Minerva Neurosciences, Inc.

Clinical Protocol

A Phase 1b, In-Patient Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of the Co-Administration of Roluperidone and Olanzapine in Adult Subjects with Moderate to Severe Negative Symptoms of Schizophrenia

Protocol MIN-101C18

Phase 1b

Roluperidone

Sponsor: Minerva Neurosciences, Inc.
[redacted]

Protocol Version	Issue Date
[redacted]	[redacted]
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Original Protocol Version 1.5	02 November 2023

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

Name of Sponsor/Company: Minerva Neurosciences, Inc.

Name of Investigational Product: Roluperidone (MIN-101)

Study Title: A Phase 1b, In-Patient Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of the Co-Administration of Roluperidone and Olanzapine in Adult Subjects with Moderate to Severe Negative Symptoms of Schizophrenia

Study Phase: Phase 1b

Study Period: October 2023 – February 2024

Objectives and Endpoints:

Objectives	Endpoints
To evaluate the pharmacodynamics (PD), including safety and tolerability of the coadministration of roluperidone 64 mg and olanzapine	Safety assessments, including adverse events (AEs), clinical laboratory, electrocardiogram (ECG), vital signs, extrapyramidal symptoms (assessed by Abnormal Involuntary Movement Scale [AIMS] and Barnes Akathisia Rating Scale [BARS]), and suicidal ideation (assessed by the Columbia Suicide Severity Rating Scale [C-SSRS])
To evaluate the effect of the coadministration of roluperidone and olanzapine on the pharmacokinetics (PK) of roluperidone in subjects with moderate to severe negative symptoms of schizophrenia	• The plasma pharmacokinetic parameters of roluperidone and its metabolite, BFB-520, following single dose and at steady state (C_{max}, T_{max}, AUC_{0-24}, AUC_{∞}) • Plasma pharmacokinetic parameters of roluperidone and BFB-520 when administered concomitantly with olanzapine • The plasma pharmacokinetic parameters of olanzapine administered concomitantly with roluperidone compared to its pharmacokinetic profile based on monotherapy administration from published literature
[redacted]	[redacted] Clinical Global Impression - Severity Rating (CGI-S)

Methodology:

This is a prospective, open-label, one-sequence, inpatient, clinical study of CYP2D6 normal metabolizer (NM) subjects with moderate to severe negative symptoms of schizophrenia. Olanzapine, a commonly used antipsychotic having dopaminergic antagonistic activities, will be coadministered to subjects already being administered roluperidone to determine its effect on the PD and PK of roluperidone. Eligible subjects will undergo 3 study phases as follows:

- **Screening Phase**: Between 2 and up to 28 days during which study eligibility will be established and subjects receiving psychotropics will be washed out. Discontinuation of psychotropics must occur at least 2 days prior to the start of Treatment Period 1 (Day 1). Subjects will be admitted to the site on Day -2 and complete a Baseline Visit on Day -1.

- **Treatment Phase 1**: After the Baseline Visit (Day -1), roluperidone 64 mg/day will be administered as a monotherapy for 7 days (Days 1-7).
- **Treatment Phase 2**: Concomitant administration of olanzapine 10 mg/day and roluperidone 64 mg/day for 10 days, starting on Day 8 (Days 8-17). Subjects may be discharged from the clinic at least 48 hours after the last administration of the study drugs and after the collection of the last plasma sample; however, the inpatient period may be extended at the discretion of the investigator.

An End of Study (EOS) visit will take place at least 14 days after the last dose of study treatment. After the EOS visit, the medications and clinical care of the subject will be managed as per the judgement of the investigator/clinician.

Number of Subjects (planned): Approximately 18 subjects may be enrolled in the study to ensure that at least 12 subjects complete the study.

Diagnosis and Main Criteria for Inclusion/Exclusion: Male and female CYP2D6 NM subjects, 18 to 55 years of age, inclusive, with moderate to severe negative symptoms of schizophrenia and no history of any clinically significant conditions that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study.

Inclusion Criteria:

Subjects must satisfy all the following inclusion criteria during screening to be enrolled in the study:

1. Subject and/or subject's legal representative, if applicable, provided informed consent prior to the initiation of any study related procedures, and the subject is judged by the investigator as being capable of understanding the study requirements.
2. Male or female subject, 18 to 55 years of age, inclusive, and body mass index (BMI) < 35 kg/m^2 at Screening.
3. Subject meets the diagnostic criteria for schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), as established by a full psychiatric interview in conjunction with the Mini International Neuropsychiatric Interview (MINI)[1].
4. Has a caregiver or family member or health care personnel who can provide information towards assessment and support the subject in terms of compliance with the protocol.
5. Has documented diagnosis of schizophrenia for at least 1 year before screening into the trial.
6. Subject is stable in terms of both positive and negative symptoms of schizophrenia over the last 3 months according to his or her clinician and/or a caregiver who knows the patient like the responsible person at the patient residence, a social worker, rehabilitation therapist or a caregiver/ family member or based on documentation in the clinical chart or medical records. Subjects with or without positive symptoms are allowed if these symptoms are stable for the last 3 months and they do not meet exclusion criterion 2.
7. Subject is currently an outpatient and has not been hospitalized for the last 3 months for acute exacerbation or symptoms worsening. Subjects who have been hospitalized for

[1] Current version for DSM-5.

social reasons for any time period during the last 3 months or are currently hospitalized for social reasons can be included only with Sponsor's Responsible Medical Officer's approval. The social reasons must be documented in the case report form (CRF).

8. Subject with a score of > 20 on the PANSS original negative symptoms subscale score (sum of N1+N2+N3+N4+N5+N6+N7) at Screening and Baseline (Day -1) AND < 4 points absolute difference between the 2 visits.
9. Subject has discontinued psychotropic medications without risk to their clinical status or safety by Baseline (Day -1). Subjects receiving treatment with long-acting or depot antipsychotic medication must have discontinued the depot antipsychotic for a full cycle of the drug (ie, 1-6 months depending on formulation).
10. No history of violence against self or others during the last 1 year.
11. Female subject, if not of childbearing potential, must be a woman who is post-menopausal (defined as spontaneous amenorrhoea for at least 1 year or spontaneous amenorrhoea for at least 6 months confirmed by follicle stimulating hormone result of ≥ 40 IU/mL) or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy).
12. Female subject, if of childbearing potential, must test negative for pregnancy and must be using 2 methods of contraception for at least 30 days after the completion of the study, one of which must be a highly effective method. The following highly effective contraception methods acceptable for this study are:

    - Surgical sterilization (for example, bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or vasectomy for her male partner provided that the partner is the sole sexual partner of the female subject and that the vasectomized partner has received medical assessment of the surgical success).
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Hormonal contraception (oral, implantable, patch, injectable).
    - True sexual abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (for example, calendar ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are NOT acceptable methods of contraception).

    The following acceptable methods can be used as a second form of contraception during the study:

    - Barrier methods for a female subject include use of an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository.
    - A male subject who has been sterilized (with medical assessment of the surgical success) or have partners of non-childbearing potential (including homosexual men) is required to use a condom with spermicide. This is to prevent unintended exposure of the partner to the study drug via seminal fluid.
    - A male subject who has partners of childbearing potential must be willing to use a condom with spermicide. Because a condom alone is not adequate contraception for this study, male subjects are strongly recommended to discuss the potential risks to a fetus with all female partners and advise them of the need to high effective contraception for up to 90 days after completion of the study. A male subject whose partner is pregnant is not allowed in the study.

- A female subject who is post-menopausal (defined as spontaneous amenorrhea for at least 1 year without an alternative medical cause) is eligible for this study. Hormone replacement therapy (HRT) is allowed during the study.

13. Subject must be normal metabolizer for P450 CYP2D6, defined as a subject that has at least one functional allele (eg, *1, *2 or *35), as determined by study-specific genotyping test before the first drug dose is administered.
14. Subject and the caregiver are considered by the investigator to be reliable and likely to cooperate with the assessment procedures.

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Current major depressive disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, or intellectual disability (intellectual developmental disorder diagnosed by age 14).
2. Subject with PANSS item score of > 4 on:
   - P4 Excitement/Hyperactivity
   - P6 Suspiciousness/persecution
   - P7 Hostility
   - G8 Uncooperativeness
   - G14 Poor impulse control
3. A CDSS total score > 6.
4. A score of ≥ 2 on any 2 of items 1, 2, or 3, or a score of ≥ 3 on item 4 of the BARS.
5. Subjects with known hypersensitivity to olanzapine.
6. Subject's condition is due to direct physiological effects of a substance (eg, a drug of abuse, or medication) or a general medical condition.
7. Has a current or recent history of serious suicidal behavior within the past 1 year.
8. Subject has a history of substance use disorder within 3 months of the Screening visit (excluding caffeine and cigarette smoking).
9. Positive urine drug screen for drugs of abuse (cocaine, methadone, amphetamines, opiates, benzodiazepines, and barbiturates), tricyclic antidepressants (TCA), and alcohol (except for prescription benzodiazepines). Recreation cannabinoids are allowed if the clinician determines that the subject does not meet criteria for cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the clinician can ensure that the subject is not using cannabis during days -2 to 17.
10. Subject cannot be discontinued from psychotropic medication(s).
11. Subject who received clozapine within 3 months of the Screening visit.
12. Subject is currently taking proton pump inhibitors (PPI).

13. Subject with a history of significant other major or unstable neurological, neurosurgical (eg, head trauma), metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, metabolic, gastrointestinal, or urological disorder.
14. Subject with a history of seizures (subject with a history of a single childhood febrile seizure may be enrolled in this study).
15. Subject who has had electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), or repetitive trans-cranial magnetic stimulation (r-TMS) within the 6 months prior to the Screening visit or who are scheduled for ECT, VNS, or r-TMS at any time during the study.
16. Subject with clinically significant abnormalities in hematology, blood chemistry, ECG, or physical examination not resolved by the Baseline visit which according to Investigator can interfere with study participation.
17. Current systemic infection (eg, Hepatitis B, Hepatitis C, human immunodeficiency virus [HIV], tuberculosis). Subjects with positive Hepatitis B core antibody test and negative Hepatitis B Surface Antigen (HBsAg) may be included in the study if aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) do not exceed 2 times upper limit of normal (ULN).
18. Positive for COVID-19 virus.
19. Subject who requires or may require concomitant treatment with any other medication likely to increase QT interval (eg, paroxetine, fluoxetine, duloxetine, amiodarone; a non-exhaustive list is provided in ATTACHMENT 1: Prohibited Concomitant Medications).
20. Subject who requires medication inhibiting CYP2D6.
21. Subject with a clinically significant ECG abnormality that could be a safety risk in the study, including QT interval value corrected for heart rate using the Fridericia's formula (QTcF) > 430 msec for males and > 450 msec for females.
22. Subject with a myocardial infarction within 6 months of Screening based on medical history or significant ECG findings at Screening.
23. Familial or personal history of long QT syndrome or with additional risk factors for Torsade de Pointes.
24. Subject whose safety laboratory results show one or more of the following: potassium <3.4 mmol/L, or calcium <2.07 mmol/L, or magnesium <0.70 mmol/L.
25. Subjects with unexplained syncope.
26. Woman of child-bearing potential, or man, who is unwilling or unable to use accepted methods of birth control.
27. Woman with a positive pregnancy test, who is lactating, or who is planning to become pregnant during the study.
28. Subject who participated in another clinical study within 3 months prior to Screening, or received roluperidone previously, or has previously participated in > 3 clinical studies with experimental medication within the past 2 years.

Test Product, Dosage, and Route of Administration:

Roluperidone will be available in a tablet form at a strength of 64 mg per day.

Oral olanzapine 10 mg will be available in a tablet form as marketed formulations.

Reference Therapy, Dosage and Mode of Administration: Not applicable

Duration of Subject Participation/Duration of Study/Duration of Treatment:

- **Screening:** Up to 28 days prior to admission to the clinical site
- **Inpatient admission:** Day -2
- **Baseline Visit:** Day -1
- **Treatment Phase 1:** Day 1 to Day 7
- **Treatment Phase 2:** Day 8 to Day 19
- **End-of-study visit:** 14 (+ 2 days) days after the last dose

Total possible study length: Up to 63 days

EVALUATION CRITERIA

Pharmacodynamics: Safety assessments, including adverse events, clinical laboratory, ECG, vital signs, extrapyramidal symptoms (assessed by AIMS and BARS), and suicidal ideation (assessed by the C-SSRS). The incidence of adverse events and clinically significant abnormal laboratory, vital signs, and ECGs values will be recorded based upon Investigator observation, central assessments as appropriate, and subject reporting.

Pharmacokinetics: The following plasma PK parameters after roluperidone single dose, at steady state, and when administered concomitantly with olanzapine will be calculated for roluperidone and its metabolites using non-compartmental methods: C_{max}, T_{max}, AUC_{24}, and AUC_{∞}. Additional PK parameters may be included if deemed appropriate.

[redacted] CGI-S.

STATISTICAL CONSIDERATIONS

Sample Size Determination: The planned sample size is approximately 18 subjects dosed with 64 mg roluperidone in Treatment Phase 1 such that at least 12 subjects can complete dosing with 64 mg roluperidone and 10 mg olanzapine during Treatment Phase 2. The selected sample size is sufficient to calculate the 90% confidence interval of the estimated ratio of C_{max} and AUC of roluperidone with and without coadministration of olanzapine for a true within-subject standard deviation of 0.25 or 0.40 with maximum imprecision of 20.5% or 30.8%, respectively.

Statistical Methods: A detailed description of subject accountability including count of subjects included, exposed, completed (ie, subjects who complete the study treatment period) and discontinued along with the main reason for discontinuation, will be generated for all subjects.

All subjects who are exposed to study treatment, regardless of the amount of treatment administered, will be included in the safety population.

All subjects with no major deviations related to study drug intake (eg, vomiting), for whom the primary pharmacokinetic data are considered sufficient and interpretable, will be included in the pharmacokinetic population.

Demographic characteristics will be listed and summarized using descriptive statistics.

[redacted] CGI-S [redacted]

Pharmacodynamic Analysis: Safety will be evaluated by an analysis of adverse events, vital signs, ECG, physical examination results, and clinical laboratory tests (including blood and urine analyses), AIMS, BARS, and C-SSRS, at specified time-points during the study.

Standard descriptive statistics for all safety variables will be tabulated for each treatment group and measuring time, as appropriate.

Laboratory data (hematology, clinical chemistry, and urine analysis) will be compared to the normal ranges given by the laboratory. Vital signs and ECG data will be compared to normal ranges as well as predefined change ranges. Frequencies of potentially clinically significant abnormalities will be tabulated.

Pharmacokinetic Analysis: The plasma pharmacokinetic parameters after roluperidone single dose, at steady state, and when administered concomitantly with olanzapine (C_{max}, T_{max}, AUC_{0-24}, and AUC_{∞}) of roluperidone and its metabolite BFB-520 will be determined from plasma concentration data using non-compartmental methods. Pharmacokinetic parameters will be summarized by arithmetic mean, SD, geometric mean, coefficient of variation (CV%, both arithmetic and geometric), median, minimum and maximum.

Plasma concentration data will be summarized by treatment group (roluperidone alone, roluperidone + olanzapine). Nominal timepoints will be used for the presentation of tables and figures.

Treatment ratios (roluperidone + olanzapine versus roluperidone alone) for C_{max}, AUC_{0-24}, and AUC_{∞}, following at steady state, will be summarized using the same descriptive statistics as above. LS means (±90% confidence interval [CI]) for log transformed C_{max}, $AUC_{0\ 24}$, and AUC_{∞} will be evaluated by a linear mixed effects model with a fixed term for treatment and a random term for subject, fit by estimated generalized least squares with restricted maximum likelihood estimates of random effects. If deemed relevant to test for a treatment difference in T_{max}, a Wilcoxon signed rank test will be used.

The plasma pharmacokinetic parameters of olanzapine from Day 17 will be compared with its pharmacokinetic profiles available in published literature.

[redacted]

[redacted] CGI-S [redacted].

TIME AND EVENTS SCHEDULE

Period	**SCR**	**Admis-sion**	**BL**	**Treatment Phase 1**							**Treatment Phase 2**												**EOS/ ET**
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**31 (+2)**
Informed consent	X																						
Inclusion & exclusion criteria	X		X[a]																				
Demographics	X																						
Medical history/update	X		X																				
Physical examination	X		X																	X			X
Institutionalization		← • →																					
Roluperidone administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Olanzapine administration											X	X	X	X	X	X	X	X	X	X			
Vital signs[b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X							X										X			X
Height	X																						
Triplicate ECG[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotype	X[d]																						
Chemistry & hematology	X		X							X										X			X
Urinalysis[e]	X		X							X										X			X
Drug screen, alcohol test, and COVID-19	X		X																				
PK samples[f]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serology	X																						
Serum pregnancy test	X		X																	X			X
FSH test	X																						
Tuberculosis test	X																						
MINI	X																						
C-SSRS	X		X	X						X	X									X			X
[redacted]	X		X							X										X			X
CGI-S	X		X							X										X			X
BARS	X		X							X	X									X			X
AIMS	X		X							X	X									X			X
[redacted]	X		X							X										X			X
Prior & Concomitant medications	X	← • →																					

Period	**SCR**	**Admis-sion**	**BL**	**Treatment Phase 1**							**Treatment Phase 2**												**EOS/ ET**
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**31 (+2)**
Adverse events	X	← • →																					

NOTE: There is no washout period between Treatment Phases.

Abbreviations: AIMS = abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; [redacted] CGI-S = Clinical Global Impression – Severity C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end-of-study; ET = early termination; PK = pharmacokinetics; SCR = screening; [redacted] SCR = screening.

[a] Verify eligibility.

[b] Vital signs include blood pressure (standing and supine), pulse, oral/tympanic temperature, and respiratory rate. During Treatment Phase 1, vital signs are assessed prior to PK sampling at pre-dose and 6 hours post-dose on Days 1-7. During Treatment Phase 2, vital signs are assessed prior to PK sampling at pre-dose and 6 hours post-dose on Days 8-17 and 24 hours and 48 hours after last dose of study drug is administered (eg, Days 18 and 19).

[c] Three sets of triplicate ECGs (1 minute apart within 5 minutes; total of 9 ECGs are recorded at Baseline (Day -1). Other ECG assessments are recorded in triplicate prior to PK sampling. During Treatment Period 1, ECGs are recorded at pre-dose and 6 hours post-dose on Days 1-7. During Treatment Phase 2, ECGs are recorded pre-dose and 6 hours post-dose on Days 8-17 and 24 hours and 48 hours after last dose of study drug is administered (eg, Days 18 and 19).

[d] CYP2D6 genotyping to be performed.

[e] Urinalysis will be performed by dipstick. Urine will be sent to the laboratory for microscopic analysis only in the event that the dipstick results are abnormal.

[f] After vital signs and triplicate ECG. During Treatment Period 1, PK samples for roluperidone will be obtained at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 24 hours post-dose on Days 1 and 7, at 6 hours post dose on Day 2, and at pre-dose and 6 hours post-dose on Days 3-6. During Treatment Phase 2, PK samples for roluperidone and olanzapine will be obtained at 6 hours post-dose on Day 8, time 0 (pre-dose) and 6 hours post-dose on Days 9-16, and starting on Day 17 at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 28, 32, 36, and 48 hours post-dose. If a significant prolongation in QT is observed, a PK sample should be obtained.

ABBREVIATIONS

5-HT_{2A}	5-hydroxytryptamine-2A
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BNSS	Brief Negative Symptoms Scale
BUN	blood urea nitrogen
[redacted]	[redacted]
CGI-S	Clinical Global Impression of Severity Score
CI	confidence interval
C_{max}	maximum drug concentration (in plasma or serum)
CPK	creatine phosphokinase
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
DA	dopamine/dopaminergic
DSM-5	Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition
EC	Ethics Committee
ECG	electrocardiogram
ECT	electroconvulsive therapy
EOS	End-of-Study
ET	Early Termination
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
LDH	lactic acid dehydrogenase
LDL	low density lipoprotein
MIN-101	roluperidone
MINI	Mini International Neuropsychiatric Interview
NM	normal metabolizer
[redacted]	[redacted]
PD	pharmacodynamic
PK	pharmacokinetic
PPI	proton pump inhibitor
QTcF	QT interval value corrected for heart rate using Fridericia's formula
RBC	red blood cell
r-TMS	repetitive trans-cranial magnetic stimulation
SAE	serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TCA	tricyclic antidepressants
T_{max}	time to maximum drug concentration (in plasma or serum)

ULN	upper limit of normal
US	United States
VNS	vagal nerve stimulation
WBC	white blood cell

1. INTRODUCTION

1.1. Background on the Disease

Worldwide, the overall lifetime prevalence of schizophrenia is around 1% of the general population and the majority of patients with schizophrenia have moderate to severe negative symptoms at different times during their life (Simeone 2015; **Error! Reference source not found.** 2010).

Negative symptoms are an integral feature of schizophrenia and often emerge during the prodromal phase, before the full-blown manifestation of positive (psychotic) symptoms that lead to the diagnosis of schizophrenia (Piskulic 2012; Yung 2019; Sauvé 2019; Carpenter WT Jr, Buchanan RW. Negative symptom therapeutics. Schizophr Bull. 2017;43:681-682.

Cohen AS, Schwartz E, Le TP, et al. Digital phenotyping of negative symptoms: the relationship to clinician ratings. Schizophr Bull. 2021;47:44-53.

Devoe 2021). Negative symptoms thus constitute a major burden on patients, their families, and society (Foussias 2014; Strauss 2010; Galderisi 2018).

Negative symptoms include emotional experiences such as avolition, asociality, and anhedonia as well as abnormal expression such as blunted affect and poverty of speech (Giordano GM, Caporusso E, Pezzella P, et al. Updated perspectives on the clinical significance of negative symptoms in patients with schizophrenia. Exp Review Neurother. 2022.

Kirkpatrick B, Strauss GP, Nguyen L, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull. 2011;37(2):300-5.

Kirkpatrick B. Developing concepts in negative symptoms: primary vs secondary and apathy vs expression. J Clin Psychiatry. 2014;75:3-7.

Kirkpatrick 2017). Avolition or the lack of will to start and continue pleasurable or essential daily activities is a central feature of primary negative symptoms (**Error! Reference source not found.** 2020; Trémeau 2012; Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms-a review of mechanisms, assessment and treatment. Schizophr Res. 2017;186:29-38.

Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry. 1997;58(12):538-46.

Messinger 2011) and reducing its severity probably drives the overall improvements in negative symptoms (Strauss 2020; Strauss 2021). Simply put, negative symptoms encompass a reduction or absence of the normal range of emotions and behaviors.

Negative symptoms are categorized by researchers and clinicians into primary negative symptoms, that are intrinsic to the schizophrenic illness, and secondary negative symptoms, that manifest as the adverse effect of antipsychotic drugs or can be the result of avoiding social interactions in response to threatening delusions and hallucinations (Artaloytia 2006; Kirschner 2017; Carpenter 2017; Giordano GM, Caporusso E, Pezzella P, et al. Updated perspectives on the clinical significance of negative symptoms in patients with schizophrenia. Exp Review Neurother. 2022.

Kirkpatrick B, Strauss GP, Nguyen L, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull. 2011;37(2):300-5.

Kirkpatrick 2014). The current instruments used to measure the severity and therapeutic induced changes in negative symptoms comprise Positive and Negative Symptom Score- (PANSS-)

derived constructs (White 1997; Marder 1997), other scales focused exclusively on negative symptoms such as the Brief Negative Symptoms Scale (BNSS) (Giordano GM, Caporusso E, Pezzella P, et al. Updated perspectives on the clinical significance of negative symptoms in patients with schizophrenia. Exp Review Neurother. 2022.

Kirkpatrick 2011) and NSA-16 (Axelrod 1993), and remote digital measurements (Cohen 2021). However, opinions about which instrument is best to measure changes in these manifestations continue to evolve (**Error! Not a valid bookmark self-reference.** 2022; Giordano 2022).

Unfortunately, there are no approved treatments for negative symptoms of schizophrenia in the United States (US). Therefore, the treatment of primary negative symptoms of schizophrenia and the resulting functional deficits remains a serious unmet need and meets the criteria for a serious or life-threatening disease or condition.

1.2. Background on the Study Drugs

Roluperidone is a novel cyclic amido derivative, with affinity and antagonistic activity at the 5-hydroxytryptamine-2A (5-HT_{2A}), $sigma_2$, α_{1A}-adrenergic, and, to a lesser extent, α_{1B}-adrenergic receptors. Its metabolite, BFB-520, has a comparable profile to roluperidone, with lower affinity for $sigma_2$ receptors, and lower affinity for 5-HT_{2A} receptors. Roluperidone has very low or no affinity to, or antagonistic activities on, dopaminergic, muscarinic, cholinergic, and histaminergic receptors. Hence, roluperidone mainly targets 5-HT_{2A}, $sigma_2$, α_{1A}- and α_{1B}-adrenergic pathways without direct blockade of dopaminergic pathways/receptors and, in particular, the D_2 dopaminergic receptor sub-type, which is the main target of most available antipsychotics to alleviate psychotic symptoms of patients afflicted by schizophrenia.

Because roluperidone lacks antagonistic activity at the D_2 receptors, it exerts its pharmacologic effect without blocking the brain's dopamine- (DA-) driven reward systems. Therefore, roluperidone does not induce secondary negative symptoms such as sedation and Parkinsonism. Unlike most antipsychotics, it does not, at therapeutic doses, increase prolactin levels or cause weight gain or akathisia.

Nevertheless, it is possible that roluperidone modulates both dopaminergic and glutamatergic pathways without blocking DA receptors, in addition to its effects on neuroplasticity and brain cholesterol metabolism (data on file). The various effects of roluperidone in the different brain areas can be explained by the complexity of the mesolimbic and mesocortical pathways and their role in schizophrenia. Moreover, the antagonist properties of roluperidone on its main targets (5-HT_{2A}, $sigma_2$, α_{1A}-adrenergic, and α_{1B}-adrenergic receptors) can contribute to the regulation of the imbalance between DA, glutamate, and serotonin. Indeed, these targets are involved in the modulation of the different pathways involved in positive and negative symptoms of schizophrenia.

Roluperidone is intended for the treatment of negative symptoms of schizophrenia. Roluperidone should be used as monotherapy, ie, non-adjunctively with antipsychotics. Due to a risk of QT prolongation that is known to be partly related to the CYP2D6 metabolism of metabolite BFB-520, roluperidone is only intended for patients who have at least 1 CYP2D6 allele with normal function.

Additional information about roluperidone is provided in the Investigator's Brochure.

Olanzapine is among the most frequently used drugs to treat acute exacerbation of psychosis in schizophrenia. Once psychosis ameliorates or stabilizes, olanzapine is used as maintenance

treatment to reduce the risk of recurrence of psychosis. Olanzapine has affinities for dopaminergic, cholinergic, serotonergic, and histaminergic receptors. As such it can produce extrapyramidal, parkinsonian effects, sedation, constipation, blurry vision, and weight gain.

1.3. Overall Rationale for the Study

The efficacy of roluperidone monotherapy in the treatment of negative symptoms of schizophrenia has been established in two adequate and well-controlled multinational clinical trials (MIN-101C03 and MIN-101C07). These effects have been demonstrated across both psychometric (PANSS, Negative Symptom Factor Score, BNSS, etc.) and global and functional outcomes (CGI-S and Personal and Social Performance, respectively). Since there exists the possibility that roluperidone might be prescribed off-label in concomitance with antipsychotics, the rationale of this clinical trial is to evaluate the pharmacodynamic and pharmacokinetic effects of the concomitant therapy of roluperidone with an established and widely used antipsychotic, such as olanzapine in order to provide further guidance to clinical practitioners that may prescribe off-label these drugs concomitantly in clinical practice.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
To evaluate the pharmacodynamics (PD), including safety and tolerability of the coadministration of roluperidone 64 mg and olanzapine	Safety assessments, including adverse events (AEs), clinical laboratory, electrocardiogram (ECG), vital signs, extrapyramidal symptoms (assessed by Abnormal Involuntary Movement Scale [AIMS] and Barnes Akathisia Rating Scale [BARS]), and suicidal ideation (assessed by the Columbia Suicide Severity Rating Scale [C-SSRS])
To evaluate the effect of the coadministration of roluperidone and olanzapine on the pharmacokinetics (PK) of roluperidone in subjects with moderate to severe negative symptoms of schizophrenia	• The plasma pharmacokinetic parameters of roluperidone and its metabolite, BFB-520, following single dose and at steady state (C_{max}, T_{max}, AUC_{0-24}, AUC_{∞}) • Plasma pharmacokinetic parameters of roluperidone and BFB-520 when administered concomitantly with olanzapine • The plasma pharmacokinetic parameters of olanzapine administered concomitantly with roluperidone compared to its pharmacokinetic profile based on monotherapy administration from published literature
[redacted]	[redacted] Clinical Global Impression- Severity Rating (CGI-S)

3. OVERVIEW OF STUDY DESIGN

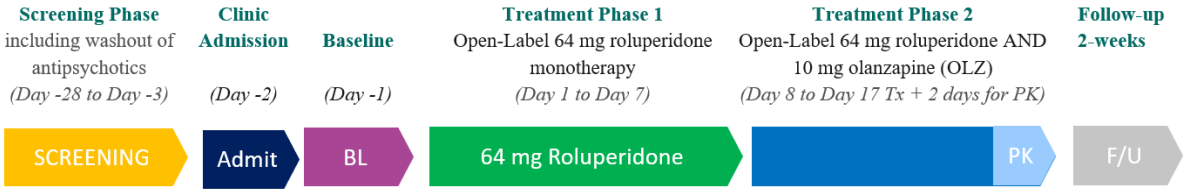
3.1. Study Design

This is a prospective, open-label, one-sequence, inpatient, clinical study of CYP2D6 normal metabolizer (NM) subjects with moderate to severe negative symptoms of schizophrenia. be coadministered to subjects already being administered roluperidone to determine its effect on the PD and PK of roluperidone. Eligible subjects will undergo 3 study phases as follows:

- **Screening Phase**: Between 2 and up to 28 days during which study eligibility will be established and subjects receiving psychotropics will be washed out. Discontinuation of psychotropics must occur at least 2 days prior to the start of Treatment Period 1 (Day 1). Subjects will be admitted to the site on Day -2 and complete a Baseline Visit on Day -1.
- **Treatment Phase 1**: After the Baseline Visit (Day -1), roluperidone 64 mg/day will be administered as a monotherapy for 7 days (Days 1-7).
- **Treatment Phase 2**: Concomitant administration of olanzapine 10 mg/day and roluperidone 64 mg/day for 10 days, starting on Day 8 (Days 8-17). Subjects may be discharged from the clinic at least 48 hours after the last administration of the study drugs and after the collection of the last plasma sample; however, the inpatient period may be extended at the discretion of the investigator.

An End of Study (EOS) visit will take place at least 14 days after the last dose of study treatment. After the EOS visit, the medications and clinical care of the subject will be managed as per the judgement of the investigator/clinician.

Figure 1: Study Design Diagram



3.2. Study Design Rationale

The objectives of this clinical trial are to evaluate the safety and tolerability, pharmacodynamics, and pharmacokinetics of treatment with roluperidone when co-administered with an established and widely used antipsychotic such as olanzapine. An open-label design serves the needs of identifying potential safety signals to guide further clinical development and will provide guidance to clinical practitioners who may prescribe in clinical practice non-prohibited antipsychotics concomitantly with roluperidone.

4. STUDY POPULATION

4.1. General Considerations

Male and female CYP2D6 NM subjects, 18 to 55 years of age, inclusive, with moderate to severe negative symptoms of schizophrenia and no history of any clinically significant conditions that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study.

4.2. Inclusion Criteria

Subjects must satisfy all the following inclusion criteria during screening to be enrolled in the study:

1. Subject and/or subject's legal representative, if applicable, provided informed consent prior to the initiation of any study related procedures, and the subject is judged by the investigator as being capable of understanding the study requirements.
2. Male or female subject, 18 to 55 years of age, inclusive, and body mass index (BMI) < 35 kg/m^2 at Screening.
3. Subject meets the diagnostic criteria for schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), as established by a full psychiatric interview in conjunction with the Mini International Neuropsychiatric Interview (MINI)[a].
4. Has a caregiver or family member or health care personnel who can provide information towards assessment and support the subject in terms of compliance with the protocol.
5. Has documented diagnosis of schizophrenia for at least 1 year before screening into the trial.

[a] Current version for DSM-5.

6. Subject is stable in terms of both positive and negative symptoms of schizophrenia over the last 3 months according to his or her clinician and/or a caregiver who knows the patient like the responsible person at the patient residence, a social worker, rehabilitation therapist or a caregiver/ family member or based on documentation in the clinical chart or medical records. Subjects with or without positive symptoms are allowed if these symptoms are stable for the last 3 months and they do not meet exclusion criterion 2.
7. Subject is currently an outpatient and has not been hospitalized for the last 3 months for acute exacerbation or symptoms worsening. Subjects who have been hospitalized for social reasons for any time period during the last 3 months or are currently hospitalized for social reasons can be included only with Sponsor's Responsible Medical Officer's approval. The social reasons must be documented in the case report form (CRF).
8. Subject with a score of > 20 on the PANSS original negative symptoms subscale (Sum of N1+N2+N3+N4+N5+N6+N7) at Screening and Baseline (Day -1) AND < 4 points absolute difference between the 2 visits.
9. Subject has discontinued psychotropic medications without risk to their clinical status or safety by Baseline. Subjects receiving treatment with long-acting or depot antipsychotic medication must have discontinued the depot antipsychotic for a full cycle of the drug (ie, 1-6 months depending on formulation).
10. No history of violence against self or others during the last 1 year.
11. Female subject, if not of childbearing potential, must be a woman who is post-menopausal (defined as spontaneous amenorrhoea for at least 1 year or spontaneous amenorrhoea for at least 6 months confirmed by follicle stimulating hormone result of ≥ 40 IU/mL) or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy).
12. Female subject, if of childbearing potential, must test negative for pregnancy and must be using a 2 methods of contraception for at least 30 days after the completion of the study, one of which must be a highly effective method. The following highly effective contraception methods acceptable for this study are:

    - Surgical sterilization (for example, bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or vasectomy for her male partner provided that the partner is the sole sexual partner of the female subject and that the vasectomized partner has received medical assessment of the surgical success).
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Hormonal contraception (oral, implantable, patch, injectable).
    - True sexual abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (for example, calendar ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are NOT acceptable methods of contraception).

    The following acceptable methods can be used as a second form of contraception during the study:

    - Barrier methods for a female subject include use of an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository.
    - A male subject who has been sterilized (with medical assessment of the surgical success) or have partners of non-childbearing potential (including homosexual men) is

required to use a condom with spermicide. This is to prevent unintended exposure of the partner to the study drug via seminal fluid.

- A male subject who has partners of childbearing potential must be willing to use a condom with spermicide. Because a condom alone is not adequate contraception for this study, male subjects are strongly recommended to discuss the potential risks to a fetus with all female partners and advise them of the need to high effective contraception for up to 90 days after completion of the study. A male subject whose partner is pregnant is not allowed in the study.
- A female subject who is post-menopausal (defined as spontaneous amenorrhea for at least 1 year without an alternative medical cause) is eligible for this study. Hormone replacement therapy (HRT) is allowed during the study.

13. Subject must be normal metabolizer for P450 CYP 2D6, defined as a subject that has at least one functional allele (eg, *1, *2 or *35), as determined by study-specific genotyping test before the first drug dose is administered.
14. Subject and the caregiver are considered by the investigator to be reliable and likely to cooperate with the assessment procedures.

4.3. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Current major depressive disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, or intellectual disability (intellectual developmental disorder diagnosed by age 14).
2. Subject with PANSS item score of > 4 on:
   - P4 Excitement/Hyperactivity
   - P6 Suspiciousness/persecution
   - P7 Hostility
   - G8 Uncooperativeness
   - G14 Poor impulse control
3. A CDSS total score > 6.
4. A score of ≥ 2 on any 2 of items 1, 2, or 3, or a score of ≥ 3 on item 4 of the Barnes Akathisia Rating Scale (BARS).
5. Subjects with known hypersensitivity to olanzapine.
6. Subject's condition is due to direct physiological effects of a substance (eg, a drug of abuse or medication) or a general medical condition.
7. Has a current or recent history of serious suicidal behavior within the past 1 year.
8. Subject has a history of substance use disorder within 3 months of the Screening visit (excluding caffeine and cigarette smoking).
9. Positive urine drug screen for drugs of abuse (cocaine, methadone, amphetamines, opiates, benzodiazepines, and barbiturates), tricyclic antidepressants (TCA), and alcohol (except for prescription benzodiazepines). Recreation cannabinoids are allowed if the

clinician determines that the subject does not meet criteria for cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the clinician can ensure that the subject is not using cannabis during days -2 to 17.

10. Subject cannot be discontinued from psychotropic medication(s).
11. Subject who received clozapine within 6 months of the Screening visit
12. Subjects is currently taking proton pump inhibitors (PPI)
13. Subject with a history of significant other major or unstable neurological, neurosurgical (eg, head trauma), metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, metabolic, gastrointestinal, or urological disorder.
14. Subject with a history of seizures (subject with a history of a single childhood febrile seizure may be enrolled in this study).
15. Subject who has had electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), or repetitive trans-cranial magnetic stimulation (r-TMS) within the 6 months prior to the Screening visit or who are scheduled for ECT, VNS, or r-TMS at any time during the study.
16. Subject with clinically significant abnormalities in hematology, blood chemistry, ECG, or physical examination not resolved by the Baseline visit which according to Investigator can interfere with study participation.
17. Current systemic infection (eg, Hepatitis B, Hepatitis C, human immunodeficiency virus [HIV], tuberculosis). Subjects with positive Hepatitis B core antibody test and negative Hepatitis B Surface Antigen (HBsAg) may be included in the study if aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) do not exceed 2 times upper limit of normal (ULN).
18. Positive for COVID-19 virus.
19. Subject who requires or may require concomitant treatment with any other medication likely to increase QT interval (eg, paroxetine, fluoxetine, duloxetine, amiodarone; a non-exhaustive list is provided in ATTACHMENT 1: Prohibited Concomitant Medications).
20. Subject who requires medication inhibiting CYP2D6.
21. Subject with a clinically significant ECG abnormality that could be a safety risk in the study, including QT interval value corrected for heart rate using the Fridericia's formula (QTcF) > 430 msec for males and > 450 msec for females.
22. Subject with a myocardial infarction within 6 months of Screening based on medical history or significant ECG findings at Screening.
23. Familial or personal history of long QT syndrome or with additional risk factors for Torsade de Pointes.
24. Subject whose safety laboratory results show one or more of the following: potassium <3.4 mmol/L, or calcium <2.07 mmol/L, or magnesium <0.70 mmol/L.
25. Subjects with unexplained syncope.
26. Woman of child-bearing potential, or man, who is unwilling or unable to use accepted methods of birth control.

27. Woman with a positive pregnancy test, who is lactating, or who is planning to become pregnant during the study.
28. Subject who participated in another clinical study within 3 months prior to Screening, or received roluperidone previously, or has previously participated in > 3 clinical studies with experimental medication within the past 2 years.

5. STUDY TREATMENT

5.1. Randomization and Blinding

This is an open-label, one-sequence study; therefore, randomization and blinding will not be performed. Eighteen (18) subjects will be enrolled in the study to ensure 12 subjects complete the study. Eligible subjects will be assigned a subject identification number in sequential order.

5.2. Dosage and Administration

A daily dose of 64 mg roluperidone will be orally administered in the clinic by the investigator or other trained designee during Treatment Period 1.

Daily doses of 64 mg roluperidone and 10 mg olanzapine will be orally administered at the same time in the clinic by the investigator or other trained designee during Treatment Period 2.

Under all conditions, roluperidone tablets must be swallowed whole and not chewed, divided, dissolved, or crushed. Roluperidone and olanzapine, as applicable, must be administered at approximately the same time of day for each subject.

5.3. Compliance

Roluperidone and olanzapine will be administered in the controlled setting of a clinical study center. Study center staff will directly observe the administration of roluperidone and olanzapine, as applicable, during both treatment periods to ensure compliance with study requirements. Mouth and hand checks will be conducted after dosing to ensure the tablets have been swallowed.

The exact date and time of each dose of roluperidone and olanzapine will be recorded in the CRF.

5.4. Labeling

The cases containing the roluperidone tablets will have a product and study-specific label with all the information that meets the applicable regulatory requirements. Dispensing instructions will be provided separately in the investigational medicinal product manual.

Oral olanzapine 10 mg will be available in a tablet form as marketed formulations (ZYPREXA 2019) and will be used with no further modifications.

5.5. Storage Conditions

All study drugs must be stored in a controlled environment at room temperature.

5.6. Drug Accountability

The clinical investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject

must be documented on the drug accountability form. Unused or partially used study drug will be stored and disposed of according to the sponsor's instructions. Contents of the study drug containers must not be combined.

Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must not be disposed of until the sponsor's site monitor has completed drug accountability during an on-site monitoring visit. The return to the sponsor or destruction on site of used and unused study drug will be documented on the Drug Return Form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees to store and dispense the study drug only at the site agreed upon with the sponsor.

5.7. Retrieval of Treatment and/or Destruction

All partially used or unused study drugs will be retrieved by the Sponsor. A detailed treatment log of the returned Investigational Product will be established with the Investigator (or the Pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the unused Investigational Product unless the Sponsor provides written authorization to the contrary.

A potential defect in the quality of Investigational Product may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor in order to recall Investigational Product and eliminate potential hazards.

5.8. Concomitant Therapy

Throughout the study, prescription or nonprescription medications (including vitamins and herbal supplements) other than the study drugs are prohibited, except for the following:

- The use of acetaminophen/antihistamines is allowed until 3 days before treatment period 1. Throughout the study, a maximum of 3 doses per day of 500 mg acetaminophen, and no more than 3 grams per week, will be allowed for the treatment of headache or other pain. If acetaminophen is used, the dose and dosage regimen and reason for use will be recorded in the CRF.
- Rescue medication for agitation (lorazepam) and sleep (zolpidem) is allowed at any time during screening and throughout the study.

Women using hormonal contraceptives as a means of birth control must continue to use the same hormonal contraceptives throughout the study. Women using hormone replacement therapy (HRT) must continue to use the same HRT throughout the study.

The sponsor must be notified immediately if prohibited therapies are administered.

All medications taken by a subject (prescription or nonprescription) other than roluperidone will be documented in the CRF. This includes medications taken before and during the study through the end-of-study visit.

6. STUDY EVALUATIONS

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of pharmacokinetic, safety, and other measurements. Prior to engaging in any study procedure, each subject must sign and date an informed consent form.

6.1. Study Procedures

Adverse event assessment will be recorded on the CRF throughout the study from the time of informed consent form signature. Concomitant medication and AE assessments will be recorded on the CRF throughout the study.

6.1.1. Screening Phase

During the screening phase subjects and their legal representatives must provide written informed consent before any study evaluations are performed or any laboratory samples are collected. After written informed consent is obtained, subjects will be evaluated for study eligibility during the screening period. A complete medical history will be documented, and a complete physical examination will be conducted, including measurement of vital signs, electrocardiogram (triplicate ECG), body weight, and height. Hematology, clinical chemistry, serology, and urinalysis will be performed for all subjects, as well as verification of CYP2D6 genotype (confirmed by study-specific testing). AIMS, [redacted] CGI-S, BARS, [redacted], and C-SSRS will also be administered. All psychotropic drugs must be discontinued by Day -2; the time and rate of psychotropic discontinuation will be at the discretion of the investigator.

6.1.2. Admission to Clinical Site

Subjects will be admitted to the research site on Day -2. Patients will remain inpatient at the clinical site at least through the end of Treatment Phase 2.

6.1.3. Baseline Visit

At the Baseline visit on Day -1, subjects will complete admission procedures and confirm eligibility for enrollment. Vital signs, electrocardiogram (3 sets of triplicate ECG), body weight, and height will be measured. Laboratory samples for hematology, clinical chemistry, and urinalysis (by dipstick) will be performed for all subjects. AIMS, [redacted] CGI-S, BARS, [redacted] and C-SSRS will also be administered.

6.1.4. Treatment Phase 1

In Treatment Phase 1, beginning on Day 1, subjects will receive 64 mg roluperidone each day at approximately the same time (between approximately 7:00 and 10:00 AM), followed by sequential collection of blood samples for measurement of plasma concentrations of roluperidone and ECG assessments, until Day 7. On Days 1 and 7, subjects will receive the study drug after fasting for at least 9 hours starting the night before. Subjects will receive standardized light meals approximately 2 hours after dosing. Vital signs, ECGs (in triplicate), and PK samples at specified time points will be collected throughout Treatment Phase 1. AIMS, [redacted] CGI-S, BARS, [redacted] C-SSRS will be administered on Day 7. Subjects will remain at the clinic after Day 7 to continue Treatment Phase 2.

6.1.5. Treatment Phase 2

In Treatment Phase 2, beginning on Day 8 subjects will receive study drugs (roluperidone and olanzapine) each day at approximately the same time followed by sequential collection of blood samples for measurement of plasma concentrations of both drugs and ECG assessments until Day 17. On Day 17, subjects will receive the study drug after fasting for at least 9 hours starting the night before. Subjects will receive standardized light meals approximately 2 hours after dosing. Vital signs, ECGs (in triplicate), and PK samples at specified time points will be collected throughout Treatment Phase 2. AIMS, BARS, and [redacted] will be administered on Day 8, and AIMS, [redacted] CGI-S, BARS, [redacted] C-SSRS will be administered on Day 17. Subjects may be released from the clinic after the collection of the last plasma sample (at least 48 hours after the last administration of the study drugs); however the inpatient period may be extended at the discretion of the investigator.

6.1.6. End of Study/Early Termination

All subjects will return to the site for subsequent EOS assessments 14 (+ 2) days after receiving their last dose in Treatment Phase 2.

If a subject is terminated early from the study, a PK sample and a blood sample for chemistry and hematology will be drawn as soon as possible together with any relevant safety assessments.

6.2. Collection of Blood

The maximum amount of blood drawn per subject in this study will not exceed 500 mL for subjects who complete the study. Repeat or unscheduled samples may be taken for safety reasons.

Table 1: Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood[a] (mL)
Safety (including screening and post-treatment assessments)			
- Hematology	4	5	20
- Clinical chemistry[b]	8.5	5	42.5
- Genotyping	4	1	4
Pharmacokinetic samples (roluperidone / BFB-520)	2.5	70	175
Pharmacokinetic samples (olanzapine)	3	35	105
Loss by use of indwelling intravenous cannula	2	1	2
		Total:	348.5

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Clinical chemistry includes lipids, serology, serum β-hCG pregnancy tests & FSH, as applicable.
Note: An indwelling intravenous cannula may be used for blood sample collection. If a mandarin (obturator) is used, blood loss due to discard is not expected.

If blood samples are collected via an indwelling cannula, an appropriate amount (ie, 1 mL) of fluid slightly more than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% pharmaceutical grade for injection sodium chloride, or sodium heparin of 100 U/mL (where applicable) and charged with a volume equal to the dead space volume of the lock.

6.3. Pharmacokinetic Evaluations

6.3.1. Sample Collection and Handling

Blood samples for determination of roluperidone and its metabolite, BFB-520, as well as olanzapine plasma concentrations will be collected at the time points indicated in the TIME AND EVENTS SCHEDULETIME AND EVENTS SCHEDULE. The exact dates and times of blood sample collection must be recorded in the CRF.

6.3.2. Analytical Procedures

Plasma samples will be stored at -80°C until analysis. Plasma samples will be analyzed to determine concentrations of roluperidone and its metabolite, BFB-520, as well as olanzapine using validated, specific, and sensitive liquid chromatography/mass spectrometry methods under the supervision of the sponsor's bioanalytical facility or designee.

Plasma samples will be disposed of after the clinical study report is finalized.

6.3.3. Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the sponsor in accordance with the current Clinical Pharmacokinetics Guideline. The following key plasma PK parameters will be calculated using non-compartmental methods:

C_{max} observed maximum plasma concentration (ng/mL)

T_{max} time to reach the observed maximum plasma concentration (h)

AUC_{0-24} area under the plasma concentration-time curve from time 0 to concentration C_{24} (ng.h/mL) at the 24-hour time point

AUC_{∞} area under the plasma concentration-time curve from time 0 to infinite time, calculated according to the following equation $AUC = AUC_{last} + C_{last} / \lambda_z$ (ng.h/mL)

Additional PK parameters may be included if deemed appropriate.

6.4. Pharmacodynamic Evaluations

The [redacted] assessments will be performed at the time points indicated in the TIME AND EVENTS SCHEDULE. Every effort should be made to ensure that all clinician reported objective measurements are completed by the same individual who made the initial Baseline determinations.

[redacted]

CGI-S is a clinician-rated scale that is designed to rate the severity of the patient's illness at the time of assessment, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function relative to the clinician's past experience with patients who have the same diagnosis and improvement with treatment. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating, according to: normal (not at all ill) = 1; borderline mentally ill = 2; mildly ill = 3; moderately ill = 4; markedly ill = 5; severely ill = 6; or extremely ill = 7. See ATTACHMENT [redacted] Clinical Global Impression – Severity Rating (CGI-S) for an example of the CGI-S.

6.5. Safety Evaluations

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 9.

Clinical Laboratory Tests

Blood samples for serum chemistry (collected after an overnight fast) and hematology and urine samples for urinalysis will be collected according to the TIME AND EVENTS SCHEDULE.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The following tests will be performed by the designated laboratory.

- ***Hematology:***
  - hemoglobin
  - hematocrit
  - white blood cell (WBC) count with differential
  - platelet count
  - red blood cell (RBC) count
- ***Serum Chemistry:***
  - sodium
  - potassium
  - chloride
  - magnesium
  - blood urea nitrogen (BUN)
  - creatinine
  - glucose (fasting)
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - total bilirubin
  - alkaline phosphatase
  - gamma-glutamyl transferase (GGT)
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - calcium
  - prolactin
  - phosphorous (inorganic)
  - albumin
  - total protein
  - cholesterol (total)
  - triglycerides
  - high density lipoprotein (HDL)
  - low density lipoprotein (LDL)
- ***Urinalysis***

Dipstick
- specific gravity
- pH
- glucose
- protein
- blood
- ketones
- bilirubin
- urobilinogen
- nitrite
- leukocyte esterase

Sediment (if dipstick result is abnormal)
- RBC
- WBC
- epithelial cells
- crystals
- casts
- bacteria

If dipstick result is abnormal, the sediment will be examined microscopically.

- In women of childbearing potential, a serum pregnancy will be performed at Screening, Day -1, Day 17 and the EOS visit (refer to the TIME AND EVENTS SCHEDULE). Additional urine pregnancy tests may be conducted throughout the study, as determined by the investigator, to establish the absence of pregnancy during the study.
- Women of non-childbearing potential and post-menopausal as defined by spontaneous amenorrhea for at least 6 months but less than 1 year will provide a blood sample for FSH testing as screening.
- Serology (HBsAg, HBcAg, hepatitis C antibody, and HIV antibodies 1 and 2) at Screening.
- Tuberculosis testing will occur at Screening.
- Urine drug screen and alcohol breath test: potential subjects will be tested for drugs of abuse (cocaine, methadone, amphetamines, cannabinoids, opiates, benzodiazepines, barbiturates, tricyclic antidepressants) and alcohol according to the TIME AND EVENTS SCHEDULE. If the results of the urine drug screen or the alcohol breath test are positive at Screening or Baseline, the subject will not be enrolled.

Vital Signs

Vital signs will include supine blood pressure, pulse, oral/tympanic temperature, and respiratory rate.

Standing and supine blood pressure and pulse will be taken after the subject has been resting quietly for 5 minutes. Blood pressure and pulse should be taken in the arm with the highest pressure, using the same arm for each reading and for all visits. An appropriately sized arm cuff will be used, and the size of the cuff should remain constant for all visits. After blood pressure has been assessed in the supine position, blood pressure will be re-measured within 3 minutes of standing).

Electrocardiogram

ECG will be recorded in triplicate (1 minute apart within 5 minutes). During the collection of ECG data, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 10 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the ECG should be performed first, followed by vital sign measurements, and blood draws.

Three 12-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity, reasonableness and online safety assessment.

ECGs will be overread by an ECG central reader. The following ECG intervals will be measured: RR, PR, QRS, and QT. Electrocardiogram monitoring will include the evaluation of lengthening of QTcF. A qualitative assessment of the T-wave morphology will be made by the central reader.

If a significant prolongation in QT is observed, a PK sample should be obtained.

Physical Examination

Physical examinations as well as anthropomorphic measurements (height and weight) will be performed at the times specified in the TIME AND EVENTS SCHEDULE.

Any abnormalities present at Baseline, or subsequent changes, will be documented in the

appropriate sections of the CRF. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

AIMS is rating scale that was designed in the 1970s to measure TD will be performed at the times specified in the TIME AND EVENTS SCHEDULE. TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The AIMS test is used not only to detect TD but also to follow the severity of a patient's TD over time. The AIMS test is usually given every 3 to 6 months to monitor the patient for the development of TD. For most patients, TD develops 3 months after the initiation of neuroleptic therapy; in elderly patients, however, TD can develop after as little as one month. The entire test can be completed in about 10 minutes. The AIMS test has a total of 12 items rating involuntary movements of various areas of the patient's body. These items are rated on a 5-point scale of severity from 0–4. The scale is rated from 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 =severe. Two of the 12 items refer to dental care. The patient must be calm and sitting in a firm chair that doesn't have arms, and the patient cannot have anything in his or her mouth. The clinician asks the patient about the condition of his or her teeth and dentures, or if he or she is having any pain or discomfort from dentures.

The remaining 10 items refer to body movements themselves. The clinician or rater asks the patient about body movements. The rater also looks at the patient in order to note any unusual movements first hand. The patient is asked if he or she has noticed any unusual movements of the mouth, face, hands or feet. If the patient says yes, the clinician then asks if the movements annoy the patient or interfere with daily activities. Next, the patient is observed for any movements while sitting in the chair with feet flat on the floor, knees separated slightly with the hands on the knees. The patient is asked to open his or her mouth and stick out the tongue twice while the rater watches. The patient is then asked to tap his or her thumb with each finger very rapidly for 10–15 seconds, the right hand first and then the left hand. Again, the rater observes the patient's face and legs for any abnormal movements.

After the face and hands have been tested, the patient is then asked to flex (bend) and extend one arm at a time. The patient is then asked to stand up so that the rater can observe the entire body for movements. Next, the patient is asked to extend both arms in front of the body with the palms facing downward. The trunk, legs and mouth are again observed for signs of TD. The patient then walks a few paces, while his or her gait and hands are observed by the rater twice.

See ATTACHMENT 5: Abnormal Involuntary Movement Scale (AIMS) for an example of the AIMS.

BARS is a multiple-choice questionnaire that clinicians may use to provide an assessment of akathisia will be performed at the times specified in the TIME AND EVENTS SCHEDULE. Akathisia is a state of motor restlessness, sometimes produced by neuroleptic medication that ranges from a feeling of inner distress to an inability to sit still. The clinician or rater is instructed to observe the subject while standing and while sitting, at least 2 minutes each (total of at least 4 minutes in total). There are 4 areas where the subject is to be evaluated, 1 of these is objective, 2 are subjective, and the final is a global assessment. This scale was generated in 1989 (Barnes 1989) and was derived from the findings of studies exploring the clinical features of antipsychotic-induced akathisia both in acute psychiatric admissions and schizophrenic out-

patients on maintenance medication. Subsequently, its validity and reliability have been established, and it has been used extensively in clinical studies worldwide.

See ATTACHMENT 6: Barnes Akathisia Rating Scale (BARS) for an example of the BARS.

C-SSRS is a measure used to identify and assess individuals at risk for suicide. Questions are phrased for use in an interview format but can be completed as a self-report measure if necessary. The C-SSRS measures four constructs: the severity of ideation, the intensity of ideation, behavior, and lethality. It includes "stem questions," which if endorsed, prompt additional follow-up questions to obtain more information.

See ATTACHMENT 7: Columbia Suicide Severity Rating Scale (C-SSRS) for an example of the C-SSRS.

7. SUBJECT COMPLETION/WITHDRAWAL

7.1. Completion

A subject will be considered to have completed the study if he or she completed all required assessments at Day 19. Subjects who prematurely discontinue for any reason before completion of Day 19 will not be considered to have completed the study.

7.2. Stopping Criteria

Subjects who meet any of the following stopping criteria will be discontinued from the study:

1. [redacted]
2. CGI-S worsening of more than 2 points.
3. Suicidal ideations or behavior.
4. Occurrence of an AE, which could jeopardize the subject's health as per investigator opinion.
5. Worsening of psychotic symptoms or occurrence of any dangerous behavior against self or others as per investigator opinion.
6. Significant increase in ALT (ie, > 5 × ULN).
7. Abnormal laboratory results with simultaneous increases of total bilirubin (> 2 × ULN), ALT or AST (> 3 × ULN) with AP (< 1.5 × ULN).
8. Sustained mean QTcF value > 500 msec (confirmed by a second ECG under strict resting position and at minimum at 30-minute duration from the first measurement). The subject's treatment must be discontinued until mean QTcF values are obtained from the ECG central reader. If values are confirmed, the subject must be discontinued from the study; if not, the study treatment may be restarted at the discretion of the investigator.
9. Sustained mean increase of > 60 msec in the QTcF compared to Baseline (confirmed by a second ECG under strict resting position and at minimum at 30-minute duration from the first measurement). The subject's treatment must be discontinued until mean QTcF values are obtained from the ECG central reader. If values are confirmed, the subject must be discontinued from the study; if not, the study treatment may be restarted at the discretion of the investigator.

10. The subject requires treatment with another therapeutic agent that had been demonstrated to increase the QT interval or inhibit CYP2D6. In this case, discontinuation from the study should occur prior to the introduction of the new agent.
11. The subject experiences a syncope or severe dizziness not explained by other known causes, eg, documented orthostatic hypotension, Ménière disease.
12. The subject has an overt seizure or reports seizure-like activity (loss of consciousness, uncontrollable tremor not due to extrapyramidal symptoms).

The study will be stopped if 4 or more subjects are discontinued due to any of the criteria, except stopping criterion 4 if the AE is considered to be definitely not related to study drug and stopping criteron 10.

7.3. Withdrawal from the Study and Replacement

The subjects have the right to withdraw from the study at any time for any reason, without the need to justify. Additionally, the investigator may withdraw the subject acording to clinical judjment.

A subject will be withdrawn from the study for any of the following reasons:

- Subject withdraws consent
- Lost to follow-up
- Termination of the study
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to stop treatment
- The subject becomes pregnant
- Failure to use an acceptable method of birth control
- Significant deviation from the protocol
- Occurrence of a treatment-related SAE
- Concurrent illness and requirement of a prohibited medication
- The subject meets any of the stopping criteria listed in Section 7.2.

If a subject is lost to follow-up, every possible effort will be made by study center staff to contact the subject and determine the reason for discontinuation; this information will be recorded on the subject's CRF.

If a subject withdraws before completing the study, the reason for withdrawal will be documented on the subject's CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

Should the sponsor elect to replace subjects who withdraw before they complete all study procedures, the replacement subjects will be of the same gender as the subjects they are replacing. A replacement subject will be assigned a new identification number which will be equal to the identification number of the subject being replaced plus 500. Replacement subjects will be assigned to the same treatment-sequence as the subjects they are replacing. Replacement subjects will start with Treatment Period 1.

8. STATISTICAL METHODS

This statistical plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data that could affect

planned analyses. These revisions will be based on blinded review of the data, and a final plan will be issued prior to database lock.

All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

Percentages of subjects with AEs or laboratory toxicities will be based on non-missing values.

A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

Statistical analysis will be performed by or under supervision of the sponsor.

8.1. Sample Size Determination

The planned sample size is approximately 18 subjects dosed with 64 mg roluperidone in Treatment Phase 1 such that at least 12 subjects can complete dosing with 64 mg roluperidone and 10 mg olanzapine during Treatment Phase 2. The selected sample size is sufficient to calculate the 90% confidence interval of the estimated ratio of C_{max} and AUC of roluperidone with and without coadministration of olanzapine for a true within-subject standard deviation of 0.25 or 0.40 with maximum imprecision of 20.5% or 30.8%, respectively.

8.2. General Methodology

A detailed description of subject accountability including count of subjects included, exposed, completed (ie, subjects who complete the study treatment period) and discontinued along with the main reason for discontinuation, will be generated for all subjects.

All subjects who are exposed to study treatment, regardless of the amount of treatment administered, will be included in the safety population.

All subjects with no major deviations related to study drug intake (eg, vomiting), for whom the primary pharmacokinetic data are considered sufficient and interpretable, will be included in the pharmacokinetic population.

Demographic characteristics will be listed and summarized using descriptive statistics.

[redacted]CGI-S[redacted]

8.3. Initial Subject Characteristics

For all subjects who received at least one dose of roluperidone, descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be performed for age, BMI, weight, and height. Sex and race will be listed and tabulated.

8.4. Pharmacokinetic Analyses

The plasma pharmacokinetic parameters after roluperidone single dose, at steady state, and when administered concomitantly with olanzapine (C_{max}, T_{max}, AUC_{0-24}, and AUC_{∞}) of roluperidone and its metabolite BFB-520 will be determined from plasma concentration data using non-compartmental methods. Pharmacokinetic parameters will be summarized by arithmetic mean, SD, geometric mean, coefficient of variation (CV%, both arithmetic and

geometric), median, minimum and maximum.

Plasma concentration data will be summarized by treatment group (roluperidone alone, roluperidone + olanzapine). A nominal time point will be used for the presentation of tables and figures.

Treatment ratios (roluperidone + olanzapine versus roluperidone alone) for C_{max}, AUC_{0-24}, and AUC_{∞}, following at steady state, will be summarized using the same descriptive statistics as above. LS means (± 90% confidence interval [CI]) for log transformed C_{max}, $AUC_{0\ 24}$, and AUC_{∞} will be evaluated by a linear mixed effects model with a fixed term for treatment and a random term for subject, fit by estimated generalized least squares with restricted maximum likelihood estimates of random effects. If deemed relevant to test for a treatment difference in T_{max}, a Wilcoxon signed rank test will be used.

The plasma pharmacokinetic parameters of olanzapine from Day 17 will be compared with its pharmacokinetic profiles available in published literature.

8.5. Safety Analyses

Safety will be evaluated by an analysis of adverse events, vital signs, ECG, physical examination results, and clinical laboratory tests (including blood and urine analyses), AIMS, BARS, and C-SSRS, at specified time-points during the study as outlined in the TIME AND EVENTS SCHEDULE.

Standard descriptive statistics for all safety variables will be tabulated for each treatment group and measuring time, as appropriate.

Laboratory data (hematology, clinical chemistry, and urine analysis) will be compared to the normal ranges given by the laboratory. Vital signs and ECG data will be compared to normal ranges as well as predefined change ranges. Frequencies of potentially clinically significant abnormalities will be tabulated.

[redacted]

[redacted] CGI-S [redacted]

9. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

9.1. Definitions

9.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational)

product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Council for Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the Baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event

An SAE is defined as any AE that results in any of the following:

- **Death**: The subject died as the result of the event.
- **Life-threatening event**: Any AE that places the subject, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, ie, does not include an AE that had it occurred in a more severe form, might have caused death.
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.
- **Persistent or significant disability/incapacity**: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the IP.
- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Adverse Event of Special Interest

AESIs are defined as the any of the following events:

- Syncope
- Sudden death, cardiac death
- TdP, QT/QTc prolongation, long QT syndrome
- ECG T wave and U wave abnormalities
- Ventricular arrhythmia, tachycardia, fibrillation / flutter

Suspected Unexpected Serious Adverse Reactions (SUSARs) Event/Reference Safety Information

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to the study drug and are both unexpected (ie, the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the appropriate competent authorities.

Adverse Drug Reaction

An adverse drug reaction is any AE where a causal relationship with the study drug is at least a reasonable possibility (possibly, probably or definitely related as by the definitions listed below).

9.1.2. Assessment of Causality

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the study drug. The temporal relationship of the event to study drug administration should be considered in the causality assessment (ie, if the event starts soon after study drug administration and resolves when the study drug is stopped).

Causality should be assessed using the following categories.

Unrelated: An adverse event that is not related to the use of the drug.

Possibly/probably related: An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive or unlikely. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Definitely: An adverse event that cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

9.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

9.1.4. Action Taken and Outcome

For all AEs reported, the following will also be specified:

- Actions taken: none, medication required, tests required, hospitalization required or prolonged, study drug withdrawn, other-specify
- Outcome and date of outcome according to the following definitions:
  - Recovered/resolved
  - Recovering/resolving
  - Not recovered/not resolved
  - Recovered with sequelae/resolved with sequelae
  - Fatal
  - Unknown
  - Seriousness: yes or no (criteria for SAE see above)

9.2. Procedures

9.2.1. All Adverse Events

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all serious adverse events that are SUSARs. The investigator (or sponsor where required) must report these events to the appropriate Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IRB.

Subjects must be provided with a “study card” indicating the name of the investigational study drug, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

9.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person and pharmacovigilance provider by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) or e-mail.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to Baseline, if a Baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for surgery or procedure planned before entry into the study (must be documented in the CRF).

9.2.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9.3. Reporting

9.3.1. Reporting Serious Adverse Events to the Sponsor

The investigator is required to notify the study sponsor and pharmacovigilance provider within 24 hours of becoming aware of the occurrence of an SAE. In accordance with ICH guidelines for Good Clinical Practice (GCP), a copy of the written report of the event should promptly be sent to the study sponsor and pharmacovigilance provider by email. The names and contact details of the individuals who should be contacted regarding safety issues or questions regarding the study as well as the email address/fax number that must be used to send SAE

report form, are listed on the Contact Information page(s), which will be provided as a separate document.

9.3.2. Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor, with the pharmacovigilance provider, to determine whether a reported SAE fits the classification of a SUSAR.

9.3.3. Expedited Reporting of Events

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the sponsor, via the pharmacovigilance provider, to report fatal or life-threatening SUSARs to the appropriate competent authorities, IRB/EC as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

The investigator is required to notify the EC of any fatal or life-threatening SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor, via the pharmacovigilance provider, to report other SUSARs to the appropriate competent authorities, and IRB/Ethics Committee (EC) as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

The investigator is required to notify the EC of any other SUSAR as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

9.4. Reporting of Urgent Safety Issues

The sponsor is required to inform the appropriate competent authorities, investigators, and ECs within 3 calendar days of the urgent safety issue.

10. SERIOUS BREACHES

It is the responsibility of the sponsor to notify the competent/licensing authority of any serious breach that is likely to affect, to a significant degree, the safety or mental integrity of the subjects in the study or the scientific value of the study.

All serious breaches will be communicated to the appropriate competent authorities within 7 days. The reporting will be performed by the party who suspects the serious breach.

11. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure
- Pharmacy manual
- Laboratory manual
- CRF and infrastructure
- Pharmacokinetic blood sampling supplies
- Subject education material

12. ETHICAL ASPECTS

12.1. Study-Specific Design Considerations

This study is being conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of roluperidone and olanzapine.

This study will be performed in subjects with schizophrenia who will receive no benefit from participation in the study. Subjects will be exposed to an investigational drug that may have adverse effects, such as headache, nausea, postural hypotension and somnolence. In addition they will be exposed to a marketed drug olanzapine which may induce well known adverse effects such as EPS, sedation, constipation, blurry vision, weight gain. In this and all clinical pharmacokinetic studies, there are risks associated with the collection of multiple blood samples.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. No undue incentives will be provided.

Safety of Dose

The potential risks to subjects in this study include exposure to study drugs, with a potential for side effects, and the inherent risks associated with venipuncture and multiple blood sample collection. Multiple dose, chronic exposure studies with 64 mg roluperidone have been conducted (Study MIN-101C03 and Study MIN-101C07), and 64 mg roluperidone was overall well tolerated. Rare instances of QTc prolongation were noted in the 64 mg dose group in the MIN-101C03 and MIN-101C07 studies. In a recently completed study in healthy subjects, doses up to 256 mg of the GR formulation were well-tolerated. Non-clinically significant increase in QTcF were observed from the 160 mg dose onwards. Subjects in this study will receive a single dose of 64 mg, which was found to be well-tolerated in healthy volunteers and in subjects with schizophrenia. All subjects will be closely monitored for adverse events throughout the study. In addition, expert investigators will be chosen to conduct the study. Measures will be taken to ensure that all subjects will be closely supervised for anticipated side effects known to occur in healthy subjects, such as those cited in Section 0. Subjects will be confined to the study center with close ECG monitoring.

Pharmacokinetic Blood Sampling

To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of intravenous indwelling catheters is permitted in this study. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacokinetics of the study drug. This minimizes the number of venipunctures and the total volume of blood collected from each subject during the study. The total amount of blood to be drawn is less than of what is collected during a routine blood donation (500 mL) and, thus, is an acceptable amount of blood to be collected over this time period from the population in this study.

Capacity to Provide Informed Consent

Only subjects who are fully able to understand the risks, benefits, potential adverse events, and alternatives to participation, provide their consent voluntarily, and are not hospitalized involuntarily will be enrolled. Subjects may withdraw their consent at any time without having to give a reason.

Risk Assessment for SAR-CoV2

This study will enroll healthy subjects between the ages of 18-55 years who are not at an increased risk for developing the symptoms of SAR-CoV2 infection. Subjects will be tested for the virus at Screening and prior to the institutionalization. If a subject is positive for the virus at Screening or prior to admission, he/she will not be permitted to enroll in the study.

12.2. Regulatory Ethics Compliance

12.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible.

12.2.2. Institutional Review Board (IRB) / Ethics Committee (EC)

Before the start of the study, the investigator (or sponsor where required) will provide the IRB/EC with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IRB/EC)

- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IRB/EC requests to fulfill its obligation.

This study will be undertaken only after the IRB/EC has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IRB/EC and the documents being approved.

During the study, the investigator (or sponsor, where required) will send the following documents and updates to the IRB/EC for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IRB/EC (at least annually)
- Reports of adverse events that are serious, unexpected, and related with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IRB/EC

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IRB/EC for review and approval before implementation of the change(s).

At the end of the study, the investigator (or sponsor, where required) will notify the IRB/EC about the study completion.

12.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating their confidentiality, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject) is authorizing such access and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

12.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate [redacted] safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

12.2.5. Country Selection

This study is being conducted in the US.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment.

All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IRB and relevant competent authority. Documentation of amendment approval by the investigator and IRB must be provided to the sponsor or its designee.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

13.2. Regulatory Documentation

13.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, as applicable. A study may not be initiated until all local regulatory requirements are met.

13.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator
- A copy of the dated and signed written IRB/EC approval of the protocol, amendments, informed consent form, any recruiting materials, and, if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IRB/EC, including a current list of the IRB/EC members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IRB/EC, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IRB/EC, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

13.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

13.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety [redacted] parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

13.5. Case Report Form Completion

Case report forms are provided in electronic format for each subject who was randomized and received at least one dose of study drug. Screen failures will not be entered.

Data must be entered into CRFs in English. The investigator must verify that all data entries in the CRFs are accurate and correct. All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

13.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for 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.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After the upload of the data into the clinical study database they will be verified for accuracy.

13.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

13.8. Monitoring

On-site monitoring visits will be performed as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRF and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be

provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

13.9. Study Completion/Termination

13.9.1. Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit at that site. The investigational site will be closed upon study completion. The investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

13.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study termination. The investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended closure.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

13.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRF. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.11. Use of Information and Publication

All information, including but not limited to information regarding roluperidone or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of roluperidone, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator, if needed. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

13.12. Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: PROHIBITED CONCOMITANT MEDICATIONS

A list of CYP2D6 substrates can be found at:
https://www.drugbank.ca/categories/DBCAT002623

Please note that the following lists of drugs inducing QT prolongation and CYP2D6 inhibitors are not exhaustive.

Drugs Inducing QT Prolongation

Anesthetic
Sevoflurane
propofol
Anticonvulsivants
Ezogabine (retigabine)
Felbamate
Anti-histamines
Diphenhydramine
Hydroxyzine
Anti-infectives
Amantadine
Artenimol+ piperaquine
Azithromycin
Bedaquiline
Chloroquine
Ciprofloxacin
Clarithromycin
Delamanid
Erythromycin
Fingolimod
Garenoxacin
Gemifloxacin
Halofantrine
hydroxychloroquine
Levofloxacin
norfloxacin
Metronidazole
Moxifloxacin
Ofloxacin
Quinine
Roxithromycin
Telavancin
Telithromycin
Antifungal
Amphotericin B
Fluconazole
Itraconazole
Ketoconazole
Pentamidine
Posaconazole
Voriconazole
Antiviral
atazanavir
Efavirenz
Nelfinavir
Ritonavir
Saquinavir
Telaprevir
Voriconazole

Cardiovascular
Antianginal
Ivabradine
Ranolazine
Antiarrhythmics
Amiodarone
Disopyramide
Dofetilide
Dronedarone
Flecainide
Ibutilide
Pilsicainide
Procainamide
Quinidine
Sotalol
Calcium Channel Blockers
Isradipine
Nicardipine
Diuretics
Bendorflumethiazide
Furosemide
Hydrochlorothiazide
Indapamide
Torasemide
Anti-HTA
ketanserin Moexipril/HCTZ
Cholinesterase inhibitor
Donepezil
Galantamine
Psychotropics
Antidepressants
Amitriptyline
Citalopram/escitalopram
Clomipramine
cyamepromazine
Desipramine
Doxepin
Imipramine
Fluoxetine
Fluvoxamine
Mirtazapine
Nortriptyline
Paroxetine
Sertraline
Trazodone
Trimipramine
Venlafaxine

Antipsychotics
Aripiprazole
Asenapine
Chlorpromazine
Clozapine
Flupentixol
Haloperidol
Iloperidone
levosulpride
Melperone
paliperidone
Pimavanserin
Pipamperone
Pimozide
Promethazine
Prothipendyl
Perphenazine
Quetiapine
Risperidone
Sertindole
Sulpiride
sultopride
Thioridazine
ziprasidone
Zotepine
Antimanic
Lithium
Sedative, hypnotics
Choral hydrate
Dexmedetomidine
Antiemetics
Domperidone
Droperidol
Ondansetron
Granisetron/ Dolasetron,
Tropisetron
Metoclopramide
Others
Phospho-diesterase 3 inhibitor:
Anagrelide
cilostazol

Protein kinase inhibitors: Lapatinib, Sunitinib, Bosutinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Lenvatinib, Nilotinib, Osimertinib, Pazopanib, Ribociclib, Sorafenib
Apomorphine
Alfuzosin
Atomoxetine
Capecitabine
Cocaine
Degarelix
Esomeprazole
Eribulin
Famotidine
Hydrocodone
Ibogaine
Lanzoprazole
Leuprolide
Levomethadyl
Loperamide
Methadone
Mifepristone
Mirabegron
Necitumumab
Nusinersen
Omeprazole
Oxytocin
Pantoprazole
Panobinostat
Papaverine
Pasireotide
Romidepsin
Solifenacin
Tacrolimus
Tamoxifen
Terlipressin
Terolidine
Tetrabenazine
Tiapride
Tizanidine
Tolterodine
Toremifene
Vandetanib
Vardenafil
Vemurafenib
Vorinostat

Underlined: known risk of TdP;
Highlighted grey: possible risk of TdP;
Otherwise: conditional risk of TdP: eg, in case of overdose, DDI or electrolytes imbalance.

CYP2D6 Inhibitors	
Anti-infectives	**Others**
Chloroquine	Bupropion
Quinacrine	Celecoxib
	Cinacalcet
Cardiovascular	Chlorpheniramine
Amiodarone	Cimetidine
Aprindine	Clemastine
Mibefradil	cocaine
Propafenone	Codeine
Labetalol	Delavirdine
Quinidine	Dextropropoxyphene
	Diltiazem
Antidepressants	Diphenhydramine
Amitriptyline	Doxorubicin
Citalopram	Entacapone (high doses)
Clomipramine	Halofantrine
Doxepin	Hydroxyzine
Duloxetine	Indinavir
Escitalopram	Imatinib
Fluoxetine	Lobelin
Fluvoxamine	Lomustine
Paroxetine	Methadone
Sertraline	Moclobemide
	Metoclopramide
Antipsychotics	Midodrine
Chlorpromazine	Moclobemide
Fluphenazine	Nortuloxeline
Haloperidol	Ranitidine
Levomepromazine	Ritonavir
Perphenazine	Ticlopidine
Promethazine	Tripelennamine
Risperidone (weak)	Vinblastine
Sertindole	Vincristine
Thioridazine	Vinorelbine
	Yohimbine

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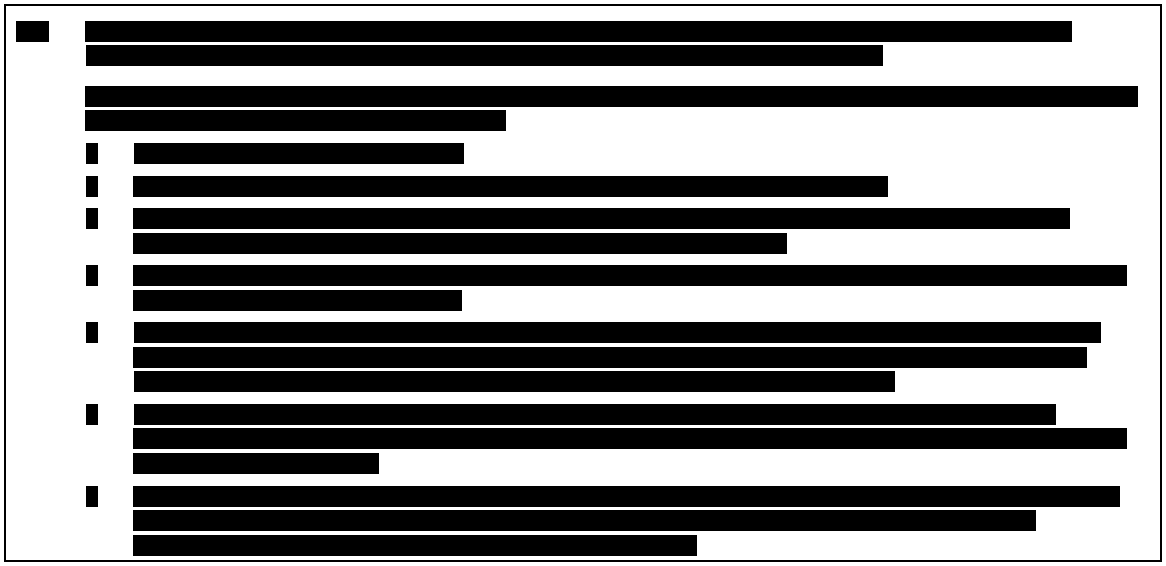

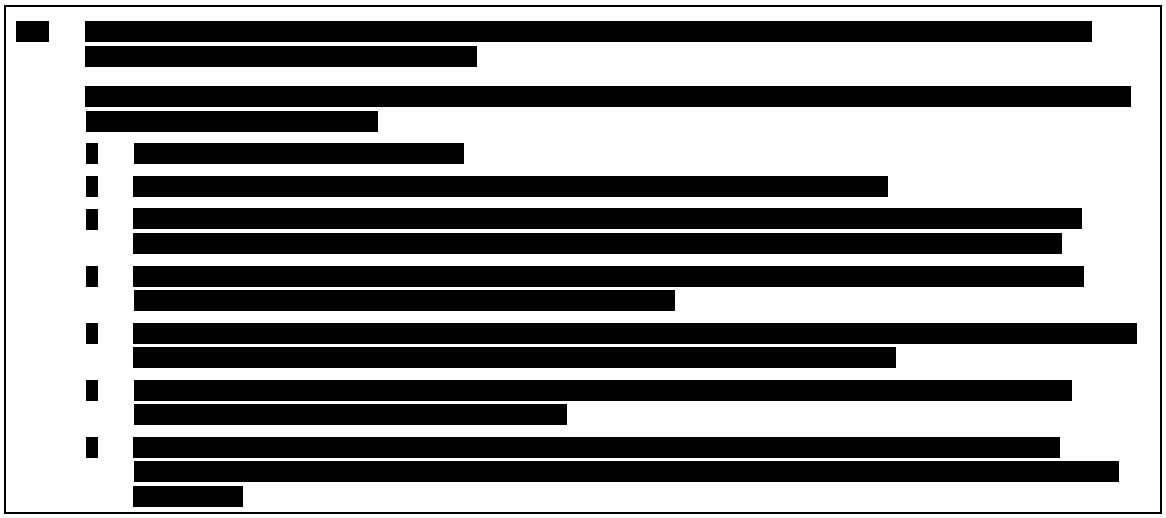

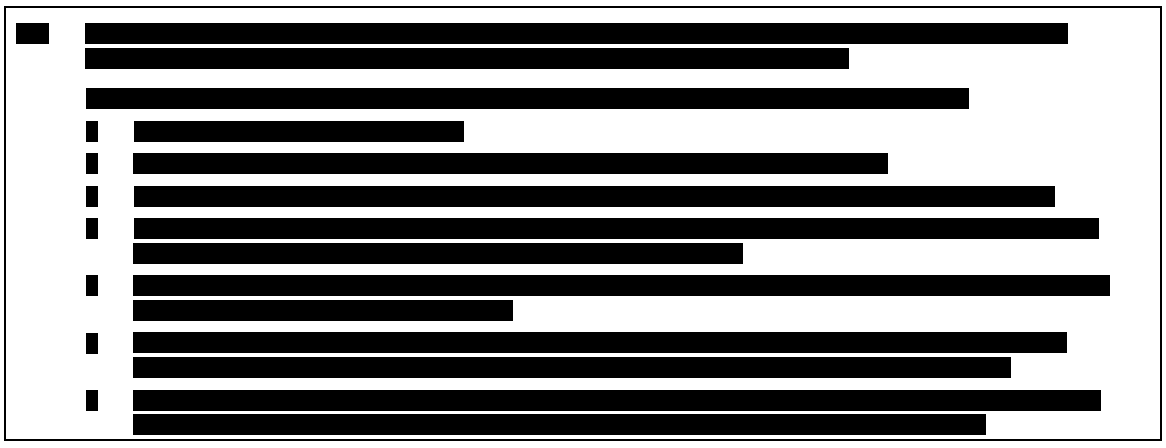

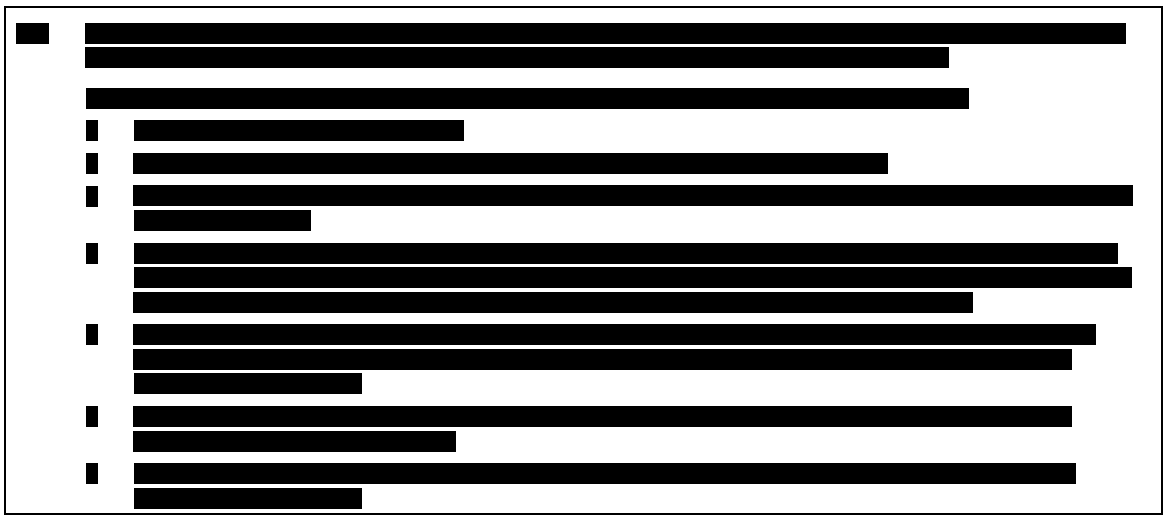

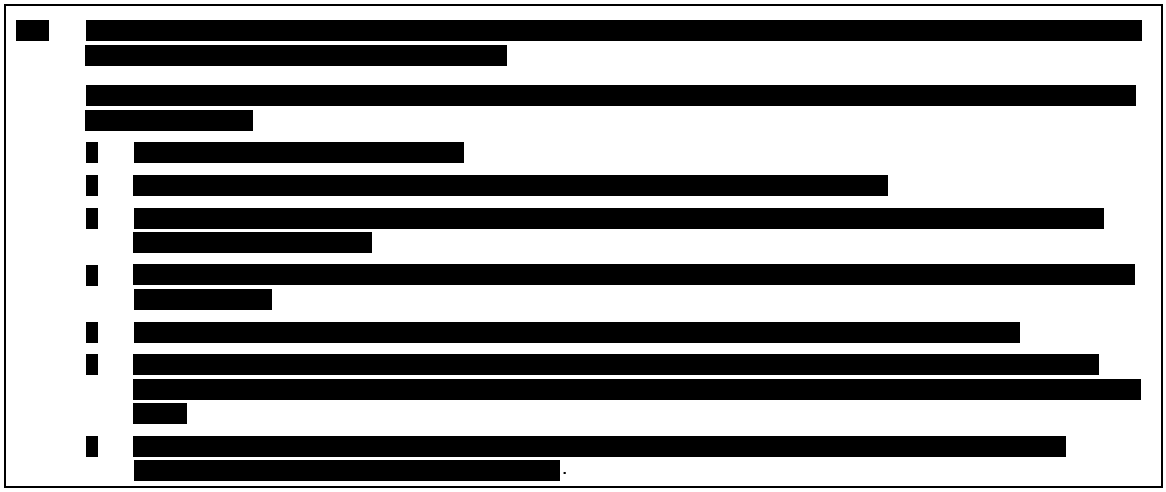

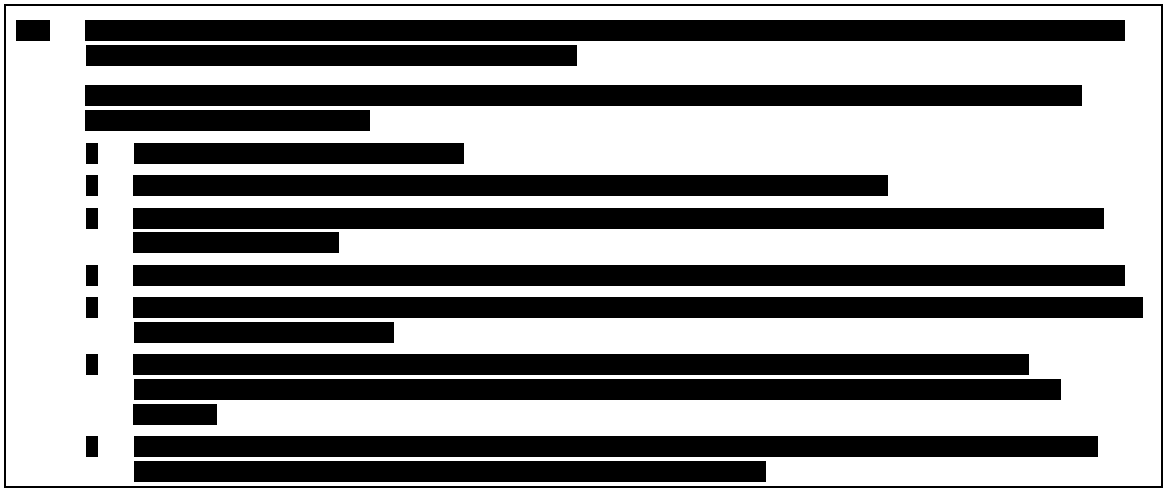

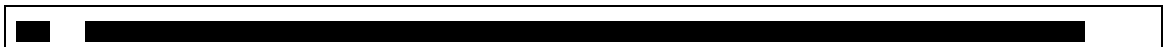

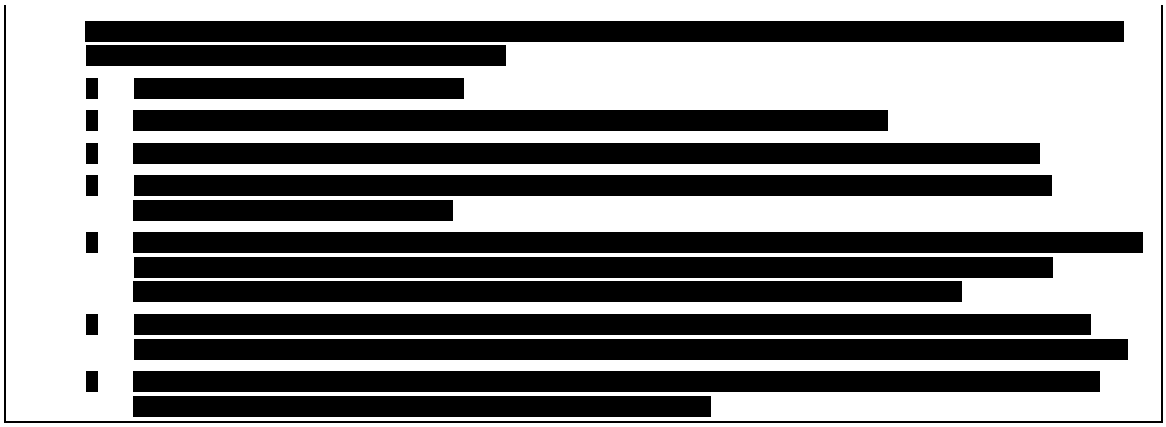

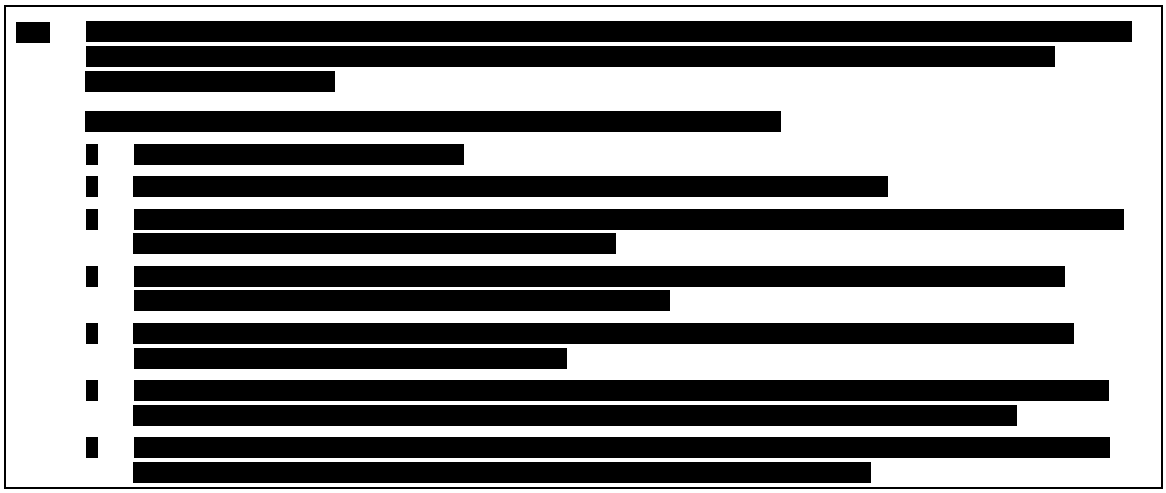

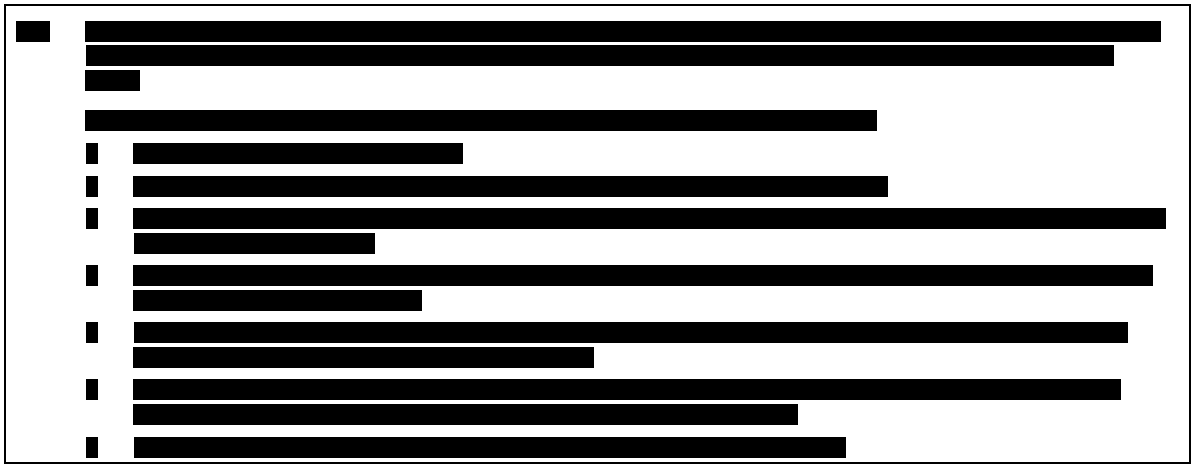

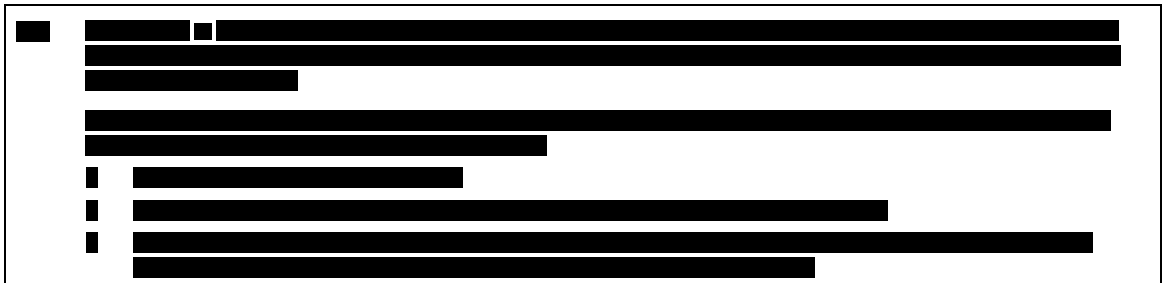

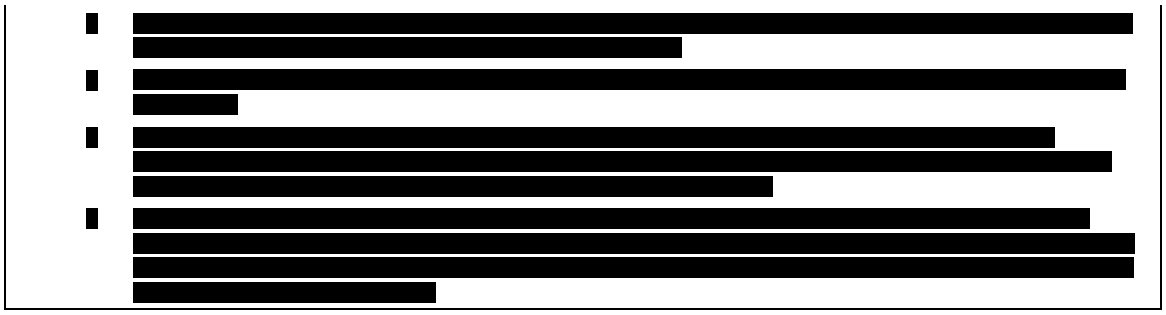

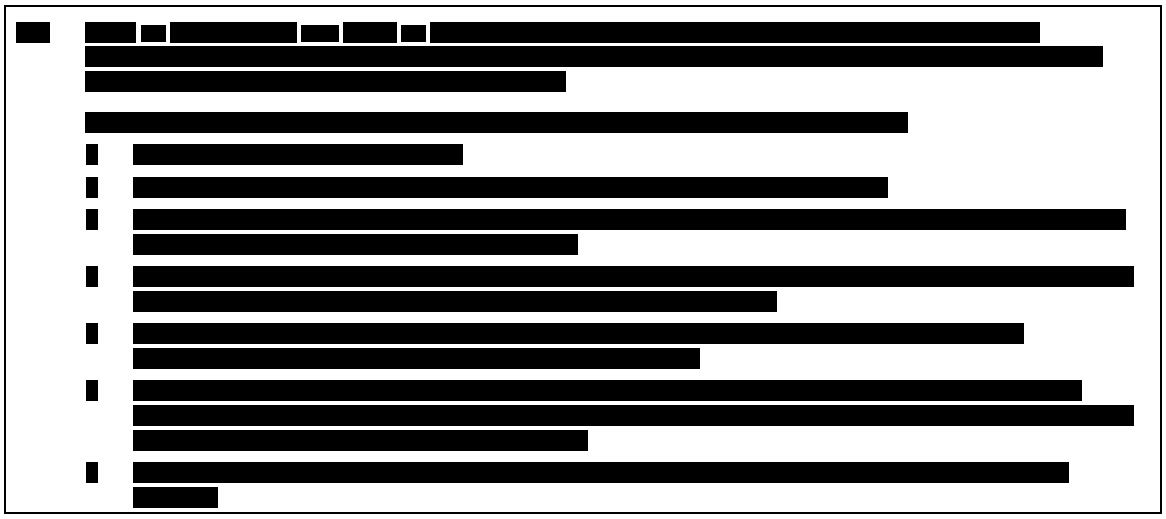

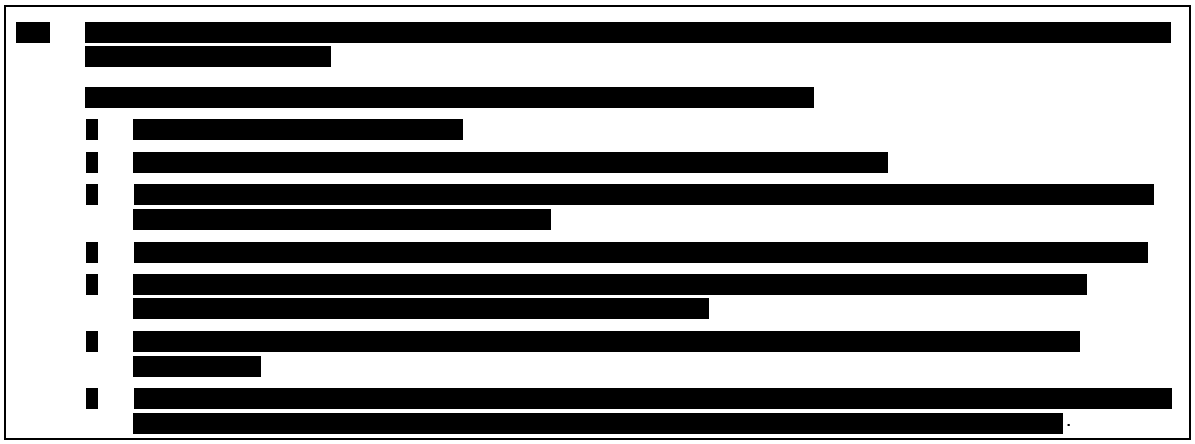

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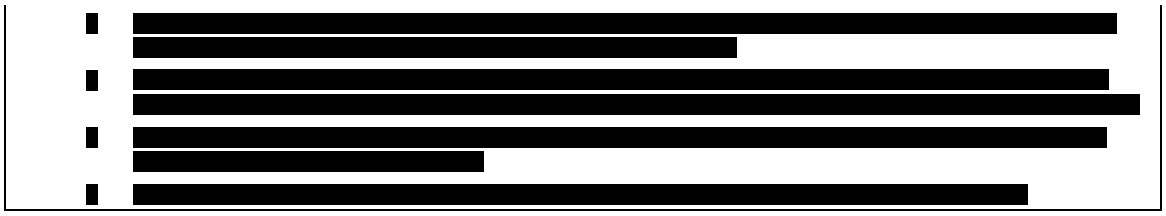

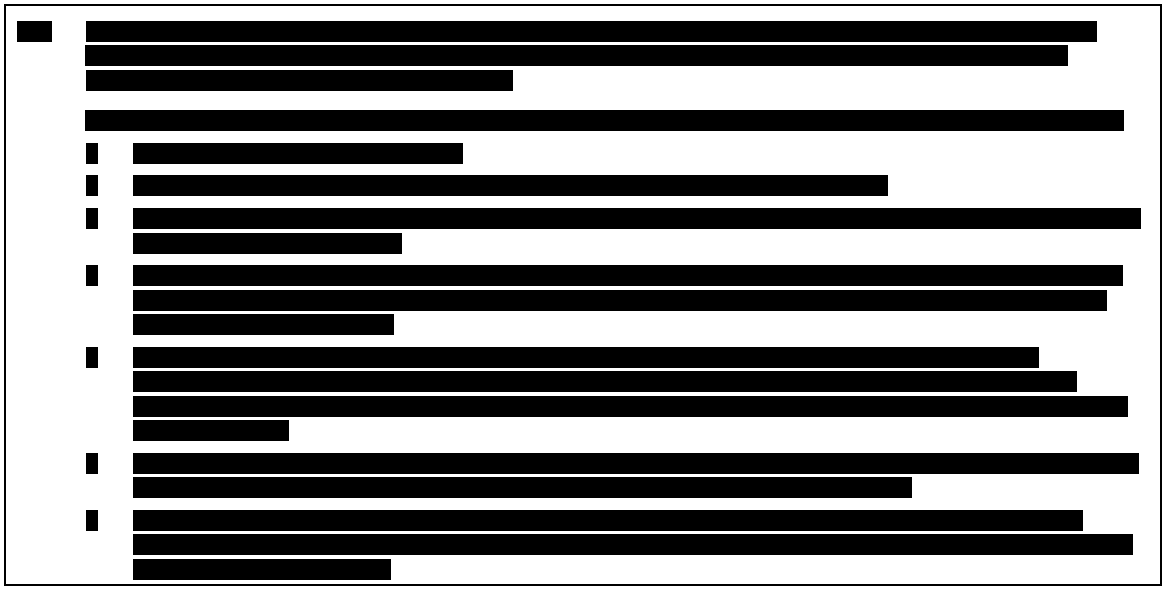

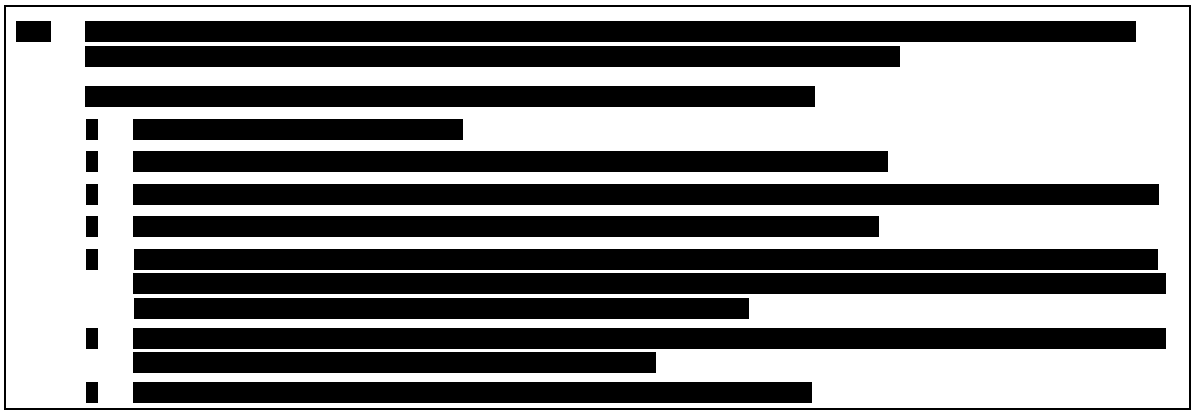

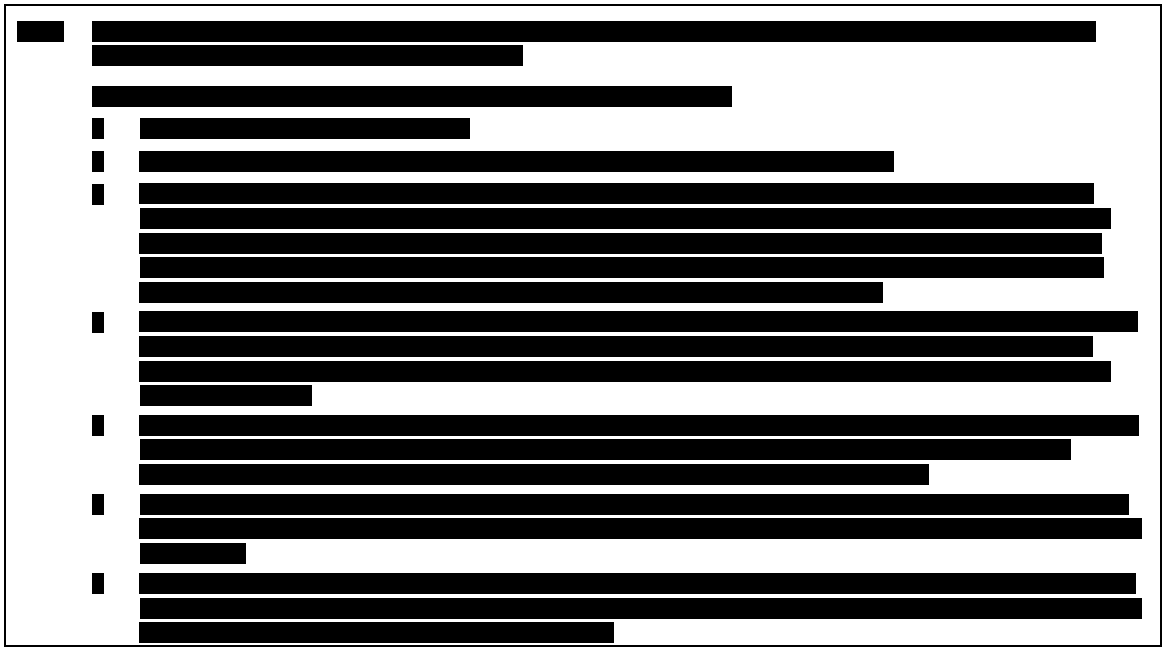

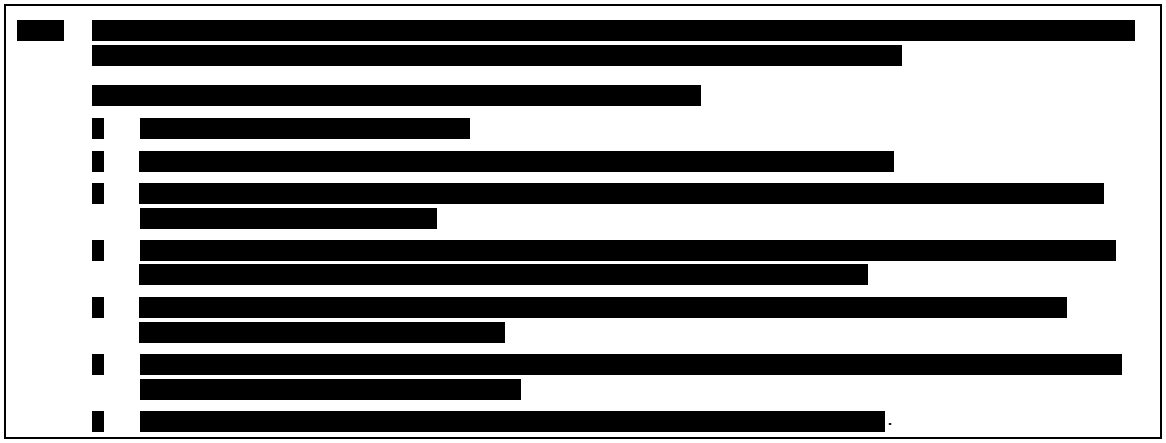

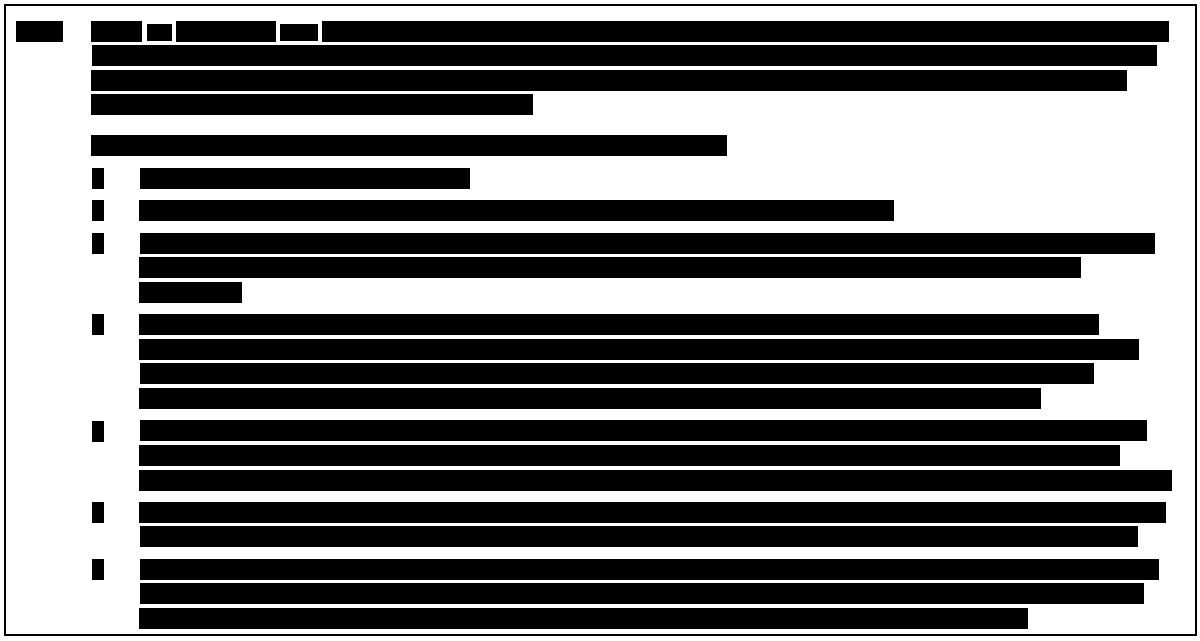

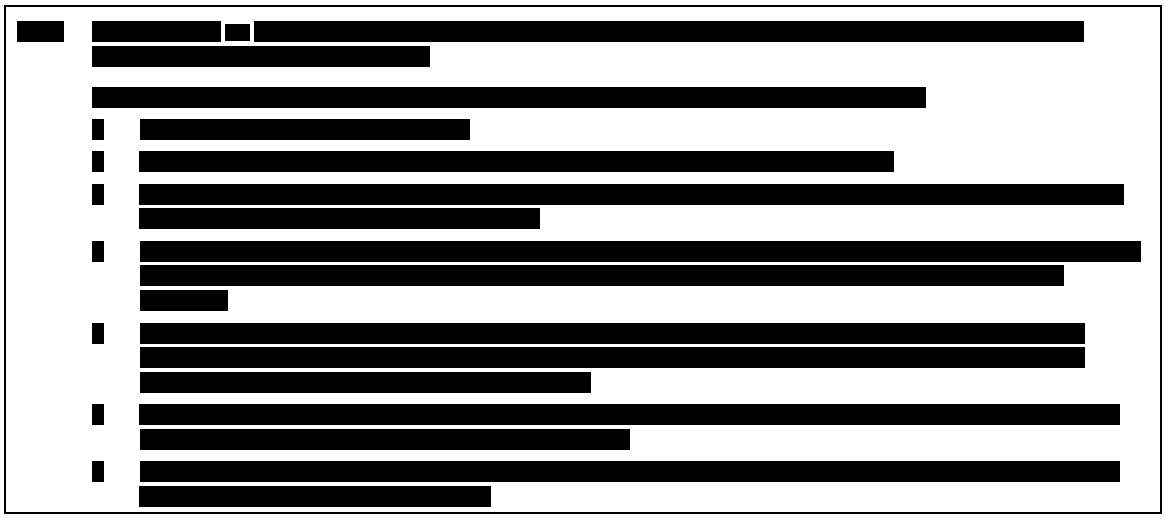

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ATTACHMENT ■ CLINICAL GLOBAL IMPRESSION – SEVERITY RATING (CGI-S)

Severity of illness

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

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

ATTACHMENT 5: ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service

Alcohol, Drug Abuse, and Mental Health Administration

National Institute of Mental Health

NAME: _____

DATE: _____

Prescribing Practitioner: _____

CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.)
before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies		RATER Date	RATER Date	RATER Date
Facial and Oral Movements	1. **Muscles of Facial Expression** e.g., movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. **Jaw** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	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	0 1 2 3 4	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	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures?**	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes
	13. Edentia?	No Yes	No Yes	No Yes
	14. Do movements disappear in sleep?	No Yes	No Yes	No Yes

Final: 9/2000

ATTACHMENT 6: BARNES AKATHISIA RATING SCALE (BARS)

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 of 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.

Scoring the Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

ATTACHMENT 7: COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

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	____	____

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* _____

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: _____

Signature: _____ Date: _____
(Day Month Year)

Note If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.