 days after EOS/ET. The study site personnel will make every effort to contact the subject for a minimum of 2 attempts after which the outcome of the AE will be reported as lost to follow-up.

If a subject experiences the onset of an SAE within 5 days following study completion and in the opinion of the Investigator, that SAE is associated with the study, it will be followed and reported as described in Section 11.2.

If an SAE occurs that is deemed related to study drug, a PK sample will be taken as soon as possible after the event is reported. If possible, an additional sample should be collected when the SAE has been resolved.

10.1.2 Assessment of Intensity

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Intensity	Definition
Mild	Causes transient or mild discomfort; no limitation of usual activities; no medical intervention required
Moderate	Causes mild-to-moderate limitation in activity; some limitation of usual activities; no or minimal medical intervention or therapy is required
Severe	Causes marked limitation in activity; some assistance is usually required; medical intervention or therapy is required; hospitalization is probable

Adverse events with changes in severity should be documented as separate events.

10.1.3 Assessment of Causality

The Investigator or a medically qualified sub-Investigator trained on this study protocol, listed on the FDA Form 1572 or equivalent and on the delegation of authority log, is responsible for determining the AE relationship to the study drug.

The following categories will be used to define the relationship of an AE to the administration of PERSERIS:

Not Related:	Data are available to identify a clear alternative cause for the AE other than the study drug.
Related:	The cause of the AE is related to the study drug and cannot be reasonably explained by other factors (e.g., the subject's clinical state, concomitant therapy and/or other interventions).

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as the natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator

will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment. For each AE/SAE the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to Indivior or designated representative. However, it is imperative that the Investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to Indivior or designated representative. The Investigator may change his/her opinion of causality in light of follow-up information and amend the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.1.4 Expectedness

An unexpected AE is an AE, the nature and severity of which is not consistent with the applicable Product Information (e.g., IB for an investigational product or product label/summary of product characteristics for an approved product).

10.1.5 Clinical Significance

The Investigator or medically qualified sub-Investigator trained on this study protocol, listed on the FDA Form 1572 or equivalent document and on the delegation of authority form, is responsible for determining the clinical significance of abnormal assessment results (e.g., laboratory or ECG results) for the subject.

10.1.6 Clinical Laboratory Changes

Changes in laboratory values, vital signs or other safety parameters (e.g., ECG, neurological and clinical symptom assessments) as noted in the protocol are a subset of AEs and are reportable only if the lab test result is associated with accompanying symptoms and/ or requires additional diagnostic testing or intervention (medical, surgical) and/or requires additional significant treatment and/or requires temporal or permanent discontinuation of PERSERIS or a change to dosing other than as permitted by protocol, or if considered to be clinically significant by Investigator or medically qualified designee.

Screening laboratory assessments are differentiated from AE/symptoms that are incurred post informed consent. These screening laboratory assessments, if determined to be clinically significant abnormal values, reflect the status of the subject prior to study participation. These clinically significant pre-dose abnormal lab evaluations without clinical symptoms will not be reported as AEs.

11 SERIOUS ADVERSE EVENTS

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an SAE.

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received PERSERIS
- Other: Important medical events that may not result in death, be life-threatening or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization

An AE is considered "life-threatening" if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, study drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though study drug-induced hepatitis can be fatal.

AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) should not be considered AEs or SAEs. If anything, untoward is reported during the procedure, that occurrence must be reported as an AE (either 'serious' or 'non-serious') according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or other outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

A PK sample will be taken as soon as possible after any SAE is reported or specify SAE(s) for which a PK sample is required. This sample should be collected as soon as the site is made aware of the SAE. If possible, an additional sample should be collected when the SAE has been resolved. Blood samples collected for PK analysis will be analysed for risperidone and 9-hydroxyrisperidone concentrations.

11.1 Documenting Serious Adverse Events

When an SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) pertaining to the event. The Investigator will then record all relevant information regarding an SAE on the appropriate electronic or paper form(s).

It is not acceptable for the Investigator to send photocopies of the subject's medical records to Indivior in lieu of completion of the SAE Reporting Form. However, there may be cases where copies of medical records are requested by Indivior or designated representative. In this instance, all subject identifiers, except for subject number, will be redacted on the copies of the medical records prior to submission to Indivior.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis will be documented as an AE or SAE and not the individual signs/symptoms.

11.2 Reporting Serious Adverse Events

11.2.1 Investigator Reporting of Serious Adverse Events

Once the Investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Indivior (or designated representative) by the Investigator (or designee) **within 24 hours** from first being aware of the event. Any follow-up information on a previously reported SAE will also be reported to Indivior within 24 hours.

Where additional information is needed or expected, the Investigator will not wait to receive all information before reporting the event to Indivior. The Investigator must provide an assessment of causality at the time of the initial report as described in Section 10.1.3.

In the event of an SAE, the Investigator or designee will notify Indivior Global safety by completing the appropriate form(s) in the eCRF. Follow-up information will also be reported in the eCRF.

- In the event that electronic data capture (EDC) (i.e. eCRF pages) is not available, a paper SAE Reporting Form should be completed and submitted to Indivior Pharmacovigilance:
  Email: PatientSafetyNA@indivior.com
  Fax : (804) 423-8951

Indivior
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

When the EDC is again available, the information recorded on the paper SAE Reporting Form should be entered into the eCRF.

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

Prompt receipt of notifications of SAEs to Indivior or designated representative from Investigators is essential in ensuring that legal obligations and ethical responsibilities regarding the safety of subjects are met.

Indivior has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of PERSERIS. Indivior or designated representative will comply with country-specific regulatory requirements pertaining to safety reporting to Regulatory Authorities, IRBs/ECs and Investigators.

The Investigator or designee must inform the IRB immediately regarding any AE (does not have to be causally related) that is both serious and unexpected; or that represents a series of AEs that on analysis is unanticipated, or occurs at an unanticipated frequency, or otherwise represents an unanticipated safety risk to the study subject. The IRB may subsequently choose to modify the informed consent or request changes to the protocol, IB and/or or Product Information.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE related to the study drug administered in any dose and that, in its nature or severity, is inconsistent with the IB or Product Information for marketed products. Indivior and PI will determine if an SAE meets the definition of a SUSAR and distribute SUSAR reports according to local regulatory requirements and Indivior policy.

A SUSAR that is fatal or life-threatening must be reported to the competent authority and to the Research Ethics Committee immediately (within 7 days) after Indivior becomes aware of the event. Any additional information must be reported within 8 days of sending the first report.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or line listing of SAEs, Dear Investigator Letter) will file it with the study binder and will notify the IRB/EC, if required according to local reporting requirements.

12 PREGNANCY

12.1 Collecting and Reporting Pregnancy Information

All pregnancies will be collected from receipt of study drug until 5 terminal half-lives following the last dose of study drug. For PERSERIS, this period is approximately 3 months. All confirmed pregnancies that occur within this study will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

Pregnancy of a study subject without associated unexpected or adverse sequelae is not a reportable AE but must be reported to Indivior Global safety or designated representative using the Clinical Trial Pregnancy Reporting Form within 24 hours of the Investigator or designee first being aware of the pregnancy (contact details for reporting are the same as SAEs).

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and infant. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure. Any pregnancy complication or elective termination for medical reasons must be reported as an AE or SAE. A spontaneous abortion must always be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study treatment, must be promptly reported to Indivior or designated representative. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

12.2 Action to be Taken if Pregnancy Occurs in a Female Subject

If a female subject suspect that she is pregnant (e.g., missed period, self-administered pregnancy test) after PERSERIS administration and before EOS, the subject will return to the site and undergo ET visit procedures and a urine pregnancy test will be performed.

If a female subjects urine pregnancy test confirms the subject is pregnant, no further study drugs will be administered. The Investigator should fully inform the female subject of the potential risk to the foetus as well as discuss the desirability of continuing the pregnancy.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered into the eCRF and will be combined with other data captured centrally outside of the eCRF into a validated system. Clinical data will be managed in accordance with the data management plan to ensure that the integrity of the data is maintained. Adverse events, medical history and indication for concomitant medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The eCRFs (including queries and audit trails) will be retained by Indivior. An electronic copy of the eCRF will be sent to the Investigator to maintain for their records. Subject identifiers will not be collected or transmitted to Indivior according to Indivior standards and procedures. Data collection will be completed according to the study plans.

13.1.1 Database Quality Assurance

The eCRFs will be reviewed and checked for omissions, apparent errors and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the eCRFs, and all corrections will be documented in an audit trail.

13.1.2 Source Documents

The Investigator is responsible for the quality of the data recorded in the eCRFs. The data recorded should be a complete and accurate account of the subject's record collected during the study.

Study data are not to be gathered directly onto the eCRF but must be gathered onto primary source documents at the clinical site. Completion of source documents will precede the completion of the eCRF. Source documents may be electronic, hard copy, or a combination of both and are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for direct inspection by the authorized study personnel outlined in the ICF.

14 STATISTICS

14.1 General Procedures

An SAP will be developed based on the latest version of the clinical protocol and eCRF and will be finalized and approved prior to database lock. No database may be locked, or analyses completed until the SAP has been approved.

The SAP will provide a detailed description of the statistical methodology for the data summary and analysis of the PK, efficacy and safety variables. This protocol describes key analyses as currently contemplated. If differences occur between analyses described in the SAP and the current protocol, those found in the SAP will assume primacy.

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

Data collected from all enrolled subjects will be presented in data listings. Unless otherwise noted, data for individual subjects will be listed. Both absolute values and change from baseline values for each subject will be listed where applicable.

Continuous variables will be summarized using the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category. In addition to the descriptive summaries, pertinent data listings will be provided to facilitate case studies.

14.2 Sample Size

No formal statistical justification was performed to determine the sample size. The sample size of 25 subjects was selected to receive the study drug treatment 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.

14.3 Analysis Populations

14.3.1 Enrolled Set

The Enrolled Set includes all subjects that sign the ICF and are assigned a subject number.

14.3.2 Safety Analysis Set

This Safety Analysis Set consists of subjects who received at least one injection of PERSERIS.

14.3.3 Pharmacokinetic Analysis Set

The PK Analyses Set will include data from all subjects who receive oral risperidone or at least one dose 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 $C_{avg\ (ss)}$ for risperidone and total active moiety after oral and SC administration. For primary analysis, only the data from those subjects will be considered who receive 3 doses of PERSERIS and provide an adequate number of blood samples for determination of $C_{avg\ (ss)}$ for risperidone and total active moiety (evaluable population).

14.3.4 Efficacy Analysis Set

The evaluable Efficacy Analysis Set will consist of subjects who receive at least one injection of PERSERIS and have at least one post-dose efficacy data.

14.3.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics, (e.g., gender, race, age, weight, height) will be summarized for all subjects using descriptive statistics for the Safety Analysis Set.

14.4 Efficacy Analysis

The efficacy analysis will be based on the Efficacy Analysis Set. Efficacy endpoints to be analysed include;

- Change from baseline in PANSS total score
- Change from baseline in PANSS positive scale score
- Change from baseline in PANSS negative scale score
- Change from baseline in PANSS general psychopathology scale score
- Change from baseline in CGI-S score

The detailed derivation of the PANSS total, positive, negative, general psychopathology scale and CGI-S scores will be described in the SAP.

The derived total scores, change from baseline and percent change from baseline for the PD endpoints will be summarized (mean, median, SD, minimum and maximum) for baseline and each post-baseline time point by treatment visit number (Day 1, Day 29, Day 57 and Day 85). The mean change from baseline in PD endpoints by visit will be plotted.

Baseline for efficacy parameters is defined as the last non-missing assessment prior to the 1st injection of PERSERIS at Visit 2.

14.5 Statistical Analysis of Safety Endpoints

Safety parameters comprise AEs and SAEs, local injection-site tolerability (i.e., injection-site reactions), concomitant medications, changes in clinical laboratory results, vital sign measurements, 12 lead ECGs, physical examination and neurological examination results, body weights and monitoring of EPS using neurological, clinical symptom assessments (AIMS, SAS, BARS and the C-SSRS), ISGS and VAS.

Safety data will be summarized for all subjects in the Safety Analysis Set. Safety assessments will be reported by dose number (1, 2, 3 and 4) using simple descriptive statistics. Data for individual subjects also be listed.

All AEs and SAEs will be coded using the latest version of MedDRA.

A TEAE is an AE that either commenced following initiation of PERSERIS or was present prior to the initiation of PERSERIS dosing but increased in frequency or severity following initiation of PERSERIS, regardless of causality. The incidence of TEAEs during the study period will be tabulated by system organ class, treatment visit number (Day 1, Day 29, Day 57 and Day 85) and preferred term. The incidence of TEAEs (any TEAE, serious TEAEs, related TEAEs, serious related TEAEs, TEAEs leading to treatment discontinuation or death) and TEAEs by severity will be summarized. If a TEAE is reported more than once by a subject within a system organ class and/or preferred term, the maximum level of severity will be used in the severity summary tables. All AEs will be listed for individual subjects, along with information regarding onset, duration, severity, relationship to study drug, treatment visit number (Day 1, Day 29, Day 57 and Day 85) and action taken.

Vital signs, body weight and 12-lead ECG will be summarized by timepoint for all subjects using descriptive statistics at baseline and at each post-baseline assessment (along with change from baseline). Clinical laboratory data (haematology and serum chemistry, urinalysis) will be summarized using descriptive statistics. For each parameter with numeric results, values at baseline and at end of treatment, together with changes from baseline, will be summarized. Other laboratory tests with categorical results, like urine pregnancy tests and UDS, will be listed only. In addition, shift from baseline tables containing the frequency and percentage of subjects with changes from values below, within and above the normal ranges at baseline to each visit will be presented. Pre-dose fasting will be listed only.

Prior and concomitant medications during the study will be coded using the most recent version of WHO Drug and will be summarized by anatomical therapeutic chemical classification categories. The definition and algorithm for coding concomitant medications will be provided in the SAP. Treatment visit compliance will be summarized and listed.

The observed and change from baseline values of AIMS, SAS and BARS will be summarized by timepoint. Baseline for AIMS, SAS, BARS is defined as the last assessment prior to the 1st injection of PERSERIS.

The results from the ISGS, VAS and the number of subjects that experience burning or stinging at the injection site will be summarized by timepoint.

For C-SSRS, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints Suicidal Ideation and Suicidal Behaviour:

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 Behaviour
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide

Suicidal Ideation since the last assessment – A "yes" answer to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS

Suicidal Behaviour since the last assessment – A "yes" answer to any one of the 5 suicidal behaviour questions (categories 6-10) on the C-SSRS

There will be no imputation of missing data for C-SSRS.

Observed and change from baseline summaries will be provided for Suicidal Ideation and Suicidal Behaviour. The responses to the categories will be listed.

14.6 Pharmacokinetic Analysis

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

Steady-state attainment after oral dosing and SC dosing will be evaluated.

See Section 8.8 for more details.

Additional PK analyses will determine the adequate exposure of PERSERIS (2 × 90 mg) at an alternate injection site (back of upper arm) when compared to the abdominal region (3rd vs. 4th doses) by analysis of the total active moiety throughout the 28-day dosing. The PK data collected

after 4th dose (an alternate site, arm) will be compared against PK data collected after 3rd dose (the abdominal site).

14.7 Handling of Missing Data

Missing data (caused by premature discontinuation or otherwise) will not be imputed.

14.8 Analysis of Safety

The safety endpoints will be analysed in Safety Analysis Set. All recorded AEs will be listed and tabulated by system organ class, preferred term by Injection. Vital signs, ECG, clinical laboratory evaluations, injection-site grading results and Injection-Site Pain VAS scores will be summarized. Any clinically significant physical examination findings and clinical laboratory results will be listed. ECG recordings will be evaluated by the Investigator or sub-Investigator and abnormalities, if present, will be listed if clinically significant or not. All concomitant medications used during the study will be listed. AIMS scores, SAS scores, BARS scales, CGI-S; and C-SSRS results will be listed and summarized.

14.8.1 Extent of Exposure

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 screening period (Days -26 to -6)
- Stabilization with 3 mg oral risperidone twice daily (for all subjects): 5 days (Days -5 to -1)
- PERSERIS treatment period: 4 doses of 180 mg PERSERIS (Days 1 to 113)
- Follow-up: 7 days (Days 120)

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

Prior to site activation, Indivior or designated representative will obtain approval/favourable opinion from the relevant regulatory agency(ies) to conduct the study in accordance with ICH/GCP and any applicable country-specific regulatory requirements.
The study will be carried out in accordance with the protocol and with local legal and regulatory requirements, ICH/GCP and all applicable subject privacy requirements.

15.2 Institutional Review Board/Independent Ethics Committee

The protocol, ICF(s) and any other written information and/or materials to be provided to subjects will be reviewed by an independent and appropriately constituted IRB/IEC. If required by local regulations, the protocol should be re-approved by the IRB/IEC annually. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH/GCP.

PERSERIS can only be released to the Investigator after all ethical and legal requirements for starting the study have been met and documentation has been received by Indivior or designated representative.

15.3 Informed Consent

The Investigator or a person designated by the Investigator (if allowed by local regulations) is to obtain written informed consent from each subject prior to entering the study. All written informed consent documents are required to have been reviewed and received a favourable opinion/approval from an IRB/IEC prior to presenting them to a potential participant.

Any changes to the ICF must be reviewed by Indivior before submission to the IRB/IEC.

The written informed consent process will include the review of oral and written information regarding the purpose, methods, anticipated duration and risks involved in study participation. The Investigator is to ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided. The Investigator or a person designated by the Investigator must also explain to each subject that participation is voluntary and that consent can be withdrawn at any time and without reason. Subjects will receive a signed and dated copy of the signed ICF before any study-specific procedures are conducted.

In the event that new safety information emerges that represents a significant change in the risk/benefit assessment, the signed ICF should be updated accordingly. All subjects should be informed of the new information, provide their consent to continue in the study and be provided with a signed and dated copy of the revised signed ICF.

If a subject is not qualified or incapable of giving legal written informed consent, a legally authorized representative must provide written informed consent. If both the subject and the legally authorized representative are unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject and his/her legally authorized

representative have provided oral consent for the subject to participate in the trial, the witness' signature on the written ICF will attest that the informed presented was accurate and understood.

15.4 Records Management

The Investigator must maintain all study-related records (except for those required by local regulation to be maintained elsewhere) in a safe and secure location throughout the conduct and following the closure of the study. The records must be accessible upon request (e.g., for an IRB/IEC, Indivior or regulatory inspection) along with the facility, study personnel and supporting systems/hardware. All documents pertaining to the study, including all versions of the approved study protocol, copy of the ICF and other documents as required per local laws and regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] documents), completed CRFs, source records (subject records, subject diaries, hospital records, laboratory records, drug accountability records, etc.) and other study-related materials will be retained in the permanent archives of the study site.

Where permitted by local laws and regulations, records may be maintained in a format other than hard copy (e.g., electronically in an electronic medical records system). The Investigator must ensure that all reproductions are an accurate legible copy of the original and that they meet necessary accessibility and retrieval standards. The Investigator must also ensure that a quality control process is in place for making reproductions and that the process has an acceptable backup of any reproductions.

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations or institutional requirements. At a minimum, records will be maintained for 7 years. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with Indivior, to a mutually agreed upon designee within the Indivior-specified timeframe.

16 AUDITING AND MONITORING

The purpose of an audit or regulatory inspection is to verify the accuracy and reliability of clinical trial data submitted to a regulatory authority in support of research or marketing applications and to assess compliance with statutory requirements regulations governing the conduct of clinical trials.

In accordance with applicable regulations, GCP and Indivior procedures, the clinical monitor(s) will periodically contact the site, including conducting on-site visits at intervals agreed by the PI and documented in the Clinical Monitoring Plan and the Site Initiation Visit Report.

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the PI shall make available for direct access all study-related records upon request by Indivior, Indivior's agents, clinical monitor(s), auditors and/or IRB/IEC. The monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and enrolment rate.

The PI must allow the clinical monitor(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the clinical monitor(s) to discuss findings and any relevant issues.

Upon completion of the study, study closeout activities must be conducted by Indivior or its designee in conjunction with the PI, as appropriate.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigators and associated personnel before the study, periodic monitoring visits by Indivior and direct transmission of clinical laboratory data from a central laboratory into Indivior's (or designee's) database. Written instructions will be provided for study drug preparation and dosing, collection, preparation and shipment of blood, plasma and urine samples. Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. Indivior (or designee) will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to Indivior (or designee). Any discrepancies will be resolved with the PI or suitably qualified designee, as appropriate.

This study will be organized, performed and reported in compliance with the protocol, Standard Operating Procedures (SOPs), working practice documents and applicable regulations and guidelines.

In accordance with the standards defined in Indivior SOPs and applicable regulatory requirements, clinical studies sponsored by Indivior are subject to Indivior Quality Assurance (QA) Investigator Site Audits that may be delegated to a contract research organization (CRO) or Indivior contract auditors. Investigator Site Audits will include review of, but are not limited to,

drug supply, presence of required documents, the informed consent process and comparison of CRFs with source documents. The PI agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the PI will be made prior to and during such an audit, which will be conducted according to Indivior's or a CRO's QA SOPs. In addition, this study is subject to inspections by Regulatory Authorities. If such a regulatory inspection occurs, the PI agrees to allow the regulatory inspector direct access to all relevant study documents. The PI must contact Indivior immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

17 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Indivior. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Indivior or designated representative will submit protocol amendments to the appropriate Regulatory Authorities for approval.

If in the judgment of the IRB/IEC, the Investigator and/or Indivior, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation, based on IRB/IEC determination.

18 STUDY REPORTS AND PUBLICATIONS

A CSR will be prepared following completion of the study. An Investigator signatory may be identified for the approval of the report if required by applicable regulatory requirements.

The study data will be owned by Indivior. Publication of any and all data will be at the discretion of Indivior. The Investigator will not disseminate, present or publish any of the study data without the prior written approval from Indivior to do so.

19 STUDY TERMINATION

Both Indivior and the PI reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Indivior, or a specified designee will inform the appropriate Regulatory Authorities of the termination of the study and the reasons for its termination, and the PI will inform the IRB/IEC of the same. In terminating the study, Indivior and the PI will assure that adequate consideration is given to the protection of the subjects' interests.

20 CONFIDENTIALITY

All subject-identifying documentation generated in this study is confidential and may not be disclosed to any persons not directly concerned with the study without written permission from the subject. However, authorized regulatory officials and Indivior personnel (or their representatives) will be allowed full access to inspect and copy the records. All subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol and the ICF signed by the subject, unless otherwise agreed to in writing by Indivior.

Each subject will be identified by initials and an assigned subject number when reporting study information to any entity outside of the study site. Data containing subject identification will not be removed from the study site without first redacting subject identifiers.

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22 APPENDICES

Appendix 1– Schedule of Events - Screening and Oral Dosing

Evaluation	Screening Days	Residential				
		6 mg Oral Risperidone Dosing Stabilization (3 mg Q12hr)				
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Days	**-26 to -6**	**-5**	**-4**	**-3**	**-2**	**-1**
Informed Consent[a]	X					
Subject Number Assignment	X					
Inclusion/Exclusion Criteria	X	X				
Medical/Psychiatric History[b]	X					
Demographics	X					
Vital Signs[h]	X	X				X
Body Weight/Height/BMI[i]	X					X
Physical Examination[c]	X					
12-Lead Electrocardiogram[d]	X					
Pre-dose Fasting[n]		X	X	X	X	X
Clinical Laboratory Assessments[e]	X					
Serology (HIV, Hepatitis B and C)[f]	X					
Urine Drug Screen[g]	X					
Urine Pregnancy Test or FSH[j,k]	X					
PGx Sample for CYP2D6 Genotyping[f]	X					
PK Blood Sample[m]		X	X	X	X	X
AE Assessment[r]	X	X	X	X	X	X
Concomitant Medications[p,q]	X	X	X	X	X	X
PANSS[l]	X					X
CGI-S[l]	X					X
AIMS[l]	X					X
SAS[l]	X					X
BARS[l]	X					X
C-SSRS (Baseline/Screening Version)[l]	X					

Evaluation	Screening Days	Residential				
		6 mg Oral Risperidone Dosing Stabilization (3 mg Q12hr)				
C-SSRS (Since-Last-Visit Version)[l]						X
Admission to CU		X				
Clinic-administration, Oral Risperdal[o]		X	X	X	X	X

BMI: body mass index; **HIV**: human immunodeficiency virus; **FSH:** Follicle Stimulating Hormone; **PGx:** Pharmacogenomics; **PK**: Pharmacokinetic; **AE:** adverse event; **PANSS:** Positive and Negative Syndrome Scale; **CGI-S**: Clinical Global Impression – Severity of Illness; **AIMS**: Abnormal Involuntary Movement Scale for Tardive Dyskinesia; **SAS**: Simpson-Angus Scale; **BARS**: Barnes Akathisia Rating Scale; **C-SSRS**: Columbia-Suicide Severity Rating Scale; **CU**: clinical unit.

[a] Informed consent form will be signed before screening procedures are initiated.
[b] Recording of medical and psychiatric history and conditions; demographic information; and tobacco, alcohol and caffeine use.
[c] Including physical examination and a brief neurological assessment as noted in Section 8.3.
[d] Resting 12-lead ECG at Screening Visit will be recorded while the subject is supine and has been at rest for at least 5 minutes and performed prior vital signs and to clinical laboratory tests (haematology, serum chemistry and urinalysis).
[e] Clinical laboratory assessments will include haematology, serum chemistry and urinalysis panels; additional clinical laboratory testing is to be performed as noted at specific study visits as per Section 8.7. Subjects should be fasting for 8 hours prior to laboratory testing except for screening visit. **HbA1c to be analysed at Screening Visit only.** Laboratory tests with exclusionary results may be repeated once during the screening period to ensure reproducibility of the value.
[f] Serology testing (HIV, Hepatitis B and C) and CYP2D6 Genotyping at Screening Visit only.
[g] Urinary drug screen includes testing as per Table 1.
[h] After a 5-minute rest in the supine position, vital sign measurements (including systolic and diastolic blood pressure, pulse, respiration rate and oral temperature) will be taken.
[i] Measurement of height and weight, and calculation of BMI. Calculation of BMI performed at Screening and EOS visits only. Height taken at Screening Visit will be used to calculate BMI at the EOS visit. Body weight should be taken in the morning if possible.
[j] FSH testing to be performed at Screening Visit only for female subjects who are postmenopausal.
[k] For female subjects of childbearing potential only, urine pregnancy test will be performed prior to dosing. ALL positive urine pregnancy tests will have a confirmatory serum pregnancy test prior to determining if the subject is a screen failure.
[l] Clinical symptom assessments to include: PANSS, AIMS, SAS, CGI-S, BARS and C-SSRS.
[m] See Appendix 6 for a detailed PK Sampling Timepoints.
[n] Oral Risperidone dosing will occur under fasted conditions (minimum 1 hour pre-dose and 1 hour post-dose) **Days -5 to -1**. Water is allowed.
[o] Oral risperidone 6 mg will be administered as 3 mg oral risperidone twice a day, with approximately 12 hours (±30 mins) between doses.
[p] Recording of all prior medications, including prescription and non-prescription medications and health, herbal and dietary supplements, taken by the subject within the last 30 days prior to the initial screening date.
[q] Changes to concomitant medications, including dose or regimen changes.
[r] Recording of AEs since the Screening visit.

Appendix 2 – Schedule of Events – PERSERIS – Dose 1

Evaluation	PERSERIS Dose 1									
	Residential			Non-Residential Days[a]						Residential
Visit[q]	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Days	**1**	**2**	**3**	**8**	**11**	**15**	**18**	**22**	**25**	**28**
Vital Signs[e]	X	X[r]		X[r]	X[r]	X	X	X	X	
Body Weight[j]										
12-Lead Electrocardiogram[b]	X									
Clinical Laboratory Assessments[c]	X									
Urine Pregnancy Test[g]	X									
Urine Drug Screen[d]	X					X				
PK Blood Sample[t]	X	X	X	X	X	X	X	X	X	
AE Assessment[n]	X	X	X	X	X	X		X		
Concomitant Medications[n]	X	X	X	X	X	X		X		
PANSS[h]		X		X		X		X		
CGI-S[h]		X		X		X		X		
AIMS[h]		X		X		X		X		
SAS[h]		X		X		X		X		
BARS[h]		X		X		X		X		
C-SSRS (Since-Last-Visit Version)[h]				X		X				
PERSERIS Injection	X									
Injection-Site Grading Scale (ISGS)[k]	X									
Injection-Site Pain (VAS)[l]	X									
Injection-Site Evaluation[m]	X									
Admission to CU										X
Discharge From CU			X							

Appendix 3 – Schedule of Events – PERSERIS – Dose 2

Evaluation	PERSERIS Dose 2									
	Residential			Non-Residential Days[a]						Residential
Visit[q]	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Days	**29**	**30**	**31**	**36**	**39**	**43**	**46**	**50**	**53**	**56**
Vital Signs[e]	X	X[r]		X[r]	X[r]	X	X	X	X	
Body Weight[j]	X									
12-Lead Electrocardiogram[b]	X									
Clinical Laboratory Assessments[c]	X									
Urine Pregnancy Test[g]	X									
Urine Drug Screen[d]	X							X		
PK Blood Sample[t]	X	X	X	X	X	X	X	X	X	
AE Assessment[n]	X	X	X	X	X	X		X		
Concomitant Medications[n]	X	X	X	X	X	X		X		
PANSS[h]	X							X		
CGI-S[h]	X							X		
AIMS[h]	X							X		
SAS[h]	X							X		
BARS[h]	X							X		
C-SSRS (Since-Last-Visit Version)[h]				X						
PERSERIS Injection	X									
Injection-Site Grading Scale (ISGS)[k]	X									
Injection-Site Pain (VAS)[l]	X									
Injection-Site Evaluation[m]	X									
Admission to CU										X
Discharge From CU			X							

Appendix 4- Schedule of Events – PERSERIS – Dose 3

Evaluation	PERSERIS Dose 3													
	Residential			Non-Residential Days[a]										Residential
Visit	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
Days	**57**	**58**	**59**	**62**	**64**	**65**	**66**	**67**	**69**	**71**	**74**	**78**	**81**	**84**
Vital Signs[e]	X	X[r]		X	X[r]	X	X	X[r]	X	X	X	X	X	
Body Weight[j]	X													
12-Lead Electrocardiogram[b]	X													
Clinical Laboratory Assessments[c]	X													
Urine Pregnancy Test[g]	X													
Urine Drug Screen[d]	X								X					
PK Blood Sample[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment[n]	X	X	X	X	X	X	X	X	X	X		X		
Concomitant Medications[n]	X	X	X	X	X	X	X	X	X	X		X		
PANSS[h]	X													
CGI-S[h]	X													
AIMS[h]	X													
SAS[h]	X													
BARS[h]	X													
C-SSRS (Since-Last-Visit Version)[h]	X				X							X		
PERSERIS Injection	X													
Injection-Site Grading Scale (ISGS)[k]	X													
Injection-Site Pain (VAS)[l]	X													
Injection-Site Evaluation[m]	X													
Admission to CU														X
Discharge From CU			X											

Appendix 5-Schedule of Events – PERSERIS – Dose 4 (Back of Upper Arm)

Evaluation	PERSERIS Dose 4 (Back of Upper Arm)														
	Residential			Non-Residential Days[a]											
Visit[q]	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**55**
Days	**85**	**86**	**87**	**90**	**92**	**93**	**94**	**95**	**97**	**99**	**102**	**106**	**109**	**ET/EOS 113**	**Follow-up Phone Call 120[p]**
Vital Signs[e]	X	X[r]		X	X[r]	X	X	X[r]	X	X	X	X	X	X	
Body Weight/BMI Calculation[f, j]	X													X	
Physical Examination														X	
12-Lead Electrocardiogram[b]	X													X	
Clinical Laboratory Assessments[c]	X													X	
Urine Pregnancy Test[g]	X													X	
Urine Drug Screen[d]	X									X					
PK Blood Sample[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment[n]	X	X	X	X	X	X	X	X	X	X		X		X	X
Concomitant Medications[n]	X	X	X	X	X	X	X	X	X	X		X		X	
PANSS[h]	X													X	
CGI-S[h]	X													X	
AIMS[h]	X													X	
SAS[h]	X													X	
BARS[h]	X													X	

Evaluation	PERSERIS Dose 4 (Back of Upper Arm)														
	Residential			Non-Residential Days[a]											
C-SSRS (Since-Last-Visit Version)[h]							X							X	
PERSERIS Injection	X														
Injection-Site Grading Scale (ISGS)[k]	X													X	
Injection-Site Pain (VAS)[l]	X													X	
Injection-Site Evaluation[m]	X														
Discharge from CU			X												

BMI: body mass index; **HIV**: human immunodeficiency virus; **FSH:** Follicle Stimulating Hormone; **PGx:** Pharmacogenomics; **PK**: Pharmacokinetic; **AE:** adverse event; **PANSS:** Positive and Negative Syndrome Scale; **CGI-S**: Clinical Global Impression – Severity of Illness; **AIMS**: Abnormal Involuntary Movement Scale for Tardive Dyskinesia; **SAS**: Simpson-Angus Scale; **BARS**: Barnes Akathisia Rating Scale; **C-SSRS**: Columbia-Suicide Severity Rating Scale; **ISGS:** Injection Site Grading Scale; **CU**: clinical unit; **VAS**: Visual Analog Scale

Footnotes below apply to Schedule of Events tables included in Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

[a] On non-residential study days, subjects will return to the CU at approximately the same time in the morning. Subjects will report to the clinic on the non-residential days with an allowed ±1 day visit window.

[b] On injection visits, ECGs will be performed up to 1-hour pre-injection and 3 hours post-injection (±30 minutes). Resting 12-lead ECG will be recorded while the subject is supine and has been at rest for at least 5 minutes and performed prior to vital signs and clinical laboratory tests (haematology, serum chemistry and urinalysis).

[c] Clinical laboratory assessments will be collected within 30 minutes (±10 minutes) prior to dosing and will include haematology, serum chemistry and urinalysis panels; additional clinical laboratory testing is to be performed as noted at specific study visits as per Section 8.7. Subjects should be fasting for 8 hours prior to laboratory testing. **HbA1c to be analysed at Screening Visit only.**

[d] Urinary drug screen includes testing for presence of the following as per Table 1. Should be collected within 30 minutes (±10 minutes) prior to dosing.

[e] After a 5-minute rest in the supine position, vital sign measurements (including systolic and diastolic blood pressure, pulse, respiration rate and oral temperature) will be taken. On injection days (Days 1, 29, 57 and 85), vital sign measurements will be taken pre-injection [0 hours (-5 minutes prior to injection)] and at 1, 2, 3 and 6 hours (±10 minutes) post-injection. On injection days, additional orthostatic blood and pulse measurements will be taken at the 6 hour post-injection timepoint: Make the subject stand. Repeat blood pressure and pulse measurement at 1 minute and 3 minutes.

[f] Measurement of height and weight, and calculation of BMI. Calculation of BMI performed at Screening and EOS visits only. Height taken at Screening Visit will be used to calculate BMI at the EOS visit.

[g] For female subjects of childbearing potential only, urine pregnancy test will be performed prior to dosing. ALL positive urine pregnancy tests will have a confirmatory serum pregnancy test prior to determining if the subject is to be early terminated.

[h] Clinical symptom assessments to include: PANSS, AIMS, SAS, CGI-S, BARS and C-SSRS.

[i] See Appendix 6 for a detailed PK Sampling Timepoints. Additional PK samples will be collected should injection issues occur on the day of injection (Days 1, 29, 57 and 85). Any additional PK samples taken on injection days will be taken within one hour of the injection.

[j] Body weight should be taken in the morning if possible.

[k] ISGS will be performed within 10 minutes after injection and again at 3 hours (±30 minutes) post-injection.

[l] Injection-site pain will be assessed by the subject with a 100mm VAS scale (See Appendix 10). The Injection-Site Pain VAS scores will be obtained (after the completion of the injection) at 1 minute (±15 seconds), 5 minutes (±2 minutes), 30 minutes (±2 minutes) and 60 minutes (±5 minutes) post-injection.

[m] Injection-Site Evaluation – Refer to Section 8.6.3 of protocol for instructions.

[n] Recording of AEs and any changes to concomitant medications including dose or regimen changes since the Screening visit

[o] Including physical examination and a brief neurological assessment as noted in Section 8.3.

[p] Follow-up phone call conducted only to assess status of ongoing AEs and determine if any new AEs have occurred since the last visit.

[q] All visits have an allowable window of ±1 day.

[r] In addition to the vital signs taken after a 5-minute rest in the supine position, orthostatic blood and pulse measurements will be taken. Make the subject stand. Repeat blood pressure and pulse measurement at 1 minute and 3 minutes.

Appendix 6– Pharmacokinetic Sampling Schedule[c]

Dosing	Cumulative Day	Day Relative to Each Injection	Time	Study Phase	Permitted PK Draw Time Windows
Oral Risperidone 6 mg	Day -5	Day -5	Pre-dose	Residential Period	within 30 min prior to morning dosing
	Day -4	Day -4	Pre-dose	Residential Period	within 30 min prior to morning dosing
	Day -3	Day -3	Pre-dose	Residential Period	within 30 min prior to morning dosing
	Day -2	Day -2	Pre-dose	Residential Period	within 30 min prior to morning dosing
	Day -1	Day -1	Pre-dose	Residential Period	within 30 min prior to AM dosing
	Day -1	Day -1	0.5 hr	Post-dose/Residential Period	±1 min
	Day -1	Day -1	1 hr	Post-dose/Residential Period	±2 min
	Day -1	Day -1	2 hr	Post-dose/Residential Period	±2 min
	Day -1	Day -1	4 hr	Post-dose/Residential Period	±5 min
	Day -1	Day -1	6 hr	Post-dose/Residential Period	±15 min
	Day -1	Day -1	12 hr	Post-dose/Residential Period	-15 min; within 15 min prior to evening dosing
SC Injection 1 (Abdominal)	Day 1	Day 1	Predose[a]	Pre-dose/ Residential Period	- 30 min; within 30 min prior to SC dose
	Day 1	Day 1	2 hr	Post-dose/Residential Period	±2 min
	Day 1	Day 1	4 hr	Post-dose/Residential Period	±5 min
	Day 1	Day 1	6 hr	Post-dose/Residential Period	±15 min
	Day 2	Day 2	24 hr	Post-dose/Residential Period	±30 min
	Day 3	Day 3	48 hr	Post-dose/Residential Period	±1 hr
	Day 8	Day 8	168 hr	Post-dose/Non-residential	±1 day
	Day 11	Day 11	240 hr	Post-dose/Non-residential	±1 day
	Day 15	Day 15	336 hr	Post-dose/Non-residential	±1 day
	Day 18	Day 18	408 hr	Post-dose/Non-residential	±1 day
	Day 22	Day 22	504 hr	Post-dose/Non-residential	±1 day
	Day 25	Day 25	576 hr	Post-dose/Non-residential	±1 day
SC Injection 2 (Abdominal)	Day 29	Day 1	Predose[b]	Pre-dose/ Residential Period	- 30 min; within 30 min prior to SC dose
	Day 29	Day 1	2 hr	Post-dose/Residential Period	±2 min
	Day 29	Day 1	4 hr	Post-dose/Residential Period	±5 min
	Day 29	Day 1	6 hr	Post-dose/Residential Period	±15 min
	Day 30	Day 2	24 hr	Post-dose/Residential Period	±1 hr
	Day 31	Day 3	48 hr	Post-dose/Residential Period	±1 hr
	Day 36	Day 8	168 hr	Post-dose/Non-residential	±1 day
	Day 39	Day 11	240 hr	Post-dose/Non-residential	±1 day
	Day 43	Day 15	336 hr	Post-dose/Non-residential	±1 day
	Day 46	Day 18	408 hr	Post-dose/Non-residential	±1 day
	Day 50	Day 22	504 hr	Post-dose/Non-residential	±1 day
	Day 53	Day 25	576 hr	Post-dose/Non-residential	±1 day
SC Injection 3 (Abdominal)	Day 57	Day 1	Predose[b]	Pre-dose/ Residential Period	- 30 min; within 30 min prior to SC dose
	Day 57	Day 1	2 hr	Post-dose/Residential Period	±2 min

Dosing	Cumulative Day	Day Relative to Each Injection	Time	Study Phase	Permitted PK Draw Time Windows
	Day 57	Day 1	4 hr	Post-dose/Residential Period	±5 min
	Day 57	Day 1	6 hr	Post-dose/Residential Period	±15 min
	Day 57	Day 1	12 hr	Post-dose/Residential Period	±30 min
	Day 58	Day 2	24 hr	Post-dose/Residential Period	±1 hr
	Day 59	Day 3	48 hr	Post-dose/Residential Period	±1 hr
	Day 62	Day 6	120 hr	Post-dose/Non-residential Period	±1 day
	Day 64	Day 8	168 hr	Post-dose/Non-residential	±1 day
	Day 65	Day 9	192 hr	Post-dose/Non-residential	±1 day
	Day 66	Day 10	216 hr	Post-dose/Non-residential	±1 day
	Day 67	Day 11	240 hr	Post-dose/Non-residential	±1 day
	Day 69	Day 13	288 hr	Post-dose/Non-residential	±1 day
	Day 71	Day 15	336 hr	Post-dose/Non-residential	±1 day
	Day 74	Day 18	408 hr	Post-dose/Non-residential	±1 day
	Day 78	Day 22	504 hr	Post-dose/Non-residential	±1 day
	Day 81	Day 25	576 hr	Post-dose/Non-residential	±1 day
SC Injection 4 (Arm)	Day 85	Day 1	Predose[b]	Pre-dose/ Residential Period	- 30 min; within 30 min prior to SC dose
	Day 85	Day 1	2 hr	Post-dose/Residential Period	±2 min
	Day 85	Day 1	4 hr	Post-dose/Residential Period	±5 min
	Day 85	Day 1	6 hr	Post-dose/Residential Period	±15 min
	Day 85	Day 1	12 hr	Post-dose/Residential Period	±30 min
	Day 86	Day 2	24 hr	Post-dose/Residential Period	±1 hr
	Day 87	Day 3	48 hr	Post-dose/Residential Period	±1 hr
	Day 90	Day 6	120 hr	Post-dose/Non-residential Period	±1 day
	Day 92	Day 8	168 hr	Post-dose/Non-residential	±1 day
	Day 93	Day 9	192 hr	Post-dose/Non-residential	±1 day
	Day 94	Day 10	216 hr	Post-dose/Non-residential	±1 day
	Day 95	Day 11	240 hr	Post-dose/Non-residential	±1 day
	Day 97	Day 13	288 hr	Post-dose/Non-residential	±1 day
	Day 99	Day 15	336 hr	Post-dose/Non-residential	±1 day
	Day 102	Day 18	408 hr	Post-dose/Non-residential	±1 day
	Day 106	Day 22	504 hr	Post-dose/Non-residential	±1 day
	Day 109	Day 25	576 hr	Post-dose/Non-residential	±1 day
	Day 113	Day 29	672 hr	Post-dose/Non-residential	±1 day

a Sample serves as the 0 hour time point for Day 1 and the 24 hour time point for the last oral dose of risperidone on Day -1.
b Sample also serves as the 672 hour time point for the previous injection of PERSERIS.
c. Additional PK samples will be collected should injection issues occur on the day of injection (Days 1, 29, 57 and 85). Any additional PK samples taken on injection days will be taken within one hour of the injection. Additional PK samples will also be collected in the event an SAE occurs that is deemed related to study drug (see section 10.1.1)

Appendix 7 -Clinically Relevant Prohibited CYP2D6 and CYP3A4 Inducers and Inhibitors

The medical monitor may be contacted for other CYP2D6 or CYP3A4 inducers and inhibitors to determine acceptability for use. (This is not an all-inclusive list.) Source: Flockhart DA (2007). *Drug Interactions: Cytochrome P450 Drug Interaction Table.* Indiana University School of Medicine. http://medicine.iupui.edu/clinpharm/ddis/main-table/ Accessed 24 March 2015.

CYP2D6 Inducers	
Medication	Brand Name(s) (if applicable)
dexamethasone	Baycadron, Dexamethasone Intensol, DexPak, Taperpak, Maxidex, Zema Pak
rifampin	Rifadin, Rimactane
CYP2D6 Inhibitors	
Medication	Brand Name(s) (if applicable)
bupropion	Aplenzin, Wellbutrin
fluoxetine	Prozac, Rapiflux, Sarafem, Selfemra
paroxetine	Aropax, Paxil, Seroxat, Sereupin
quinidine	Cardioquin, Quinaglute, Quinalan, Quinidex Extentabs
duloxetine	Cymbalta
terbinafine	Lamisil, Terbinex
amiodarone	Cordarone, Nexterone, Pacerone
cimetidine	Tagamet
sertraline	Lustral, Zoloft
celecoxib	Celebrex
chlorpheniramine	Allerlief , Cotabflu, Colrex, Genallerate, Prohist-8, Ridramin, Triaminic Allergy
chlorpromazine	Thorazine
citalopram	Celexa
clemastine	Allerhist-1, Antihist-1, Contac 12 Hour Allergy, Dayhist-1, Tavist
clomipramine	Anafranil
diphenhydramine	Alka-Seltzer Plus Allergy, Allermax, Benadryl, Diphedryl, Simply Sleep, Theraflu Multi Symptom, Triaminic Cough & Runny Nose
doxepin	Adapin, Silenor, Sinequan
doxorubicin	Adriamycin, Rubex
escitalopram	Lexapro
halofantrine	Halfan

histamine H1 receptor antagonists	Benadryl, Dimenhydrinate, Doxylamine, Meclozine, Orphenadrine, Quetiapine
hydroxyzine	Anx, Atarax, Atazine, Hypam, Rezine, Vistaril
levomepromazine	Nosinan Nozinan, Levoprome
methadone	Dolophine, Methadose
metoclopramide	Maxolon, Metozolv, Reglan
mibefradil	Posicor
midodrine	Amatine, ProAmatine, Gutron
moclobemide	Aurorix, Manerix
perphenazine	Trilafon
ranitidine	Tritec, Wal-Zan, Zantac
red-haloperidol	Haldol
ritonavir	Norvir
ticlopidine	Ticlid
tripelennamine	Pyribenzamine

Appendix 8-Investigational Product Preparation and Dispensing Instructions

FOLLOW THE INSTRUCTIONS AS DIRECTED TO ENSURE PROPER PREPARATION OF THE PRODUCT PRIOR TO ADMINISTRATION.

Instructions for Use

IMPORTANT INFORMATION

- For abdominal subcutaneous injection, only. Do not administer by any other route.
- Please read the instructions carefully before handling this product.
- Allow package to come to room temperature for at least 15 minutes prior to preparation.
- Only prepare medication when you are ready to administer the dose. Once mixed, the product must be administered within 5 minutes.
- As a universal precaution, always wear gloves.

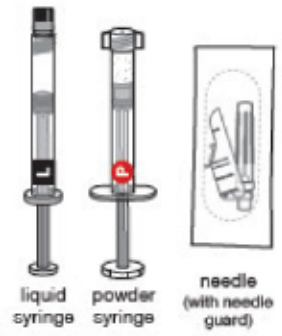
1 CHECK CONTENTS

See Figure 1

- One Liquid Syringe (L) prefilled with the delivery system. Inspect liquid solution for foreign particles. This is the syringe you will use to inject the patient.
- One Powder Syringe (P) prefilled with Risperidone powder. Inspect syringe for consistency of powder colour and for foreign particles.
- One sterile 18-gauge, 5/8-inch safety needle.

Parenteral drug products should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Figure 1



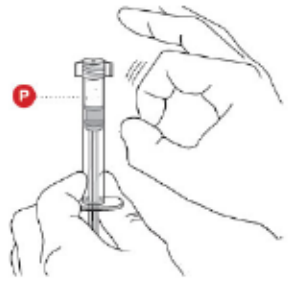
2 TAP POWDER SYRINGE

See Figure 2

Hold the Powder Syringe upright and tap the barrel of the syringe to dislodge the packed powder.

NOTE: Powder can become packed during shipping.

Figure 2



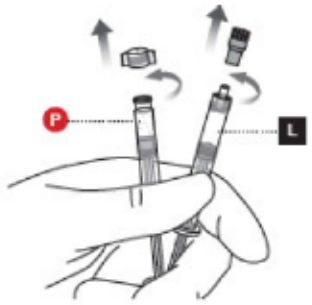
3 UNCAP LIQUID AND POWDER SYRINGES

See Figure 3

Remove the cap from the Liquid Syringe, then remove the cap from the Powder Syringe.

Holding both syringes in your non-dominant hand can help with this step.

Figure 3



4 CONNECT THE SYRINGES

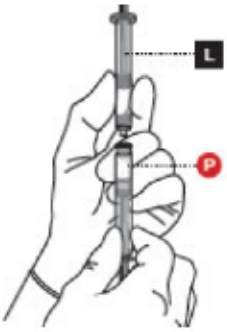
See Figure 4

Place the Liquid Syringe on top of the Powder Syringe (to prevent powder spillage) and connect the syringes by twisting approximately ¾ turn.

Do not over tighten.

Keep your fingers off the plungers during this step to avoid spillage of the medication.

Figure 4

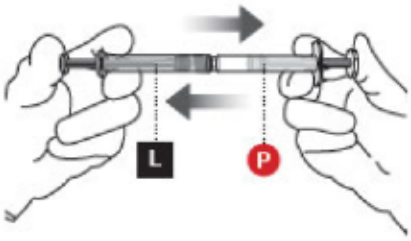


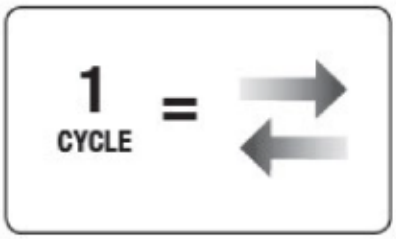
5 MIX THE PRODUCT

See Figure 5

Failure to fully mix the medication could result in incorrect dosage.

Figure 5





Premixing

- Transfer the contents of the Liquid Syringe into the Powder Syringe.
- Gently push the Powder Syringe plunger until you feel resistance (to wet powder and avoid compacting).
- Repeat this gentle back-and-forth process for **5 cycles**.

Complete mixing

- Continue mixing the syringes for an additional **55 cycles**.
- This mixing can be more vigorous than when premixing.

- **Figure 5** illustrates a correct full cycle.

When fully mixed, the product should be a cloudy suspension that is uniform in colour. It can vary from white to yellow-green in colour. If you see any clear areas in the mixture, continue to mix until the distribution of the color is uniform. The product is designed to deliver risperidone 90 mg or 120 mg.

6 PREPARE INJECTION SYRINGE

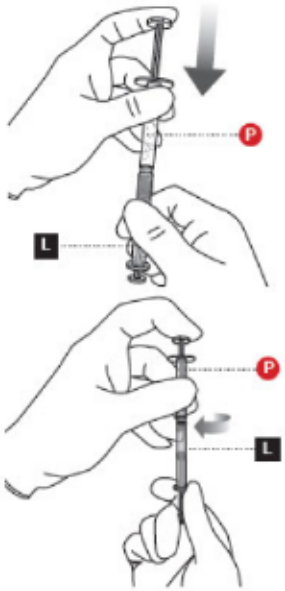
See Figure 6

Failure to aspirate the liquid from the Powder Syringe may result in incorrect dosage.

- First, transfer all contents into the Liquid Syringe.
- Next, perform the following actions **SIMULTANEOUSLY**:
  - maintain slight pressure on the Powder Syringe plunger and
  - pull back gently on the Liquid Syringe plunger while twisting the syringes apart.
- Finally, attach the safety needle by twisting until finger tight.

Check that medication is uniform in colour and free from foreign particles.

Figure 6



7 PREPARE THE ABDOMINAL INJECTION SITE

See Figure 7

Please note: Each dose of 180 mg (comprised of 2 injections of 90 mg) is to be administered subcutaneously in 2 different quadrants of the abdomen at the same clinic visit. The 4th dose of 180 mg which comprises of 2 injections of 90 mg is to be administered subcutaneously on the back of each upper arm in the same clinic visit (See Figure 14)

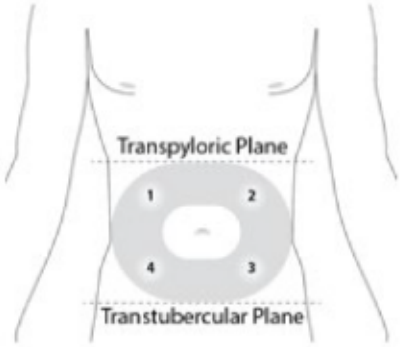
Choose an injection site on the abdomen with adequate subcutaneous tissue that is free of skin conditions (e.g., nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position. The subject's position at the time of the injection will be captured in eCRF.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol pad.

To help minimize irritation, rotate injection sites following a pattern similar to the illustration (Figure 7).

Figure 7



8 REMOVE EXCESS AIR FROM SYRINGE

See Figure 8

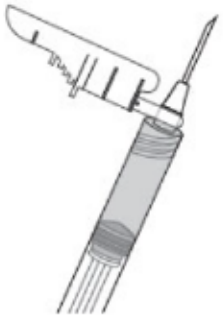
Hold the syringe upright for several seconds to allow air bubbles to rise.

Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

Figure 8

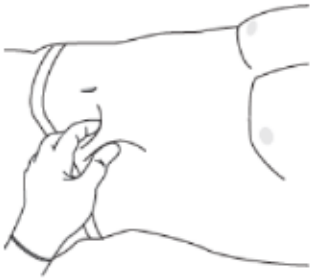


9 PINCH INJECTION SITE

See Figure 9

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 9



10 INJECT THE MEDICATION

See Figure 10

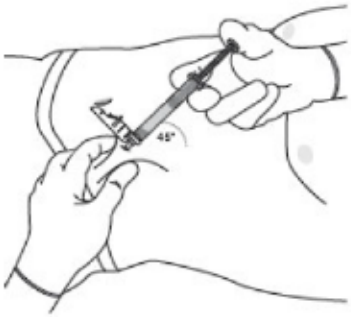
Insert needle fully into the subcutaneous tissue.

Inject the medication slow and steady.

PERSERIS is for subcutaneous administration only. Do not inject by any other route.

NOTE: Actual angle of injection will depend on the amount of subcutaneous tissue.

Figure 10



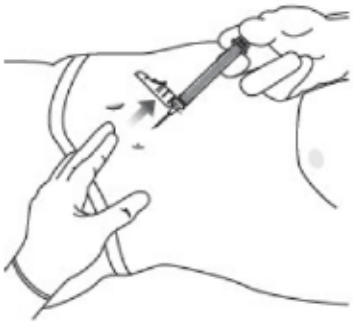
11 WITHDRAW NEEDLE

See Figure 11

Withdraw the needle at the same angle used for insertion and release pinched skin.

Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.

Figure 11



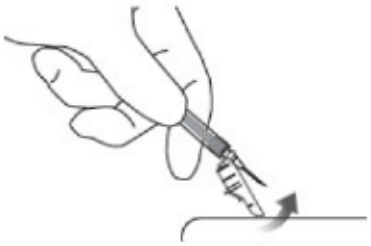
12 LOCK THE NEEDLE GUARD AND DISPOSE OF SYRINGE

See Figure 12

Lock the needle guard into place by pushing it against a hard surface such as a table.

Dispose of all syringe components in a secure sharps disposal container.

Figure 12



13 INSTRUCT THE PATIENT

See Figure 13

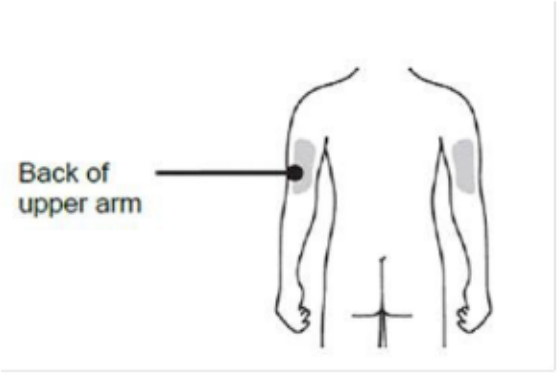
Advise the patient that they may have a lump for several weeks that will decrease in size over time. It is important that the patient not rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

Figure 13

14 INJECTION INTO BACK OF UPPER ARM (4th DOSE)

All instructions as noted above should be followed when administering the 4th dose, but the location of the injections will be the back of the upper arm.

Figure 14



Appendix 9– Injection-Site Grading Scale

Injection Site Grading Scale

Time point: ☐ 10 minutes ☐ 12 hours ☐ 24 hours ☐ Day ____

Local Reaction to Injectable Product	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Source: U.S. Food and Drug Administration. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* Retrieved January 15, 2014, from http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm

Appendix 10– Injection-Site Pain Visual Analog (VAS) Scale

Injection Site Pain Visual Analog Scale

Protocol:	Subject Initials:	Subject #:
INDV-7000-401		

Visit Day:	Date of Assessment:	Time of Assessment:	Time point:
	- - (DD-MMM-YYYY)	: : 24 Hour Clock (HH:MM:SS)	☐ 1 min ☐ 5 min ☐ 30 min ☐ 60 min

Injection Site Pain Analog Scale

Describe the extent of your current pain at the injection site by marking the line below at the appropriate distance between "No injection site pain" and "Worst imaginable injection site pain".

Are you currently experiencing any burning or stinging at the injection site? ☐Yes ☐No

_____ / _____
Subject initials / Date

version 1.0 23December2013

Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain. *Arthritis Care Res* 2011;63:S240–S252

Appendix 11– Positive and Negative Syndrome Scale (PANSS)

Positive and Negative Syndrome Scale (PANSS) – Rating Criteria

Positive Scale (P)

P1. Delusions. Beliefs which are unfounded, unrealistic, and idiosyncratic. *Basis for rating:* thought content expressed in the interview and its influence on social relations and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presence of one or two delusions, which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.
4	Moderate	Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations, or behavior.
5	Moderate Severe	Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.
6	Severe	Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.
7	Extreme	Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.

Positive Scale (P)

P2. Conceptual disorganization. Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations, non-sequiturs, gross illogicality, or thought block. *Basis for rating:* cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directing thoughts toward a goal, and some loosening of associations may be evidenced under pressure.
4	Moderate	Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.
5	Moderate Severe	Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevancies, disconnectedness, or loosening of associations even when not under pressure.
6	Severe	Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.
7	Extreme	Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad" or mutism.

Positive Scale (P)

P3. Hallucinatory behavior. Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. *Basis for rating:* verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions, which do not result in distortions of thinking or behavior.
4	Moderate	Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.
5	Moderate Severe	Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.
6	Severe	Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions and functioning is impeded by frequent emotional and verbal responses to them.
7	Extreme	Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.

Positive Scale (P)

P4. Excitement. Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. *Basis for rating:* behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.
4	Moderate	Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.
5	Moderate Severe	Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.
6	Severe	Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating and sleeping.
7	Extreme	Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

Positive Scale (P)

P5. Grandiosity. Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. *Basis for rating:* thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.
4	Moderate	Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.
5	Moderate Severe	Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.
6	Severe	Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.
7	Extreme	Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power, and/or moral stature, which may take on a bizarre quality.

Positive Scale (P)

P6. Suspiciousness/persecution. Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. *Basis for rating:* thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.
4	Moderate	Distrustfulness is clearly evident and intrudes on the interview and/or behavior, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5	Moderate Severe	Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavior.
6	Severe	Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.
7	Extreme	A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.

Positive Scale (P)

P7. Hostility. Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. *Basis for rating:* interpersonal behavior observed during the interview and reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.
4	Moderate	Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5	Moderate Severe	Patient is highly irritable and occasionally verbally abusive or threatening.
6	Severe	Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.
7	Extreme	Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.

Negative Scale (N)

N1. Blunted affect. Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. *Basis for rating:* observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.
4	Moderate	Reduced range of facial expression and few expressive gestures result in a dull appearance.
5	Moderate Severe	Affect is generally "flat," with only occasional changes in facial expression and a paucity of communicative gestures.
6	Severe	Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.
7	Extreme	Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.

Negative Scale (N)

N2. Emotional withdrawal. Lack of interest in, involvement with, and affective commitment to life's events. *Basis for rating:* reports of functioning from primary care workers or family and observation of interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Usually lacks initiative and occasionally may show deficient interest in surrounding events.
4	Moderate	Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.
5	Moderate Severe	Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6	Severe	Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.
7	Extreme	Patient is almost totally withdrawn, uncommunicative, and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

Negative Scale (N)

N3. Poor rapport. Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. *Basis for rating:* interpersonal behavior during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation is characterized by a stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4	Moderate	Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.
5	Moderate Severe	Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6	Severe	Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7	Extreme	Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

Negative Scale (N)

N4. Passive/apathetic social withdrawal. Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living. *Basis for rating:* reports on social behavior from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4	Moderate	Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5	Moderate Severe	Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6	Severe	Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7	Extreme	Profoundly apathetic, socially isolated, and personally neglectful.

Negative Scale (N)

N5. Difficulty in abstract thinking. Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. *Basis for rating:* responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.
4	Moderate	Often utilizes a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.
5	Moderate Severe	Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.
6	Severe	Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.
7	Extreme	Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

Negative Scale (N)

N6. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. *Basis for rating:* cognitive-verbal processes observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.
4	Moderate	Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.
5	Moderate Severe	Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.
6	Severe	Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive.
7	Extreme	Verbal output is restricted to, at most, an occasional utterance, making conversation impossible.

Negative Scale (N)

N7. Stereotyped thinking. Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. *Basis for rating:* cognitive-verbal processes observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.
4	Moderate	Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.
5	Moderate Severe	Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.
6	Severe	Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.
7	Extreme	Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.

General Psychopathology Scale (G)

G1. Somatic concern. Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. *Basis for rating:* thought content expressed in the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.
4	Moderate	Complains about poor health or bodily malfunction, but there is no delusional conviction, and over-concern can be allayed by reassurance.
5	Moderate Severe	Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.
6	Severe	Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.
7	Extreme	Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.

General Psychopathology Scale (G)

G2. Anxiety. Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. *Basis for rating:* verbal report during the course of interview and corresponding physical manifestations.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidenced.
4	Moderate	Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.
5	Moderate Severe	Patient reports serious problems of anxiety, which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.
6	Severe	Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.
7	Extreme	Patient's life is seriously disrupted by anxiety, which is present almost constantly and, at times, reaches panic proportion or is manifested in actual panic attacks.

General Psychopathology Scale (G)

G3. Guilt feelings. Sense of remorse or self-blame for real or imagined misdeeds in the past. *Basis for rating:* verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.
4	Moderate	Patient expresses distinct concern over his or her responsibility for a real incident in his or her life but is not preoccupied with it, and attitude and behavior are essentially unaffected.
5	Moderate Severe	Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he or she deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.
6	Severe	Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he or she should receive harsh sanctions for the misdeeds and may even regard his or her current life situation as such punishment.
7	Extreme	Patient's life is dominated by unstable delusions of guilt, for which he or she feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.

General Psychopathology Scale (G)

G4. Tension. Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. *Basis for rating:* verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.
4	Moderate	A clearly nervous appearance emerges from various manifestations, such as fidgety behavior, obvious hand tremor, excessive perspiration, or nervous mannerisms.
5	Moderate Severe	Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.
6	Severe	Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.
7	Extreme	Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

General Psychopathology Scale (G)

G5. Mannerisms and posturing. Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. *Basis for rating:* observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight awkwardness in movements or minor rigidity of posture.
4	Moderate	Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.
5	Moderate Severe	Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.
6	Severe	Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods.
7	Extreme	Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

General Psychopathology Scale (G)

G6. Depression. Feelings of sadness, discouragement, helplessness, and pessimism. *Basis for rating:* verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior as reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4	Moderate	Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behavior or social functioning, and the patient usually can be cheered up.
5	Moderate Severe	Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.
6	Severe	Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7	Extreme	Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or actions.

General Psychopathology Scale (G)

G7. Motor retardation. Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. *Basis for rating:* manifestations during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.
4	Moderate	Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.
5	Moderate Severe	A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.
6	Severe	Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.
7	Extreme	Patient is almost completely immobile and virtually unresponsive to external stimuli.

General Psychopathology Scale (G)

G8. Uncooperativeness. Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. *Basis for rating:* interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.
4	Moderate	Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.
5	Moderate Severe	Patient frequently is incompliant with the demands of his or her milieu and may be characterized by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.
6	Severe	Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.
7	Extreme	Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.

General Psychopathology Scale (G)

G9. Unusual thought content. Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those, which are remote or atypical to those which are distorted, illogical, and patently absurd. *Basis for rating:* thought content expressed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.
4	Moderate	Ideas are frequently distorted and occasionally seem quite bizarre.
5	Moderate Severe	Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling).
6	Severe	Patient expresses many illogical or absurd ideas or some, which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).
7	Extreme	Thinking is replete with absurd, bizarre, and grotesque ideas.

General Psychopathology Scale (G)

G10. Disorientation. Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. *Basis for rating:* responses to interview questions on orientation.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	General orientation is adequate but there is some difficulty with specifics. For example, patient knows his or her location but not the street address; knows hospital staff names but not their functions; knows the month but confuses the day of week with an adjacent day; or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the Mayor, Governor, or President.
4	Moderate	Only partial success in recognizing persons, places, and time. For example, patient knows he or she is in a hospital but not its name; knows the name of his or her city but not the borough or district, knows the name of his or her primary therapist but not many other direct care workers; knows the year and season but is not sure of the month.
5	Moderate Severe	Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he or she is and seems unfamiliar with most people in his or her milieu. He or she may identify the year correctly or nearly so but not know the current month, day of week, or even the season.
6	Severe	Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his or her whereabouts; confuses the date by more than one year; can name only one or two individuals in his or her current life.
7	Extreme	Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.

General Psychopathology Scale (G)

G11. Poor attention. Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. *Basis for rating:* manifestations during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Limited concentration evidenced by occasional vulnerability to distraction or faltering attention toward the end of the interview.
4	Moderate	Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.
5	Moderate Severe	Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.
6	Severe	Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.
7	Extreme	Attention is so disrupted that even brief conversation is not possible.

General Psychopathology Scale (G)

G12. Lack of judgment and insight. Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short-term and long-range planning. *Basis for rating:* thought content expressed during the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.
4	Moderate	Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgment of being ill or little awareness of major symptoms, which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.
5	Moderate Severe	Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.
6	Severe	Patient denies ever having had a psychiatric disorder. He or she disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.
7	Extreme	Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.

General Psychopathology Scale (G)

G13. Disturbance of volition. Disturbance in the willful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. *Basis for rating:* thought content and behavior manifested in the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.
4	Moderate	Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alteration in thinking, and in consequence verbal and cognitive functioning are clearly impaired.
5	Moderate Severe	Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.
6	Severe	Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.
7	Extreme	Almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.

General Psychopathology Scale (G)

G14. Poor impulse control. Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. *Basis for rating:* behavior during the course of interview and reported by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.
4	Moderate	Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.
5	Moderate Severe	Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.
6	Severe	Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands.
7	Extreme	Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

General Psychopathology Scale (G)

G15. Preoccupation. Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. *Basis for rating:* interpersonal behavior observed during the course of interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.
4	Moderate	Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.
5	Moderate Severe	Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.
6	Severe	Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself or herself.
7	Extreme	Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.

General Psychopathology Scale (G)

G16. Active social avoidance. Diminished social involvement associated with unwarranted fear, hostility, or distrust. *Basis for rating:* reports of social functioning by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient seems ill at ease in the presence of others and prefers to spend time alone, although he or she participates in social functions when required.
4	Moderate	Patient grudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.
5	Moderate Severe	Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.
6	Severe	Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he or she appears to isolate himself or herself from others.
7	Extreme	Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he or she avoids all interactions and remains isolated from others.

Kay S.R., Opler, L.A., Fiszbein, A. (1999). *Positive and Negative Syndrome Scale (PANSS) Rating Criteria*. North Tonawanda, NY: Multi-Health Systems.

Appendix 12 – Abnormal Involuntary Movement Scale (AIMS) for Tardive Dyskinesia

Abnormal Involuntary Movement Scale (AIMS)

Movement ratings: rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously.		Code for items 1-7: 0 = None 1 = Minimal, may be extreme normal 2 = Mild 3 = Moderate 4 = Severe					
		(Circle One)					
FACIAL AND ORAL MOVEMENTS:	1. MUSCLES OF FACIAL EXPRESSION e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	0	1	2	3	4
	2. LIPS AND PERIORAL AREA e.g. puckering, pouting, smacking	0	1	2	3	4
	3. JAW e.g. biting, clenching, chewing, mouth opening, lateral movement.	0	1	2	3	4
	4. TONGUE Rate only increase in movement both in and out of mouth, not inability to sustain movement.	0	1	2	3	4
EXTREMITY MOVEMENTS:	5. UPPER (ARMS, WRISTS, HANDS, FINGERS) Include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do not include tremor (i.e. repetitive, regular, rhythmic).	0	1	2	3	4
	6. LOWER (LEGS, KNEES, ANKLES, TOES) e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0	1	2	3	4
TRUNK MOVEMENTS:	7. NECK, SHOULDERS, HIPS e.g. rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
GLOBAL JUDGMENTS:	8. Severity of abnormal movements	None, normal 0				
		Minimal 1				
		Mild 2				
		Moderate 3				
		Severe 4				
	9. Incapacitation due to abnormal movements	None, normal 0				
		Minimal 1				
		Mild 2				
		Moderate 3				
		Severe 4				
	10. Patient's awareness of abnormal movements Rate only subject's report.	No awareness 0				
		Aware, no distress 1				
		Aware, mild distress 2				
		Aware, moderate distress 3				
		Aware, severe distress 4				

DENTAL STATUS:	11. Any current problems with teeth and/or dentures?	No 0
		Yes 1
	12. Does patient usually wear dentures?	No 0
		Yes 1

Guy W. ECDEU *Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare publication (ADM) 76-338 Rockville, MD: National Institute of Mental Health; 1976.

Appendix 13– Simpson-Angus Scale (SAS)

Simpson-Angus Scale (SAS)

Circle the appropriate score for each item:

1. GAIT The patient is examined as he walks into the examining room; his gait, the swing of arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:	
0	Normal
1	Mild diminution in swing while the patient is walking
2	Obvious diminution in swing suggesting shoulder rigidity
3	Stiff gait with little or no arm swing noticeable
4	Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion
2. ARM DROPPING The patient and the examiner both raise their arms to shoulder height and let them fall to their sides, in a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly.	
0	Normal, free fall with loud slap and rebound
1	Fall slowed slightly with less audible contact and little rebound
2	Fall slowed, no rebound
3	Marked slowing, no slap at all
4	Arms fall as though against resistance, as though through glue
3. SHOULDER SHAKING The subject's arms are bent at a right angle at the elbow and taken one at a time by the examiner who grabs one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:	
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
4. ELBOW RIGIDITY The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to the procedure is rated. (The presence of cogwheel rigidity is noted separately.)	
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

5.	WRIST RIGIDITY The wrist is held in one hand and then the fingers held by the examiner's other hand with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

6.	HEAD ROTATION The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patienth head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.
0	Loose, no resistance
1	Slight resistance to movement although the time to rotate may be normal
2	Resistance is apparent and time of rotation is slowed
3	Resistance is obvious and rotation is slowed
4	Head appears stiff and rotation is difficult to carry out

7.	GLABELLA TAP Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
0	0-5 blinks
1	6-10 blinks
2	11-15 blinks
3	16-20 blinks
4	21 and more blinks

8.	TREMOR Patient is observed walking into examining room and then is examined for this item.
0	Normal
1	Mild finger tremor, obvious to sight and touch
2	Tremor of hand or arm occurring spasmodically
3	Persistent tremor of one or more limbs
4	Whole body tremor

9.	SALIVATION Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
0	Normal
1	Excess salivation so that pooling takes place if the mouth is open and the tongue raised
2	Excess salivation is present and might occasionally result in difficulty in speaking
3	Speaking with difficulty because of excess salivation
4	Frank drooling

10.	AKATHISIA Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient report can help make the assessment.
0	No restlessness reported or observed
1	Mild restlessness observed
2	Moderate restlessness observed
3	Restlessness is frequently observed
4	Restlessness persistently observed

Adapted and used with permission. Reference: Simpson GN, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica. 1970;45(suppl 212):11-9.

Appendix 14– Clinical Global Impression – Severity of Illness (CGI-S)

Clinical Global Impression - Severity of Illness (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill subjects

Guy W. ECDEU Assessment Manual For Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338 Rockville, MD: National Institute of Mental Health; 1976.

Appendix 15 – Barnes Akathisia Rating Scale (BARS)

Barnes Akathisia Rating Scale (BARS)

Rating scale for drug-induced akathisia (Barnes Akathisia Rating Scale)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective	
0	Normal, occasional fidgety movements of the limbs
1	Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2	Observed phenomena, as described in (1) above, which are present for at least half the observation period
3	Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective *Awareness of restlessness*	
0	Absence of inner restlessness
1	Non-specific sense of inner restlessness
2	The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3	Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness	
0	No distress
1	Mild
2	Moderate
3	Severe

Global clinical assessment of akathisia	
0	*Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1	*Questionable.* Non-specific inner tension and fidgety movements
2	*Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress
3	*Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4	*Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing
5	*Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: A rating scale for drug-induced akathisia. T.R.E. Barnes, *British Journal of Psychiatry* (1989), 154, 672-676.

Appendix 16 – Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer If Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____