CLINICAL RESEARCH PROTOCOL

DRUG:	Risperidone
STUDY NUMBER:	LYN-005-C-004
PROTOCOL TITLE:	A Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder
IND NUMBER:	143074
SPONSOR:	Lyndra® Therapeutics Inc, (US); hereafter referred to as Lyndra
ORIGINAL PROTOCOL DATE:	10 July 2020
AMENDMENT NUMBER:	1.0 (Protocol Version 2.0)
AMENDMENT DATE:	27 August 2020

Document History and Summary of Changes

Document	Date
Amendment 1	Current version
Original Protocol	10 July 2020

Section	Description of Change
5.2 (Exclusion Criteria)	Added exclusion criterion for significant history of diarrhea or constipation within 3 months of Screening to reduce the possibility of unrelated diarrhea or constipation confounding assessments of treatment-emergent adverse events.
5.2 (Exclusion Criteria)	Changed HBA1c exclusion criterion from ≥7.0% at Screening to ≥6.5% so that it is consistent with the level for diagnosis of diabetes.
5.2 (Exclusion Criteria)	Added systolic blood pressure <100 mm Hg or diastolic blood pressure <60 mmHg as exclusion criterion because orthostatic hypertension is a known risk of risperidone.
5.2 (Exclusion Criteria)	Modified the exclusion criterion for positive fecal occult blood test to exclude all subjects who have a positive fecal occult blood test at Screening.
6.5 (Prior and Concomitant Medications and Therapies)	Prohibited the use of nonsteroidal anti-inflammatory medications from Day -8 to the End of Study visit because chronic use of these medications may be associated with gastritis.
7.1 (Pausing and Stopping Guidelines)	Added the following as one of the criteria for pausing dosing of study subjects: "[redacted]
8.1.6.4 (Assessment of Suicidal Ideation and Behavior – Columbia Suicide Severity Rating Scale)	In the list of requirements for when subjects must be evaluated by a mental health professional, modified the second criterion to be response of "YES" to any behavioral question of the C-SSRS. Also added that subjects who meet the listed criteria must have additional assessments.
8.1.7 (Fecal Samples for Occult Blood) and 18.1 (Schedules of Events)	Added fecal occult blood testing on Days 1, 7, 14, and 21, and the End of Study visit.

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1 PROTOCOL SUMMARY

1.1 Study Synopsis

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
Title:	A Randomized, Placebo-controlled, Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder
Phase:	Phase 2
Rationale:	Lyndra is developing an oral, extended release (ER) formulation of risperidone (LYN-005) presented in a capsule dosage form with the intent of reducing the frequency of dosing orally-administered medications to once weekly or less and thereby improving the management of schizophrenia. Current treatment options for schizophrenia consist of acute symptom management for psychosis as well as efforts to prevent relapse and improve access to supportive treatments. Antipsychotic drug therapy is effective in most subjects in managing and stabilizing schizophrenia symptoms. Despite the benefits from treatment, approximately 75% of diagnosed subjects will experience a relapse, generally within two years, and the majority of subjects will experience multiple relapses over the course of the illness [1]. A major known risk factor leading to relapse is non-adherence with antipsychotic drug therapy [1]. In addition to improving adherence, an extended release oral risperidone may offer more consistent plasma levels of the pharmacologically active forms of risperidone, reducing both inter-subject and intra-subject variability. The target population for the Lyndra formulation (LYN-005) is subjects with schizophrenia who require maintenance treatment with risperidone and who have demonstrated tolerability of immediate release (IR) risperidone. An oral once weekly form of risperidone would offer a treatment opportunity facilitating greater clinician and subject contact and which could be integrated into a variety of community psychiatric treatment models, without need for specialized administration spaces or training. Once weekly dosing is anticipated to be highly convenient for both subjects and caregivers and provides certainty of dosing with only weekly supervision. Further, an oral extended release formulation, if demonstrated to be effective at achieving therapeutic systemic drug levels, could offer an opportunity to initiate a long-acting treatment earlier in the disease course, potentially prior to discharge from hospitalization. Study LYN-005-C-004 will evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple dose administration of the ER formulation at two dose levels of LYN-005 relative to IR risperidone.

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
OBJECTIVES	
Primary Objectives:	• To determine the safety and tolerability of risperidone extended release capsules (LYN-005) administered as repeat weekly doses compared to IR risperidone tablets at 2 dose levels; • To characterize the PK of risperidone, active metabolite 9-hydroxyrisperidone and active moiety (risperidone and 9-hydroxyrisperidone combined) after repeat weekly doses of LYN-005 ER capsules relative to IR risperidone tablets at 2 dose levels.
Secondary Objectives:	• To assess the exposure to risperidone, 9-hydroxyrisperidone and active moiety during the switch from IR risperidone to LYN-005.
Exploratory Objectives:	• To model the PK of risperidone, 9-hydroxyrisperidone and active moiety when administered as a LYN-005 extended-release capsule.
ENDPOINTS	
Primary Endpoints:	• Incidence of treatment emergent adverse events (TEAEs). • Risperidone, 9-hydroxyrisperidone, and active moiety PK after oral administration of LYN-005 capsules and IR risperidone to include, as possible and appropriate, C_{max}, C_{min}, T_{max}, Kel, $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-168)}$ and $AUC_{(0-\infty)}$.
Secondary Endpoints:	• Exposure to risperidone, 9-hydroxyrisperidone and active moiety as assessed from C_{max}, T_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ after switching from IR risperidone to LYN-005.
Exploratory Endpoints:	• PK modelling of risperidone, 9-hydroxyrisperidone, and active moiety exposure.
METHODOLOGY	
Study Duration:	Up to 55 days
Study Design:	LYN-005-C-004 is a blinded, multiple-dose, randomized, parallel group, safety, tolerability and PK study of LYN-005 in subjects with a primary diagnosis of schizophrenia or schizoaffective disorder in general good health. Eligible subjects must be clinically stable and receiving a therapeutic dose of an approved oral antipsychotic drug for a minimum of 6 weeks at the time of Screening. Enrolled subjects will be evaluated under steady-state conditions on commercially-available IR risperidone tablets and then assigned in blinded fashion either to LYN-005 weekly or continued encapsulated IR risperidone daily for 3 weeks to attain (or continue) steady-state exposure.

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	A total of 32 subjects will participate in this study. Subjects will be randomized to LYN-005 plus IR risperidone matched placebo OR LYN-005 matched placebo or IR risperidone as follows: • Arm 1: LYN-005 (14 or 28 mg weekly) plus IR risperidone matched placebo (N=24). • Arm 2: LYN-005 matched placebo plus IR risperidone (2 or 4 mg/day) (N=8). Per above, in order to maintain the blind, all subjects will either receive LYN-005 and IR risperidone-matched placebo or LYN-005 matched placebo and IR risperidone, as follows: Arm 1: • LYN-005: Size 00EL capsules containing LYN-005 stellate; the 14mg dose of LYN-005 contains 3 active arms containing risperidone, and 3 inactive arms and the 28 mg dose of LYN-005 contains 6 active arms containing risperidone. AND • IR Risperidone Matched Placebo: Orange capsule-shaped tablets containing inactive ingredient. Arm 2: • LYN-005 Matched Placebo: Size 00EL capsules containing inactive ingredient with no stellate. AND • IR Risperidone: Risperidone 2 mg (orange) capsule-shaped tablets. Although treatment assignment is blinded; the dose level is not blinded. The dose of LYN-005 (14 or 28 mg)/IR risperidone (2 or 4 mg/day) administered will be based on the subject's current antipsychotic medication dose. Randomization will be stratified by risperidone dose (LYN-005 14 mg/IR risperidone 2 mg/day [low dose] and LYN-005 28 mg/IR risperidone 4 mg/day [high dose], with a maximum of 16 subjects enrolled in each strata. Within each strata, subjects will be randomized on a 3:1 basis to either LYN-005 or risperidone, respectively. All administrations of LYN-005/matched placebo will be supervised. Complete PK evaluations will be performed after each LYN-005 dose, as designated in the Schedules of Events (Section 18.1.1 and Section 18.1.2) and over 24 hours at steady-state for IR risperidone at the beginning of the study.

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	LYN-005 will be evaluated in subjects who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of schizophrenia or schizoaffective disorder of at least 2 years, who have already been stabilized on an oral antipsychotic medication for a minimum of 6 weeks at the time of Screening with no psychiatric hospitalizations for relapse in the past 6 months. Subjects who are prescribed an antipsychotic agent other than risperidone or a dose of risperidone outside the range are also eligible for study participation if they are a) able to tolerate risperidone and b) be completed switched to 2 or 4 mg daily oral risperidone for a minimum of 2 weeks prior to the first dose of LYN-005/placebo on Day 1 (see Section 6.3.1). Eligible subjects must be clinically stable (i.e., mildly or moderately ill psychiatrically), with a low risk of relapse and otherwise healthy without history of significant gastrointestinal (GI) diseases. Guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. In the event of worsening of schizophrenia symptoms while receiving risperidone during the study, another medication can be administered at the discretion of the Principal Investigator (PI), with notification of the Study Medical Monitor. Risperidone is primarily metabolized by cytochrome P450 (CYP) 2D6 and genetic testing for CYP2D6 will be conducted at Screening to determine metabolizer status. To reduce the inter-subject variability in exposure, subjects identified as poor metabolizers (PMs) will be excluded from the study.
Study Conduct	Subjects will be screened for study eligibility between Days -21 and -14. Subjects who are initially determined to be eligible, based on Screening assessments, will then participate in a 10-day IR risperidone run-in period, during which adherence with study treatment will be assessed. Subjects who remain eligible for the study will enter the inpatient unit on Day -2. After admittance to the inpatient unit and prior to the first LYN-005/matched placebo administration, samples for determination of IR risperidone PK will be collected from Days -2 to -1. Over the course of the study, subjects are to receive 3 doses of LYN-005/matched placebo, per their random assignment, 1 each on Days 1, 8, and 15, all on an inpatient basis. All subjects will also receive IR risperidone or matched placebo, again per their random assignment, from Days 1 to 21. Overall, during study participation, subjects will be housed in the inpatient unit twice, from Days -2 to 9 (Inpatient Stay 1) and then again from Days 14 to 16 (Inpatient Stay 2). Subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled. In between each inpatient stay, subjects will have study assessments performed on an outpatient basis daily from Days 10, 11, 12, and 13. After discharge from Inpatient Stay 2, subjects will again have assessments performed on an outpatient basis on Days 17, 18, 21, 22, and 23. An End of Study (EOS) visit will be conducted on Day 35. During study participation, guidelines will be in place for the use of recommended medications for agitation, anxiety, and insomnia. Rescue administration of an agent other than risperidone or paliperidone in the event of worsening of schizophrenia symptoms during the study can be administered at the discretion of the PI, with notification of the Study Medical Monitor. Extrapyramidal symptoms will be monitored throughout the study at regular intervals using the Extrapyramidal Symptom Rating Scale (ESRS). Severity of schizophrenia

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	symptoms will be monitored throughout the study at regular intervals using the CGI-S scale. Concomitant medications, adverse events (AEs), safety laboratory tests, and vital signs will be assessed throughout the study, as per the Schedule of Events (Section 18.1.1 and Section 18.1.2).
Schedule of Events	The Schedules of Events are presented in Section 18.1.1 and Section 18.1.2.
SUBJECT POPULATION	
Number of Subjects:	Approximately 32 subjects of whom 24 will receive LYN-005 will be enrolled in the study. Subjects who discontinue prematurely may be replaced at the Sponsor's discretion.
Target Population:	Male and female subjects between the ages of 18 to 50 years of age, inclusive, with schizophrenia or schizoaffective disorder, as defined by DSM-5 criteria.
Entry Criteria	***Inclusion criteria:*** Eligibility for this study is met if each one of the following inclusion criteria is satisfied at Screening (or at baseline when specified): 1. Male or female aged ≥18 and ≤50 years. 2. Current diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria as confirmed by the MINI 7.0.2. 3. The following psychiatric criteria are to be used to determine subject eligibility: a. Duration of diagnosis of schizophrenia or schizoaffective disorder of ≥2 years. b. Outpatient; not hospitalized for worsening of schizophrenia within the last 6 months (partial hospitalization for social management within this time period is acceptable). c. Medically stable over the last month and psychiatrically stable without significant symptom exacerbation over the last 3 months. 4. Stabilized on an oral antipsychotic medication (single agent) for a minimum of 6 weeks at the time of Screening. 5. On a stable dosage of all permitted non-antipsychotic medications (except for medication to be used on an as-needed basis) for at least 1 month prior to the Screening visit and for the duration of the study. 6. CGI-S score of ≤4 (moderately ill). 7. PANSS score of ≤80 points. 8. Body mass index (BMI) of ≥18 kg/m^2 and ≤35 kg/m^2. 9. Able to read and understand study procedures and provide written informed consent before the initiation of any protocol-specific procedures. 10. Willing to comply with all protocol-specified procedures and availability for the duration of the study.

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	11. Subject has identified a caregiver or personal contact with whom the subject communicates with at least once a week. ***Exclusion Criteria:*** Subject will not be considered eligible to participate in this study if any one of the following exclusion criteria is satisfied at Screening (or at baseline when specified): 1. Subjects with known clinically significant esophageal or GI disease, including but not limited to: a. Known strictures such as esophageal web, pyloric stenosis, or small intestinal stricture, or subjects with high risk of stricture, e.g., Crohn's disease. b. Diagnosis of a condition known to elevate or lower gastric pH, e.g., achlorhydria or hypochlorhydria. c. Prior varices or small or large bowel obstructions. d. Prior abdominal or upper gastrointestinal surgery (prior uncomplicated laparoscopic procedures including appendectomy or colectomy). e. History of dysphagia or aspiration in the last 5 years. f. History of an esophageal motility disorder or undergoing treatment for a gastric motility disorder. g. Significant history of diarrhea or constipation within 3 months of Screening. h. Multiple episodes of abdominal pain within 3 months of Screening. i. Subjects who experience moderate or severe dysmenorrhea or menorrhagia (with use of pain medication) within 3 months of Screening. j. History of moderate to severe Acid Reflux Disease or a score of ≥2 on the Acid Reflux Severity Scale (ARSS) [2], indicating moderate to severe symptoms. The ARSS scale is as follows: None = 0 no symptoms Mild = 1 awareness of symptom, but easily tolerated Moderate = 2 discomfort sufficient to cause interference with normal activities Severe = 3 incapacitating, with inability to perform normal activities. 2. Subjects with PILL-5 questionnaire score of 5 or greater.

	3. Medical history or current diagnoses indicating the presence of any of the below conditions: a. Presence of an uncontrolled, unstable, clinically significant medical condition could that could put the subject at risk because of participation in the study, interfere with the subject's ability to participate in the study or influence the interpretation of safety or PK evaluations. b. History of a major cardiovascular event (myocardial infarction, cardiac surgery or revascularization, unstable angina, stroke, or transient ischemic attack) or a hospitalization for heart failure with 6 months of Screening. c. Any clinically significant illness, medical or surgical procedure or trauma within 4 weeks of Screening. d. Known immunocompromised status, including individuals who have undergone organ transplantation, on immunosuppression for an immune mediated disease, or are positive for human immunodeficiency virus (HIV). e. Subjects with a positive test for active hepatitis B or C at Screening. Subjects with successfully treated hepatitis B infection which has been resolved for greater than 1 year or successfully treated hepatitis C infection will not be excluded. f. Subjects who have donated more than 250 mL of blood within 30 days of Screening. g. Subjects who have difficulties with venipuncture/cannulation, including difficulty accessing veins for blood sampling and/or history of coagulopathy or endocarditis. h. Subjects with a current DSM-5 diagnosis of major depressive episode, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder on the MINI 7.0.2 or in the judgment of the Investigator. (Note that individuals with depression secondary to schizoaffective disorder are eligible). i. Suicidal ideation associated with actual intent and a method or plan in the past 6 months, as measured by the C-SSRS (i.e., "Yes" answers on items 4 or 5) at Screening or having made a suicide attempt within the last 2 years. j. Known or suspected (non-febrile) seizure disorder. k. History of neuroleptic malignant syndrome. l. Current or history of clinically significant tardive dyskinesia.

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	m. Known or suspected diagnosis of intellectual disability or organic brain disorder or other diagnosis that is primarily responsible for current symptoms and functional impairment. n. Medically non-adherent in the management of their schizophrenia/schizoaffective disorder. 4. Use of the below medications/treatments in the 2 weeks before enrollment, including: a. Proton pump inhibitors or H2 blockers. b. Prokinetic agents. c. Medications that may interfere with the absorption, metabolism, or excretion of risperidone, e.g.: i. Drugs metabolized via CYP3A4 pathway, such as macrolide antibiotics and azole antifungals). ii. Moderate or strong CYP3A4 p-glycoprotein (P-gp) enzyme inducers and inhibitors (carbamazepine, phenytoin, rifampicin, phenobarbital, itraconazole, verapamil). iii. Moderate or strong CYP2D6 inhibitors (e.g., fluoxetine, fluoxetine combinations, paroxetine), or quinidine. d. Concomitant medications, natural remedies, supplements or vitamins which are associated with changes to gastric motility or pH. Use of antacids is permissible, except within 2 hours of dosing with LYN-005. e. Benzodiazepines; except lorazepam, diazepam and oxazepam, which are acceptable if for the treatment of depression, anxiety or insomnia. f. Use of more than one antidepressant; or if on just one, a change in dose within 6 weeks of Screening. g. Depot antipsychotic use within 9 months of Screening. h. Electroconvulsive therapy within 3 months of Screening. 5. Subjects with clinically significant abnormal safety (e.g. physical examination, vital sign) or safety laboratory assessments, specifically: a. Presence of a clinically significant abnormal laboratory result on blood or urine safety tests at Screening. b. Anemia (hemoglobin below lower limit of normal reference range) at Screening.

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	c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN), or total bilirubin ≥1.5 × ULN. d. Moderate or severe renal insufficiency at Screening (glomerular filtration rate <60 mL/min, as determined using the Cockcroft-Gault formula). e. Heart rate of <50 beats per minute (bpm) at Screening. f. Systolic blood pressure <100 or ≥150 mmHg and/or diastolic blood pressure <60 mmg Hg or ≥100 mmHg at Screening. g. HbA1c ≥6.5% at Screening. h. Positive fecal occult blood test at Screening. i. Clinically significant prolactin elevation (≥200 ng/mL for females; ≥100 ng/mL for males). 6. Subjects with the below specified patterns of substance use at Screening: a. Fulfillment of the DSM-5 criteria for moderate or severe substance use disorder (excluding nicotine and caffeine) within 6 months of Screening. b. History of alcohol consumption exceeding moderate use; in males exceeding 21 units per week and in females exceeding 14 units per week (1 unit = 360 ml beer, 25 mL of 40% spirit or a 125 mL glass of wine) over the past month. Subjects are not permitted to consume alcohol during the inpatient stay nor 12 hours before any clinic visit while outpatient. c. Positive ethanol breathalyzer. d. Positive urine drug screen for substances of abuse other than cannabis. e. Heavy nicotine use (consumption of >40 cigarettes or >36 mg of nicotine from other sources [e.g., vaping products] daily) or daily use of smokeless tobacco. 7. Subjects of reproductive potential who are (hetero) sexually active but unwilling to use acceptable means of contraception through the EOS. For clarity, subjects who are at least 1 year post-menopausal are not of reproductive potential. Acceptable means of contraception include: a. Subjects who have been surgically sterilized. b. Females of reproductive potential: diaphragm, injectable, oral/patch contraceptives for a minimum of 6 weeks, contraceptive sponge, implant, or intrauterine device in use prior to enrollment.

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	c. Males: condom in combination with any of the above means of contraception. d. All subjects: abstinence may be an acceptable means of contraception as long as the individual consents to initiate immediate use of double barrier protection for the duration of the study should (hetero) sexual intercourse occur. 8. Subjects who are nursing or who have positive or indeterminate pregnancy tests at either Screening (serum test) or enrollment (urine test). 9. Use of any experimental agent within 1 month or 5 half-lives of Screening, whichever is longer. 10. Subjects who are employees or immediate family members of employees of the site, Sponsor or study-related vendors. 11. History of a serious allergic or hypersensitivity reaction to risperidone or LYN-005 excipients (refer to Investigator's Brochure). 12. Subjects with history of X-ray, computed tomography (CT) scan or angiogram of the abdomen within one year of Screening. 13. Subjects with CYP2D6 poor or underdetermined metabolizer status based on genetic testing.
STATISTICAL METHODS AND ANALYSIS	
Sample Size	The sample size of 32 (24 assigned to LYN-005 and 8 assigned to IR risperidone) is driven by clinical rather than statistical considerations for providing data in the evaluation of the endpoints.
Pharmacokinetics and Pharmacodynamics	Plasma concentration data for risperidone and 9-hydroxyrisperidone separately and combined as active moiety will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration-time data obtained will be performed using appropriate non-compartmental analysis to obtain estimates of the standard PK parameters. The pharmacokinetics of LYN-005 relative to IR at 2 dose levels will be determined. There are no pharmacodynamic endpoints in this study.
Safety	Safety data will be summarized by dose group, study period and overall.
Planned Analyses	There is a planned safety review by the Investigator and Medical Monitor on interim blinded PK through Day 14 from 12 subjects. Blinded safety data will also be reviewed at this time and will include adverse events, laboratory data,

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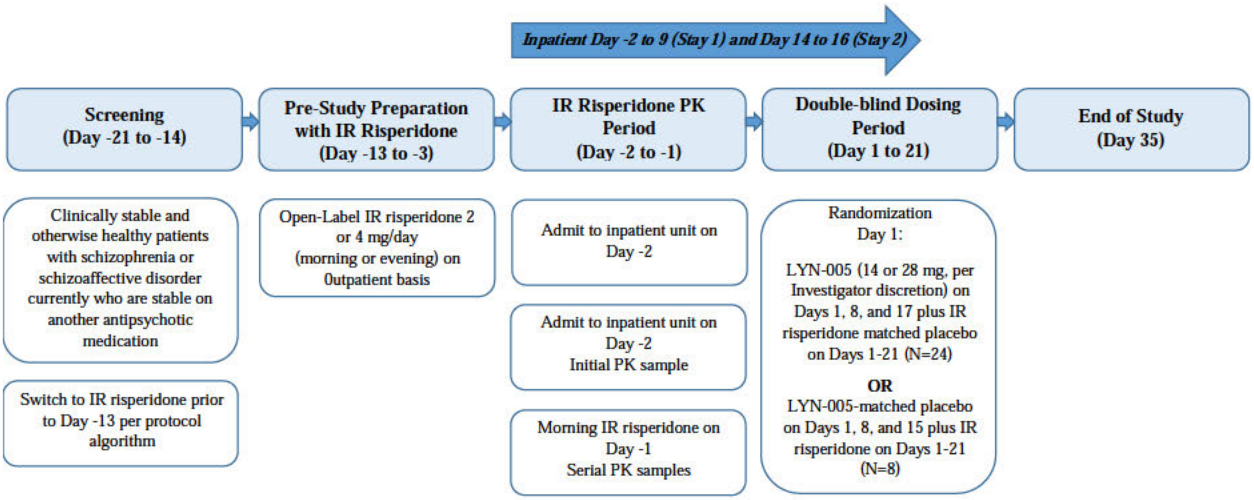
	suicidality, and illness severity. Additionally, the PI or Sponsor may request an ad hoc review of safety information, e.g., serious adverse events, at any time during the study.

1.2 Study Schematic



1.3 List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
APD	Antipsychotic drug
AST	Aspartate aminotransferase
AUC_{0-168}	Area under the concentration versus time curve, time zero to 168 hours
AUC_{0-24}	Area under the concentration versus time curve, time zero to 24 hours
$AUC_{0-\infty}$	Area under the concentration versus time curve: time zero to infinity
AUC_{0-t}	Area under the concentration versus time curve: time zero to t (time point to be specified)
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximal observed concentration
C_{min}	Minimum observed concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DIMD	Drug-induced movement disorders
DIP	Drug-induced parkinsonism
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive therapy
EDC	Electronic Data Capture
EL	Extra Long
EOS	End of Study
EPS	Extrapyramidal symptoms
ER	Extended release
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
h	hour or hours
HbA1C	Glycated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
ICF	Informed consent form

Abbreviation	Term
ICH	International Council for Harmonization
ID	Identifier
IR	Immediate release
IRB	Institutional Review Board
Kel	First order elimination rate constant
LYN-005	Lyndra Extended Release Capsule containing risperidone
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional
MINI	Mini International Neuropsychiatric Interview version 7.0.2
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PK	Pharmacokinetic (adj.) *or* pharmacokinetics (singular noun)
QTcF	Corrected QT interval, Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOE	Schedule of Events
SUSAR	Serious unexpected suspected adverse reaction
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

2 INTRODUCTION AND RATIONALE

2.1 Impact of Schizophrenia and Schizoaffective Disorder

Schizophrenia and schizoaffective disorder are chronic and debilitating psychiatric illnesses which have a massive global burden. There are millions of adults in the United States alone living with schizophrenia. The estimated prevalence rate of schizophrenia is around 0.5% in the United States (US) [3] and globally rates can be even higher, to above 1% [4]. In 2013, the total societal costs of schizophrenia were estimated at $155 billion in the US, with emergency room care alone estimated at $2.6 billion reflecting an emphasis on acute care for patients with schizophrenia [5]. When non-direct healthcare costs, such as lost productivity of patients and their caregivers are taken into account, schizophrenia could total up to 3% of the total healthcare budget of western countries [6].

Many patients suffer from lifelong persistent psychiatric symptoms and cognitive effects, which result in reduced quality of life and significant socio-economic impacts [7]. Approximately 75% of all patients diagnosed with schizophrenia will experience a relapse, generally within two years, and most will experience multiple relapses over the course of the illness [1]. Relapse associated with psychotic exacerbation can increase the risk of patients harming themselves or others and it can have potential negative effects on their relationships, education and work [8]. Furthermore, relapse can lead to long-term disability and an increased burden of health care needs in these patients [1, 9]. There are many factors that contribute to the risk of relapse, including patient-related, treatment-related, lifestyle, and disease-related factors such as an earlier onset of disease, severity at Baseline, lower social functioning, or substance abuse [10]. However, it is widely acknowledged that improving access to antipsychotic drug (APD) treatment for patients experiencing symptom exacerbation is critical to reduce relapses [1, 11, 12], and that non-adherence to APD treatment is the most frequently cited risk factor for relapse [10].

2.2 Role of Adherence

It is estimated that as many as half of all patients in developed countries are not taking their medications properly, and the level may be even higher in developing countries according to the World Health Organization (WHO) [13]. The collective impact to patients of not taking or not appropriately taking one's medicines is profound, leading to disease under-treatment, treatment resistance, drug toxicity, and other adverse outcomes.

> "Poor adherence to long-term therapies severely compromises the effectiveness of treatment making this a critical issue in population health both from the perspective of quality of life and of health economics. Interventions aimed at improving adherence would provide a significant positive return on investment through primary prevention (of risk factors) and secondary prevention of adverse health outcomes." [13]

In schizophrenia, non-adherence to APD treatment is common. A study of pharmacy records between 1998 and 1999 demonstrated medication possession ratios under 80% in almost 40% of patients prescribed APDs, with adherence fluctuating over time such that more than 60% of

patients experienced periods of significant nonadherence over a four-year period [14]. Few studies have assessed APD non-adherence directly via random blood drug sampling, but one such study showed rates of poor adherence were even higher, at 58% [15]. The associated treatment costs, disease progression and risk of relapse associated with poor control of disease, especially in relation to non-adherence to APD treatment, have been extensively studied.

Dosing frequency is the primary regimen factor that has been shown to influence adherence, where greater dosing frequency is associated with poorer outcomes [16]. A meta-analysis of all available randomized controlled studies of oral once daily versus oral once weekly therapy has demonstrated a consistent improved adherence by patients to their treatment across studies with a odds ratio of weekly therapy versus daily therapy of approximately 1.9 [17]. These data indicate that once weekly oral therapy for chronic disease could offer improved adherence as compared to daily oral therapy. In some analyses, the magnitude of the benefit of once weekly therapy versus once daily therapy expands over time, demonstrating substantial differences in the persistence to chronic therapy after two years [18].

2.3 Therapeutic Approach

The treatment of schizophrenia begins with acute symptom management for those who are in crisis and is followed by relapse prevention and access to supportive treatments. APD therapy is effective in most patients with schizophrenia or schizoaffective disorder in managing and stabilizing their symptoms. However, in order to avoid symptom exacerbation, continuous treatment with antipsychotic medication is recommended. Longer term (e.g., >6 months) and abrupt discontinuation with APD therapy has been associated with an increased risk of relapse [19-22].

The etiology of relapse in patients with schizophrenia or schizoaffective disorder is complex and multifaceted. Although some patients may never experience recurrence after their first episode, some patients on uninterrupted maintenance therapy may still experience changes in symptomology and relapse, which may require a change in treatment. It is essential that any intervention including treatment with an antipsychotic medication is appropriate and efficacious [23]. Selecting the correct medication for maintenance therapy is critical, and is largely driven by individual factors including symptomology (positive and negative symptoms), response to treatment, relapse risk profile as determined by a clinician, as well as by patient preference [24]. Among the second-generation atypical antipsychotics, risperidone is considered one of, if not the most, effective agent and is the most commonly prescribed agent in patients with schizophrenia. Numerous studies have shown the effectiveness of this medication, particularly with longer acting formulations [8, 25, 26], which is also related to the demonstrated improved medication adherence to these formulations of APDs [14]. For example, clinically stable patients with schizophrenia or schizoaffective disorder who switched to a long acting depot formulation of risperidone (RISPERDAL CONSTA), have demonstrated greater occurrence of sustained remission compared to patients on quetiapine [26]. PERSERIS is another once-monthly risperidone injection approved for the treatment of schizophrenia [27].

Lyndra Therapeutics is developing oral, extended release therapies with the intention to change how people take medicines to sustain therapeutic outcomes and benefits. Lyndra is targeting

therapeutic areas such as schizophrenia as well as Alzheimer's disease and transplant rejection where the replacement of daily (or more frequently), medication doses with weekly doses would improve pharmacologic consistency as well as medication adherence and lead to better health outcomes.

2.4 Study Rationale

Discussions with practicing psychiatrists and key opinion leaders around the world have identified a high level of interest and desire for a once-weekly oral therapeutic option. Lyndra's objective is to meet this need by offering long-acting oral once-weekly formulations of approved antipsychotic drugs to clinicians and patients. The development of an oral, extended release formulation of risperidone provides an alternative to bi-weekly intramuscular depot delivery of risperidone or daily oral risperidone. Lyndra's aim is to reduce the frequency of daily dosing to once weekly or less to help improve the management of this chronic debilitating illness. The target population for the Lyndra formulation (LYN-005) is subjects with schizophrenia already stabilized on US Food and Drug Administration-approved APDs and requiring maintenance therapy.

This study will evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple doses of LYN-005, a once-weekly, 14 and 28 mg extended release capsule of risperidone in otherwise healthy subjects with schizophrenia or schizoaffective disorder. Following a thorough review of the literature, it was determined subjects already taking risperidone may be a safer population for evaluating LYN-005 than healthy volunteers. Healthy volunteers who are naïve to risperidone or other second-generation antipsychotic agents may experience significant adverse events (AEs) due to D2 receptor antagonist activity when administered multiple doses at therapeutic levels [28]. Early clinical pharmacology studies with risperidone and other atypical antipsychotics involving healthy volunteers did observe dose-related AEs and laboratory changes (including hyperprolactinemia). The risk of side effects including extrapyramidal symptoms (EPS) such as drug-induced parkinsonism (DIP) and tardive dyskinesia (TD), the latter which can be permanent in some individuals [29], and possible AEs such as weight gain, anticholinergic effects, hyperprolactinemia and sexual impairment [30, 31] were considered unduly high. There is precedence for conducting early studies in patients rather than healthy volunteers for extended-release injectable risperidone products in the US with RISPERDAL CONSTA [32] and PERSERIS [27] due to these unnecessary risks to healthy volunteers.

2.5 Lyndra Extended Release Capsule

The LYN-005 ER capsule is designed with modular components to ensure the safe and controlled administration of risperidone in the gastrointestinal (GI) tract over several days.

Risperidone is contained only within the [redacted] which provide controlled drug release based on hydration that is intended to be independent of food, pH, or alcohol effects. [redacted]

Figure 2-1: LYN-005 Extended Release Capsule and Components

Figure 2-2: Overview of Mechanism of Action

Colors for illustrative purposes only

When the coated capsule reaches the gastric environment (Figure 2-2), the exposure to acid causes dissolution of the acid-soluble (reverse enteric) coating, allowing the capsule to disintegrate and the formulation to unfold. The formulation opens into a configuration designed for retention within the stomach for a certain duration (i.e., gastric residence). Thereafter the formulation releases drug in a controlled and linear fashion, followed by safe exit and passage out of the stomach, transits through the intestinal tract until the formulation is excreted like other non-soluble materials. The design features by which the ER capsule achieves these targets are described in further detail in the current Investigator's Brochure.

2.6 Active Ingredient – Risperidone

Risperidone is an established second-generation antipsychotic belonging to the class of antipsychotic agents, the benzisoxazole-derivatives. Risperidone is a selective monoaminergic antagonist with a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors with no affinity for cholinergic receptors. The antipsychotic activity of risperidone is attributed to both risperidone and its active metabolite 9-hydroxyrisperidone, considered together as the active moiety of risperidone. The mechanism of action in improving positive symptoms of schizophrenia is considered related to central dopamine D2 receptor antagonism. The balance of 5-HT2 to D2 receptor binding is thought to reduce extrapyramidal side effect liability from dopamine antagonism and extend the therapeutic activity to reducing negative and affective symptoms of schizophrenia.

Risperidone is primarily metabolized by cytochrome P450 (CYP) 2D6 to 9-hydroxyrisperidone which has two enantiomers with similar pharmacological activity to risperidone. Risperidone and 9-hydroxyrisperidone together form the pharmacologically active moiety that is similar in extensive and poor metabolizers; approximately 24 hours. The elimination half-life of risperidone alone is approximately 3 hours in extensive metabolizers and 17-20 hours in poor

metabolizers. Clinical studies do not suggest that poor and extensive metabolizers have different rates of adverse effects, and risperidone is generally well-tolerated [33].

2.7 Benefits/Risks

The LYN-005 extended release (ER) capsule is a novel investigational formulation of risperidone designed to provide sustained oral drug delivery over 1 week, further described in the Investigator's Brochure. It is being developed for patients with schizophrenia whose tolerability and symptom management have already been established with oral administration of immediate release (IR) risperidone. The oral dose range considered effective in maintaining clinical stability of psychiatric symptoms from schizophrenia following acute therapy is 2 to 6 mg daily or 14 to 42 mg per week.

This study will evaluate 3 oral doses of once-weekly risperidone using the LYN-005 ER capsule at doses of 14 and 28 mg, designed to release the equivalent of 2 or 4 mg risperidone daily over 7 days. The study will be conducted in clinically stable subjects diagnosed with schizophrenia or schizoaffective disorder receiving a therapeutic dose of an APD for at least 6 weeks prior to Screening. Subjects will be in general good physical health who are mildly or moderately psychiatrically ill but clinically stable for at least 3 months prior to Screening and no hospitalization due to worsening of schizophrenia within the prior 6 months.

LYN-005 risperidone extended release capsule development has been informed by the results of previous clinical studies. The Sponsor has adopted several risk mitigation measures to protect subjects participating in Lyndra studies, described in the following subsections.

2.7.1 Risks Associated with Active Ingredient

Reference is made to the current LYN-005 Investigator's Brochure, Section 6.3, which includes reference material for marketed risperidone products and potential risks associated with risperidone.

2.7.2 Risks Associated with Extended Release Capsule

As described in the Investigator's Brochure, LYN ER capsules have a favorable safety profile in previous clinical studies with different active pharmaceutical ingredients. Over time, modifications have been made to the dosage form to improve its safety and tolerability. Clinical experience now exceeds 100 subjects dosed with ER capsules. Gastrointestinal adverse events, particularly nausea and abdominal pain, have been the most frequent adverse events in subjects dosed with LYN ER capsules. To mitigate the risk of GI events, the present study has exclusion criteria for GI conditions that may increase any potential risks of LYN ER capsules. In addition, subjects will be closely monitored for safety, including GI adverse events, during the study. LYN-005 dosing will be supervised while the subject is housed in the inpatient unit, and exit of the formulation components from the body will be assessed by X-ray.

2.7.3 Risks Associated with Study Related Procedures

The following additional risks may occur associated with study-related procedures:

- X-Rays: detection of underlying anatomic abnormality or previously unknown health condition, injury from radiation exposure.
- Detection of unknown disease necessitating further evaluation and follow-up.
- Blood sampling: excessive bleeding, bruising, presyncope/syncope, nerve damage, or infection at the venipuncture site.
- Electrocardiogram (ECG) tracing: irritation or rash of the skin due to the use of adhesive leads.

2.7.4 Benefits/Risks Conclusions

There are no direct benefits to the subjects in this study. Subjects will be housed in the inpatient unit for 2 inpatient periods, totaling 11 days, for the evaluation of LYN-005, allowing daily monitoring for AEs or changes in symptomatology that might require treatment. APD dosing during the inpatient portion of the study will be supervised by the study site to ensure compliance with therapy and control of symptoms. Following discharge from the site, in addition to follow-up study center visits, subjects will be contacted periodically to help ensure medication compliance during the outpatient phase of the study.

There is risk of AEs from risperidone; to minimize this risk, doses are limited to the low to mid-range.

There is a possibility that the screening and evaluation tools employed in this study may suggest or detect a previously unknown health condition that may warrant additional investigation by the individual's general practitioner and in the case of positive human immunodeficiency virus (HIV) results, notification of health authorities in accordance with local and national requirements.

Detailed information for potential benefits and risk for LYN-005 (risperidone) extended release capsules may be found in the current LYN-005 Investigator's Brochure, Section 6.3.

3 STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives along with the associated endpoints are summarized in Table 3-1.

Table 3-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary:	
• To determine the safety and tolerability of risperidone extended release capsules (LYN-005) administered as repeat weekly doses compared to IR risperidone tablets at 2 dose levels;	• Incidence of treatment emergent adverse events (TEAEs).
• To characterize the PK of risperidone, active metabolite 9-hydroxyrisperidone and active moiety (risperidone and 9-hydroxyrisperidone combined) after repeat weekly doses of LYN-005 ER capsules relative to IR risperidone tablets at 2 dose levels.	• Risperidone, 9-hydroxyrisperidone, and active moiety PK after oral administration of LYN-005 capsules and IR risperidone to include, as possible and appropriate, C_{max}, C_{min}, T_{max}, Kel, $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-168)}$ and $AUC_{(0-\infty)}$.
Secondary:	
• To assess the exposure to risperidone, 9-hydroxyrisperidone and active moiety during the switch from IR risperidone to LYN-005.	• Exposure to risperidone, 9-hydroxyrisperidone and active moiety as assessed from C_{max}, T_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ after switching from IR risperidone to LYN-005.
Exploratory:	
• To model the PK of risperidone, 9-hydroxyrisperidone and active moiety when administered as a LYN-005 extended-release capsule.	• PK modelling of risperidone, 9-hydroxyrisperidone, and active moiety exposure.

4 STUDY PLAN

4.1 Study Design

LYN-005-C-004 is a blinded, multiple-dose, randomized, parallel group, safety, tolerability and PK study of LYN-005 in subjects with a primary diagnosis of schizophrenia or schizoaffective disorder in general good health. Eligible subjects must be clinically stable and receiving a therapeutic dose of an approved oral antipsychotic drug for a minimum of 6 weeks at the time of Screening. Enrolled subjects will be evaluated under steady-state conditions on commercially-available IR risperidone tablets and then assigned in blinded fashion either to LYN-005 weekly or continued encapsulated IR risperidone daily for 3 weeks to attain (or continue) steady-state exposure.

A total of 32 subjects will participate in this study. Subjects will be randomized to LYN-005 plus IR risperidone matched placebo OR LYN-005 matched placebo or IR risperidone as follows:

- Arm 1: LYN-005 (14 or 28 mg weekly) plus IR risperidone matched placebo (N=24).
- Arm 2: LYN-005 matched placebo plus IR risperidone (2 or 4 mg/day) (N=8).

Per above, in order to maintain the blind, all subjects will either receive LYN-005 and IR risperidone-matched placebo or LYN-005-matched placebo and IR risperidone, as follows:

Arm 1:

- LYN-005: Size 00EL capsules containing LYN-005 stellate; the 14 mg dose of LYN-005 contains 3 active arms containing risperidone, and 3 inactive arms and he 28 mg dose of LYN-005 contains 6 active arms containing risperidone.

  AND

- IR Risperidone Matched Placebo: Orange capsule-shaped tablets containing inactive ingredient.

Arm 2:

- LYN-005 Matched Placebo: Size 00EL capsules containing inactive ingredient with no stellate.

  AND

- IR Risperidone: Risperidone 2 mg (orange) capsule-shaped tablets.

Although treatment assignment is blinded; the dose level is not blinded. The dose of LYN-005 (14 or 28 mg)/IR risperidone (2 or 4 mg/day) administered will be based on the subject's current antipsychotic medication dose. Randomization will be stratified by risperidone dose (LYN-005 14 mg/IR risperidone 2 mg/day [low dose] and LYN-005 28 mg/IR risperidone 4 mg/day [high dose], with a maximum of 16 subjects enrolled in each strata. Within each strata, subjects will be randomized on a 3:1 basis to either LYN-005 or risperidone, respectively.

All administrations of LYN-005 will be supervised. Complete PK evaluations will be performed after each LYN-005 dose, as designated in the Schedules of Events (SOE) (Section 18.1.1 and Section 18.1.2) and over 24 hours at steady-state for IR risperidone at the beginning of the study.

LYN-005 will be evaluated in subjects who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of schizophrenia or schizoaffective disorder of at least 2 years, who have already been stabilized on an oral antipsychotic medication for a minimum of 6 weeks at the time of screening with no psychiatric hospitalizations for relapse in the past 6 months. Subjects who are prescribed an antipsychotic agent other than risperidone or a dose of risperidone outside the range are also eligible for study participation if they are a) able to tolerate risperidone and b) be completed switched to 2 or 4 mg daily oral risperidone for a minimum of 2 weeks prior to the first dose of LYN-005/matched placebo on Day 1 (see Section 6.3.1).

Eligible subjects must be clinically stable (i.e., mildly or moderately ill psychiatrically), with a low risk of relapse and otherwise healthy without history of significant GI diseases. Guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. In the event of worsening of schizophrenia symptoms while receiving risperidone during the study, another medication can be administered at the discretion of the Principal Investigator (PI), with notification of Lyndra's Medical Monitor.

Subjects will be screened for study eligibility between Days -21 and -14. Subjects who are initially determined to be eligible, based on initial Screening assessments, will then participate in a 10-day IR risperidone run-in period, during which adherence with study treatment will be assessed. Subjects who remain eligible for the study will enter the inpatient unit on Day -2. After admittance to the inpatient unit and prior to the first LYN-005/matched placebo administration, samples for determination of IR risperidone PK will be collected from Days -2 to -1.

Over the course of the study, subjects are to receive 3 doses of LYN-005/matched placebo, per their random assignment, 1 each on Days 1, 8, and 15, all on an inpatient basis. All subjects also will receive IR risperidone or matched placebo, again per their random assignment, from Days 1 to 21.

Overall, during study participation, subjects will be housed in the inpatient unit twice, from Days -2 to 9 (Inpatient Stay 1) and then again from Days 14 to 16 (Inpatient Stay 2). Subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled. In between each inpatient stay, subjects will have study assessments performed on an outpatient basis daily from Days 10, 11, 12, and 13. After discharge from Inpatient Stay 2, subjects will again have assessments performed on an outpatient basis on Days 17, 18, 21, 22, and 23. An End of Study (EOS) visit will be conducted on Day 35.

During study participation, guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. Rescue administration of an agent other than risperidone or paliperidone in the event of worsening of schizophrenia symptoms during the study can be administered at the discretion of the PI, with notification of Lyndra's Medical Monitor. Extrapyramidal symptoms will be monitored throughout the study at regular intervals

using the Extrapyramidal Symptom Rating Scale (ESRS). Severity of schizophrenia/schizoaffective disorder symptoms will be monitored throughout the study at regular intervals using the Clinical Global Impression-Severity (CGI-S) scale. Concomitant medications, AEs, safety laboratory tests, and vital signs will be assessed throughout the study, as per the SOE (Section 18.1.1 and Section 18.1.2).

Details regarding each study period follow.

4.1.1 Screening Period (Day -21 to Day -14):

All screening procedures will be performed on an outpatient basis. Prior to any screening procedures, the subject or designated representative must provide written informed consent. Male and female subjects between 18 to 50 years of age who have a diagnosis of schizophrenia or schizoaffective disorder, as defined by DSM-5 criteria and as confirmed by the Mini International Neuropsychiatric Interview (MINI) version 7.0.2. The MINI will also be used to exclude comorbid psychiatric diagnoses. Further eligibility requirements will include a CGI-S score of ≤4 (moderately ill). Subjects must have been medically stable within the last month, and stable in their psychiatric illness on a stable antipsychotic treatment regimen and without significant symptom exacerbation over the last 3 months. Additionally, subjects must be receiving outpatient treatment and not have been hospitalized for worsening schizophrenia in the last 6 months (hospitalization for social management within this time is acceptable). Subjects should have a Positive and Negative Syndrome Scale (PANSS) score aligned with stable and mild-moderate disease (i.e., ≤80 points).

An assessment of pill swallowing will be assessed with a questionnaire, PILL-5, where a score of 4 or below is regarded as “normal” pill swallowing. Additional screening measures to confirm general good health will be performed as described in the SOE (Section 18.1.1).

To be eligible for this study, subjects must either have been stable on a therapeutic dose of an oral IR risperidone between 2 and 8 mg/day or been on a stable dose of another antipsychotic medication (single agent) for a minimum of 6 weeks. As shown in Figure 6-1, subjects already receiving 2 to 4 mg IR risperidone will transition to 2 mg daily administration by Day -13 to complete the run-in. Subjects on a daily dose of approximately 4 mg to 8 mg IR risperidone will be placed in a cohort based on clinical judgement of the Investigator and fully transitioned to this dose by Day -13 and remain at this dose during the run-in.

Subjects who currently are on antipsychotic medications other than IR risperidone are also eligible for the study and are to be switched to either 2 or 4 mg/day IR risperidone based on the clinical judgement of the Investigator are to begin the transition to IR risperidone starting on Day -13; by Day -13, these subjects should only be receiving 2 or 4 mg IR daily during the run-in. To improve toleration and management of symptoms during the transition to risperidone run-in, short-term changes to the daily risperidone dose during the run-in may be considered in consultation with the PI. A home or clinic visit may also be considered at the discretion of the PI in order to assure subject stability.

4.1.2 Pre-study Preparation with IR Risperidone

All subjects who are eligible for study participation at the end of Screening will receive a medication log for use Days -13 through -3 to record the timing and dose of their IR risperidone during the run-in period. IR Risperidone must be taken once a day and at approximately the same time of day (morning or evening) on Days -13 to -3. Guidelines for switching antipsychotic medication to risperidone 2 or 4 mg/day prior to Day -13 are provided in Figure 6-1 in Section 6.3.1.

Eligible subjects will be contacted daily on Days -13 to -3 prior to admission to the study unit on Day -2 to ensure medication adherence and check on safety, concomitant medications, and AEs. The subject must be adherent (self-report) with risperidone administration for 5 consecutive days prior to Day -3 to be eligible for enrollment into the study. Additional days may be added to the pre-study preparation to ensure 5 consecutive days of medication adherence prior to Day -3. Subjects who confirm medication adherence will be prepared by the site regarding the arrangements for subject arrival at the study unit the next day (Day -2) and the subsequent 10-night stay. Subjects will be instructed on Day -3 to take their risperidone dose at the normal time and to bring risperidone tablets to the unit on Day -2.

4.1.3 IR Risperidone PK Period

Subjects will be admitted to the study unit on Day -2.

Medication adherence for IR risperidone based on the medication log should be assessed upon arrival to the unit on Day -2, and subjects who are non-adherent are not to be admitted to the inpatient unit at that time. The site should confirm the dose and time of last IR risperidone for subjects who remain eligible to begin the inpatient phase of the study, and a blood sample collected for PK analysis.

Subjects who are switching from evening to morning dosing will be given half the regimen of daily oral risperidone in the evening of Day -2 (i.e., either 1 or 2 mg risperidone) to minimize overlapping exposure. This dose should be given after the evening (6 pm) PK sample has been collected. Morning administration of the full dose of IR risperidone, 2 or 4 mg respectively, must begin by Day -1 for all subjects.

Patients will receive IR risperidone on Day -1, as described in Section 6.3.2, with PK samples collected thereafter.

4.1.4 Randomization (Day 1)

Subjects who successfully complete the admission procedures will be randomized on Day 1 in a 3:1 ratio to LYN-005 or IR risperidone, as follows:

- LYN-005: Subjects randomly assigned to LYN-005 ER will receive a single LYN-005 ER capsule (14 or 28 mg) taken once-weekly (on Days 1, 8, and 15) plus dummy IR risperidone-matched placebo daily though Day 21.

- IR Risperidone: Subjects randomly assigned to IR risperidone will receive a single weekly dummy capsule (placebo capsule representing LYN-005, but containing no stellate) taken once-weekly (On Days 1, 8, and 15) plus IR risperidone (2 or 4 mg/day) daily though Day 21.

Subjects will be split into 2 groups based on their IR risperidone run-in dose prior to randomization. Subjects receiving 2 mg/day IR risperidone will be randomized to receive either 14 mg/week LYN-005 or continued 2 mg/day IR risperidone and those receiving 4 mg/day IR risperidone will be randomized to receive either 28 mg/week LYN-005 or continue with 4 mg/day risperidone, respectively. Although treatment assignment is blinded; the dose level is not blinded. Randomization will be stratified by risperidone dose (LYN-005 14 mg/IR risperidone 2 mg/day [low dose] and LYN-005 28 mg/IR risperidone 4 mg/day [high dose], with a maximum of 16 subjects enrolled in each strata. Within each strata, subjects will be randomized on a 3:1 basis to either LYN-005 or risperidone, respectively.

4.1.5 Double-blind Dosing Period (Days 1 to 21)

During the LYN-005 dosing period, subjects are to receive 3 doses of LYN-005 or matched placebo, one each on Days 1, 8, and 15. Following an overnight fast, subjects are to consume a light breakfast over 30 minutes or less, with the meal started 30 minutes prior to study drug administration. Subjects also will receive IR risperidone Study assessments are to be performed before and after each dose per the Schedule of Events (Section 18.1.1 and Section 18.1.2).

Subjects will remain in the inpatient unit until Day 9 for continued safety monitoring. On Day 9, the Investigator will perform study assessments to confirm the subject is eligible to leave the inpatient unit and continue outpatient treatment with study drug.

After discharge from the inpatient unit on Day 9, subjects will be followed on an outpatient basis from Days 10 to 13 until their return to the unit on Day 14. During this period, subjects will continue taking their daily dummy or IR risperidone as prescribed.

In the evening of Day 14, subjects will return to the clinic for Inpatient Period 2 in advance of the third LYN-005/matched placebo administration on Day 15. AEs and concomitant medications will be assessed upon arrival.

On the morning of Day 15, a pre-dose PK-sample will be collected, and as on Days 1 and 8, subjects will be administered either the third dose of LYN-005/matched placebo. PK samples will be collected and safety assessments performed as per the SOE (Section 18.1.1 and Section 18.1.2). Subjects are to remain in the unit for a minimum of 8 hours for observation prior to discharge on Day 16.

On Days 16 through 21, subjects will continue taking their daily IR risperidone or matched placebo as outpatients, as per their random treatment assignment.

4.1.6 End of Study Visit (Day 35)

On Day 35, subjects will be asked to return to the clinic for follow-up assessments, as per the SOE (Section 18.1.2). Thereafter, additional follow-up telephone calls may occur as warranted if there are ongoing AEs at the time of the EOS Visit.

4.2 Blinding Procedures

Subjects and site and Sponsor personnel associated with study conduct will be blinded to treatment assignment.

During the conduct of the study, the blind should only be broken on an individual subject basis in the event of an emergency where it is necessary for the Investigator to know which treatment the subject is receiving before the subject can be treated. The code may also be broken if someone not in the study uses study drug (e.g., if a child in the subject's household takes study drug, the blind may be broken to determine treatment for the child).

When it is necessary to break the blind, the Investigator may unblind the treatment immediately (i.e., without prior notice to the Medical Monitor, sponsor, or other) via the Interactive Response Technology system, but must notify the IRB per local regulations and Sponsor as soon as possible, preferably by telephone and then in writing, regarding the necessity of code breaking.

If the code is broken for a subject, this must be documented in the electronic case report form (eCRF) and source documents, together with the reasons for breaking the code.

4.3 Justification of Dose Selection

The justification for dose selection is based on the target oral dose range for risperidone ranging from 2 to 8 mg/day in subjects with schizophrenia and schizoaffective disorder [33]. These doses would be expected to correspond to therapeutically equivalent weekly doses of 14 to 56 mg risperidone using LYN-005. Accordingly, for this study, 14 and 28 mg LYN-005 ER capsule formulations of risperidone will be evaluated.

LYN-005 containing 14 and 28 mg risperidone is expected to deliver comparable exposures to risperidone active moiety concentrations associated with 2 mg/day and 4 mg/day, respectively, given orally as an immediate release formulation over 1 week. Given the metabolism of risperidone to the equipotent metabolite, 9-hydroxyrisperidone, and due to the exposure differences between poor and extensive metabolizers, it was decided to exclude poor metabolizers to minimize study variability.

5 SUBJECT POPULATION

5.1 Inclusion Criteria

To be eligible to participate in the study, subjects must meet ALL of the following inclusion criteria at Screening (or at enrollment when specified):

1. Male or female aged ≥18 and ≤50 years.

2. Current diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria as confirmed by the MINI 7.0.2.

3. The following psychiatric criteria are to be used to determine subject eligibility:

    a. Duration of diagnosis of schizophrenia or schizoaffective disorder of ≥2 years.

    b. Outpatient; not hospitalized for worsening of schizophrenia within the last 6 months (partial hospitalization for social management within this time period is acceptable).

    c. Medically stable over the last month and psychiatrically stable without significant symptom exacerbation over the last 3 months.

4. Stabilized on an oral antipsychotic medication (single agent) for a minimum of 6 weeks at the time of Screening.

5. On a stable dosage of all permitted non-antipsychotic medications (except for medication to be used on an as-needed basis) for at least 1 month prior to the Screening visit and for the duration of the study.

6. CGI-S score of ≤4 (moderately ill).

7. PANSS score of ≤80 points.

8. Body mass index (BMI) of ≥18 kg/m^2 and ≤35 kg/m^2.

9. Able to read and understand study procedures and provide written informed consent before the initiation of any protocol-specific procedures.

10. Willing to comply with all protocol-specified procedures and availability for the duration of the study.

11. Subject has identified a caregiver or personal contact with whom the subject communicates with at least once a week.

5.2 Exclusion Criteria

In order to be eligible to participate in the study, subjects must meet NONE of the following exclusion criteria at Screening (or at enrollment when specified):

1. Subjects with known clinically significant esophageal or GI disease, including but not limited to:

    a. Known strictures such as esophageal web, pyloric stenosis, or small intestinal stricture, or subjects with high risk of stricture, e.g., Crohn's disease.

    b. Diagnosis of a condition known to elevate or lower gastric pH, e.g., achlorhydria or hypochlorhydria.

    c. Prior varices or small or large bowel obstructions.

    d. Prior abdominal or upper gastrointestinal surgery (prior uncomplicated laparoscopic procedures including appendectomy or colectomy).

    e. History of dysphagia or aspiration in the last 5 years.

    f. History of an esophageal motility disorder or undergoing treatment for a gastric motility disorder.

    g. Significant history of diarrhea or constipation within 3 months of Screening.

    h. Multiple episodes of abdominal pain within 3 months of Screening.

    i. Subjects who experience moderate or severe dysmenorrhea or menorrhagia (with use of pain medication) within 3 months of Screening.

    j. History of moderate to severe Acid Reflux Disease or a score of ≥2 on the Acid Reflux Severity Scale (ARSS) [2], indicating moderate to severe symptoms. The ARSS scale is as follows:

    None = 0 no symptoms

    Mild = 1 awareness of symptom, but easily tolerated

    Moderate = 2 discomfort sufficient to cause interference with normal activities

    Severe = 3 incapacitating, with inability to perform normal activities.

2. Subjects with PILL-5 questionnaire score of 5 or greater.

3. Medical history or current diagnoses indicating the presence of any of the below conditions:

    a. Presence of an uncontrolled, unstable, clinically significant medical condition could that could put the subject at risk because of participation in the study, interfere with the subject's ability to participate in the study or influence the interpretation of safety or PK evaluations.

    b. History of a major cardiovascular event (myocardial infarction, cardiac surgery or revascularization, unstable angina, stroke, or transient ischemic attack) or a hospitalization for heart failure with 6 months of Screening.

    c. Any clinically significant illness, medical or surgical procedure or trauma within 4 weeks of Screening.

    d. Known immunocompromised status, including individuals who have undergone organ transplantation, on immunosuppression for an immune mediated disease, or are positive for HIV.

    e. Subjects with a positive test for active hepatitis B or C at Screening. Subjects with successfully treated hepatitis B infection which has been resolved for greater than 1 year or successfully treated hepatitis C infection will not be excluded.

    f. Subjects who have donated more than 250 mL of blood within 30 days of Screening.

    g. Subjects who have difficulties with venipuncture/cannulation, including difficulty accessing veins for blood sampling and/or history of coagulopathy or endocarditis.

    h. Subjects with a current DSM-5 diagnosis of major depressive episode, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder on the MINI 7.0.2 or in the judgment of the Investigator. (Note that individuals with depression secondary to schizoaffective disorder are eligible).

    i. Suicidal ideation associated with actual intent and a method or plan in the past 6 months, as measured by the C-SSRS (i.e., "Yes" answers on items 4 or 5) at Screening or having made a suicide attempt within the last 2 years.

    j. Known or suspected (non-febrile) seizure disorder.

    k. History of neuroleptic malignant syndrome.

    l. Current or history of clinically significant tardive dyskinesia.

    m. Known or suspected diagnosis of intellectual disability or organic brain disorder or other diagnosis that is primarily responsible for current symptoms and functional impairment.

n. Medically non-adherent in the management of their schizophrenia/schizoaffective disorder.

4. Use of the below medications/treatments in the 2 weeks before enrollment, including:

   a. Proton pump inhibitors or H2 blockers.

   b. Prokinetic agents.

   c. Medications that may interfere with the absorption, metabolism, or excretion of risperidone, e.g.:

      i. Drugs metabolized via CYP3A4 pathway, such as macrolide antibiotics and azole antifungals).

      ii. Moderate or strong CYP3A4 p-glycoprotein (P-gp) enzyme inducers and inhibitors (carbamazepine, phenytoin, rifampicin, phenobarbital, itraconazole, verapamil).

      iii. Moderate or strong CYP2D6 inhibitors (e.g., fluoxetine, fluoxetine combinations, paroxetine), or quinidine.

   d. Concomitant medications, natural remedies, supplements or vitamins which are associated with changes to gastric motility or pH. Use of antacids is permissible, except within 2 hours of dosing with LYN-005.

   e. Benzodiazepines; except lorazepam, diazepam and oxazepam, which are acceptable if for the treatment of depression, anxiety or insomnia.

   f. Use of more than one antidepressant; or if on just one, a change in dose within 6 weeks of Screening.

   g. Depot antipsychotic use within 9 months of Screening.

   h. Electroconvulsive therapy within 3 months of Screening.

5. Subjects with clinically significant abnormal safety (e.g. physical examination, vital sign) or safety laboratory assessments, specifically:

   a. Presence of a clinically significant abnormal laboratory result on blood or urine safety tests at Screening.

   b. Anemia (hemoglobin below lower limit of normal reference range) at Screening.

   c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN), or total bilirubin ≥1.5 × ULN.

   d. Moderate or severe renal insufficiency at Screening (glomerular filtration rate <60 mL/min, as determined using the Cockcroft-Gault formula).

e. Heart rate of <50 beats per minute (bpm) at Screening.

f. Systolic blood pressure <100 or ≥150 mmHg and/or diastolic blood pressure <60 mmHg or ≥100 mmHg at Screening.

g. HbA1c ≥6.5% at Screening.

h. Positive fecal occult blood test at Screening.

i. Clinically significant prolactin elevation (≥200 ng/mL for females; ≥100 ng/mL for males).

6. Subjects with the below specified patterns of substance use at Screening:

   a. Fulfillment of the DSM-5 criteria for moderate or severe substance use disorder (excluding nicotine and caffeine) within 6 months of Screening.

   b. History of alcohol consumption exceeding moderate use; in males exceeding 21 units per week and in females exceeding 14 units per week (1 unit = 360 ml beer, 25 mL of 40% spirit or a 125 mL glass of wine) over the past month. Subjects are not permitted to consume alcohol during the inpatient stay nor 12 hours before any clinic visit while outpatient.

   c. Positive ethanol breathalyzer.

   d. Positive urine drug screen for substances of abuse other than cannabis.

   e. Heavy nicotine use (consumption of >40 cigarettes or >36 mg of nicotine from other sources [e.g., vaping products] daily) or daily use of smokeless tobacco.

7. Subjects of reproductive potential who are (hetero) sexually active but unwilling to use acceptable means of contraception through the EOS. For clarity, subjects who are at least 1 year post-menopausal are not of reproductive potential. Acceptable means of contraception include:

   a. Subjects who have been surgically sterilized.

   b. Females of reproductive potential: diaphragm, injectable, oral/patch contraceptives for a minimum of 6 weeks, contraceptive sponge, implant, or intrauterine device in use prior to enrollment.

   c. Males: condom in combination with any of the above means of contraception.

   d. All subjects: abstinence may be an acceptable means of contraception as long as the individual consents to initiate immediate use of double barrier protection for the duration of the study should (hetero) sexual intercourse occur.

8. Subjects who are nursing or who have positive or indeterminate pregnancy tests at either Screening (serum test) or enrollment (urine test).

9. Use of any experimental agent within 1 month or 5 half-lives of Screening, whichever is longer.

10. Subjects who are employees or immediate family members of employees of the site, Sponsor or study-related vendors.

11. History of a serious allergic or hypersensitivity reaction to risperidone or LYN-005 excipients (refer to Investigator's Brochure).

12. Subjects with history of X-ray, computed tomography (CT) scan or angiogram of the abdomen within one year of Screening.

13. Subjects with CYP2D6 poor or underdetermined metabolizer status based on genetic testing.

5.3 Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet inclusion/exclusion criteria and hence are not subsequently enrolled in the study. (For the purposes of this study, subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled.) A minimal set of screen failure information is required to be captured to ensure transparent reporting of screen failure subjects and to respond to queries from Regulatory Authorities. Information to be captured on screen failure subjects includes demography, screen failure details including any inclusion/exclusion criteria that were not met, the primary reason and the relevant data (e.g., laboratory, medical historical details) that support the determination. Where applicable, potential subjects may be rescreened to reassess eligibility. These subjects should be assigned the same subject numbers as for the initial screening.

Subjects who consent to participate in the clinical study, meet eligibility criteria but are not enrolled will be referred to as Alternates (not screen failures) and may be considered for future enrollment.

5.4 Discharge Instructions at End of Study or Early Termination Visit

The site will facilitate a review with the study subject of the planned schedule for when information relating to their study information (e.g., study results, treatment assignments) will be available. The site will also discuss how information relating to their participation in the study will be shared with their healthcare provider, if they choose to share this information, and with the relevant health authorities in the event of a positive HIV or hepatitis result.

5.5 Study Completion

The site will complete the Study Termination eCRF page and this will mark the completion of the individual's participation in the study.

The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further

safety follow-up, it is the date consent is withdrawn. This date should be recorded on the Study Termination eCRF page.

6 STUDY DRUG MANAGEMENT

6.1 Description of Study Drugs

The term 'study drug' refers to those drugs provided by the Sponsor, which will be evaluated as part of the study objectives.

6.1.1 LYN-005 ER

The Lyndra ER product, LYN-005, contains risperidone 14 or 28 mg. The LYN-005 (risperidone) ER capsule is designed with modular components to ensure the safe and controlled administration of risperidone in the GI tract over several days. Drug is contained only within the [redacted] drug layers, which provide controlled drug release based on hydration. Refer to the Investigator's Brochure for additional details.

Lyndra will provide LYN-005 14 and 28 mg capsules and matched placebo.

6.1.2 IR Risperidone

RISPERDAL® (risperidone) is an atypical antipsychotic agent. Lyndra will provide risperidone 2 mg (orange) capsule-shaped tablets and matched placebo.

6.2 Storage

All drugs associated with this study (study drugs) are to be stored separately from other drugs and medications in a secure location under appropriate storage conditions with temperature monitoring. All drugs associated with this study must be checked for expiration or retest date prior to use. Expired drugs or those beyond their retest date must not be administered to subjects.

The Investigator or designee will be responsible for oversight of the administration of drug to subjects enrolled in the study according to the procedures stipulated in this study protocol. All drugs will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

6.2.1 LYN-005

LYN-005/matched placebo is to be stored at 15 to 25ºC (59° to 77°F). The capsules are to be handled in a manner to avoid squeezing or crushing.

6.2.2 IR Risperidone

IR risperidone tablets/matched placebo should be stored at controlled room temperature 15° to 25°C (59° to 77°F) and protected from light and moisture.

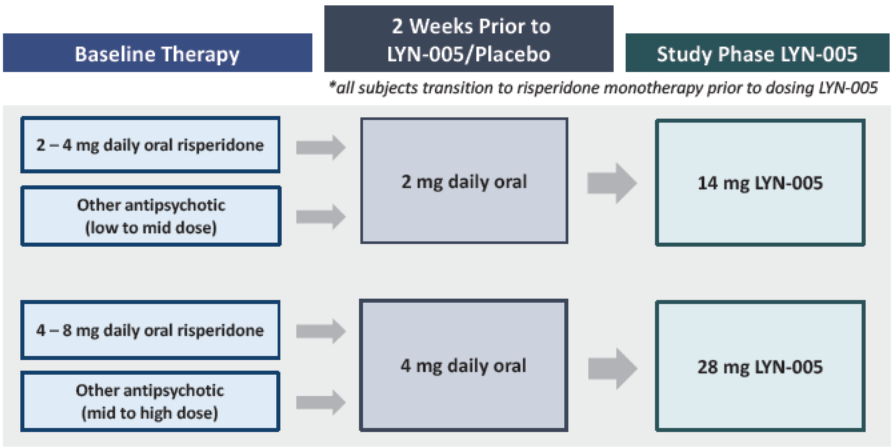
6.3 Dosing and Administration

6.3.1 Run-in Preparation with IR Risperidone

All subjects must take IR risperidone once a day and at approximately the same time of day (morning or evening) on Days -13 to -3.

Subjects who are receiving antipsychotic medications must switch to either 2 or 4 mg/day IR risperidone based on the clinical judgement of the Investigator are to begin the transition to IR risperidone starting on Day -13; by Day -13, these subjects should only be receiving 2 or 4 mg IR daily. Guidelines for switching antipsychotic medication to risperidone 2 or 4 mg/day prior to Day -13 are provided in Figure 6-1.

Figure 6-1: IR Risperidone Switch and Dosing Guidelines



6.3.2 IR Risperidone PK Period

Morning administration of the full dose of IR risperidone, 2 or 4 mg respectively, must begin by Day -1 for all subjects.

Subjects who must switch from evening to morning dosing will be given half the regimen of daily oral risperidone in the evening of Day -2 (i.e., either 1 or 2 mg risperidone) to minimize overlapping exposure. This dose should be given after the evening (6 pm) PK sample has been collected.

On Day -1, following an overnight fast, subjects will consume a light breakfast over 30 minutes or less, with the mean started 30 minutes prior to study drug administration. IR risperidone will be administered thereafter with 250 mL of water with the option for additional water (increments of 50 mL), as needed. Following risperidone administration, blood samples for PK will be obtained per the SOE (Section 18.1.1 and Section 18.1.2).

6.3.3 Blinded Treatment (LYN-005 or Placebo)

Subjects who successfully complete the admission procedures will be randomized on Day 1 in a 3:1 ratio to LYN-005 or IR risperidone, as follows:

- LYN-005: Subjects randomly assigned to LYN-005 ER will receive a single LYN-005 ER capsule (14 or 28 mg) taken once-weekly (on Days 1, 8, and 15) plus dummy IR risperidone-matched placebo daily though Day 21.

- IR Risperidone: Subjects randomly assigned to IR risperidone will receive a single weekly dummy capsule (placebo, representing LYN-005) taken once-weekly (On Days 1, 8, and 15) plus IR risperidone (2 or 4 mg/day) daily though Day 21.

6.3.3.1 LYN-005/Placebo Administration

LYN-005 capsules are to be taken orally following a light breakfast with approximately 250 mL of water immediately after capsule administration, while the subject is in a standing position. If the subject requests more fluid for swallowing, they may be given additional water in increments of 50 mL to chase. The volume of water consumed by the subject will be recorded in the eCRF. The subject is to remain upright after dosing for a total of at least 15 minutes. The subject must not bite or chew the capsule nor hold the capsule in the mouth prior to swallowing.

6.3.3.2 IR Risperidone/Placebo Administration

IR risperidone or matched placebo tablets are to be taken orally in the morning with 250 mL of water with the option for additional water (increments of 50 mL), as needed.

6.4 Accountability and Compliance

The United States Food and Drug Administration (FDA) requires accounting of all investigational treatment received by each study center. Records of treatment disposition required by federal law include the date received by the center, date administered, quantity administered, and the subject to whom study treatment was administered. The investigator is responsible for the accountability of all used and unused study treatment containers and unused study treatment.

Each study center is to use a study treatment accountability log to document study treatment disposition. All items on this form are to be completed in full. The area where study treatment accountability records are to be maintained is to be approved by the Sponsor or designee. The Clinical Research Associate (CRA) is to routinely review study treatment accountability records.

6.5 Prior and Concomitant Medications and Therapies

All medications, drugs and blood products taken or received by the subject within 3 months and any over-the-counter medications, natural supplements or vitamins taken within 4 weeks (28 days) prior to Day -2 are to be recorded on the Concomitant Medications eCRF. Similarly, any medication, drug, blood product, over-the-counter medication, herbal remedy taken by the

subject after study enrollment through EOS will also be recorded on the Concomitant Medications eCRF.

Subjects on medication who do not discontinue medications within 2 weeks of study dosing (unless otherwise specified in the Exclusion Criteria, Section 5.2) are not eligible for dosing with LYN-005 on Day 1.

During the study, the use of contraceptives (oral or other acceptable method) to prevent pregnancy in subjects of childbearing potential is required. Aside from contraceptives and necessary psychotropic medications, the use of other concomitant medications is generally discouraged during the study unless deemed appropriate by the Investigator to treat new or worsening medical conditions, including AEs. If pain relief is required during the study, the Investigator is encouraged to prescribe paracetamol. Nonsteroidal anti-inflammatory medications are prohibited from Day -8 until the end of the study.

Psychotherapy should not be started or stopped during a subject's participation in the study. It is acceptable for a subject already receiving psychotherapy to continue such therapy during study participation.

Concomitant medications include all medications (including drugs) taken by/administered to the subject at and after enrollment and must be documented on the Concomitant Medications eCRF. As a reminder: any change to medical history or onset of AEs must also be captured in the respective Medical History and Adverse Event eCRFs.

7 PAUSING AND STOPPING GUIDELINES AND SUBJECT DISCONTINUATION/ WITHDRAWAL

7.1 Pausing and Stopping Guidelines

Dosing of study subjects is to be **paused** if any of the following occurs:

- [redacted]
- Any emerging trend identified by ongoing review of safety data suggesting unacceptable risk to subjects (based on the joint decision between the Principal Investigator[s] and Sponsor).

Under these circumstances, clinical study dosing would be **paused** to allow for the evaluation of potential underlying causes and treatment assignments. If a clinically significant injury (or risk thereof) is directly attributed to the [redacted], further study dosing will be **stopped**. Should study dosing resume, the study would remain observer blinded for subsequent subject dosing.

The study will be **stopped** if any subject experiences clinically significant injuries including:

- [redacted]
- Any confirmed trend identified by ongoing review of safety data suggesting unacceptable risk of clinically significant injury to subjects.

In addition, if a trend in the review of the safety data suggests the risk of a clinically significant injury for subjects participating in other clinical studies evaluating the modified release

formulations, this information will be reviewed in a timely manner to understand the risks to these subjects.

7.2 Premature Withdrawal from Study

Subjects may withdraw at any time or be removed from the study at the discretion of the Investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the Investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The Investigator or Study Coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an AE.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The Investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal.

If a subject wishes to withdraw from the study after dosing with LYN-005 and before the last planned study visit, efforts should be made to obtain an X-ray in lieu of the scheduled X-rays for all subjects without fecal recovery or prior negative X-ray demonstrating GI exit of the formulation.

When a subject withdraws, or is withdrawn, from the study after dosing with any study drug, the procedures described for the EOS visit (Section 18.1.2) should be completed, if possible. If a subject withdraws or is withdrawn from the study after enrollment but before dosing with LYN-005, that subject would complete EOS visit procedures, excluding abdominal X-ray and would be considered a premature withdrawal.

8 STUDY ASSESSMENTS AND PROCEDURES

After signing informed consent, individual subject data will be collected from subjects throughout the duration of their study participation. All data collected will use deidentified subject identifiers such as Screening and enrollment/subject IDs.

This study utilizes eCRFs to collect study-related data for each subject. A qualified site staff member(s) is required to enter subject data in the eCRFs based on the medical information available in each subject's source record.

The study day and time each assessment will be performed relative to dosing is shown in the SOE (Section 18.1.1 and Section 18.1.2). However, when study assessments fall on the same time point, the site may arrange the order of procedures according to their usual practice.

8.1 Screening and Safety Assessments

8.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks, and potential benefits, and the requirements of the research to be able to make an informed decision.

Written informed consent following local IRB guidance must be obtained from each subject before conducting any study-specific procedure (i.e., all procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

Subjects who are unable to read must not be enrolled in the study.

8.1.2 PILL-5 Questionnaire

The PILL-5 Questionnaire is to be administered to subjects during Screening. Refer to Section 18.2 for details.

8.1.3 Breath Test for H. Pylori

Breath testing will be used at Screening to test for active *H. pylori* infection, and all results will be documented. Subjects will not be excluded on the basis of the rest results. Methods for evaluating the *H. pylori* breath test are described in the Laboratory Instruction Manual.

8.1.4 Medical and Psychiatric History

Medical and psychiatric history for the past 12 months will be assessed at Screening and may be reassessed o prior to dosing to determine if there are any clinically relevant updates. The assessment of medical history will include but will not be limited to any history that may be relevant to subject eligibility for study participation such as concomitant medications, previous

and ongoing illnesses or injuries, and duration of medical and psychiatric stability. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem. Relevant psychiatric history should include any psychiatric history relevant to the duration and understanding of diagnosis of mental illness and time of last hospitalization. The Investigator or delegate should update the medical and psychiatric history as needed while investigating treatment-emergent AEs.

8.1.5 Acid Reflux Severity Scale

History of moderate to severe Acid Reflux Disease, or a score of ≥ 2 as assessed by the Acid Reflux Severity Scale (ARSS) [2] at Screening is exclusionary. The ARSS is presented in Section 18.7.

8.1.6 Psychiatric and Extrapyramidal Symptom Assessment

The following table lists the typical times to complete the psychiatric and EPS assessments in this study by visit date. The longest completion time occurs at Screening, lasting ~1.5 hours for all assessments. Thereafter, the total time to complete the assessments is <30 minutes or less.

Table 8-1: Psychiatric and EPS Assessment Timing and Durations

Assessment Scale	Assessment Duration [Reference]	Screening	Day 7	Day 9	Day 15	Day 21	Day 35
PANSS	45 to 50 min [34]	√					
MINI	19 min [35]	√					
CGI-S	2 min [36] (after clinical interview)	√	√	√	√	√	√
C-SSRS	10 min [37]	√	√	√	√	√	√
ESRS	15 min [38]	√	√	√	√	√	√
Total Time		96 minutes	27 minutes	27 minutes	27 minutes	27 minutes	27 minutes

8.1.6.1 Mini International Neuropsychiatric Interview (MINI) version 7.0.2

The Mini International Neuropsychiatric Interview version 7.0.2 is a short, structured diagnostic interview that was developed to assess DSM-5 and ICD-10 psychiatric disorders. The MINI was developed for use in clinical and epidemiological studies as a short but accurate clinical assessment and has been validated against the Structured Clinical Interview for DSM diagnoses [35]. This study will utilize the MINI at Screening in order to ascertain inclusion and exclusion criteria. To assess the diagnosis of schizophrenia or schizoaffective disorder for study inclusion, the below modules of the MINI will be assessed:

- Module A: Major Depressive Episode;

- Module C: Manic and Hypomanic Episode;
- Module K: Psychotic Disorders and Mood Disorder with Psychotic Features.

Depression, mania, and hypomania are components of a diagnosis for schizophrenia/ schizoaffective disorder. However, recent major depressive episodes may be exclusionary at the discretion of the Investigator.

In addition to Modules A, C and K, several further modules of the MINI will be used to assess for excluded psychiatric conditions, as outlined in the study exclusion criteria:

- Module D: Panic Disorder;
- Module E: Agoraphobia;
- Module F: Social Anxiety Disorder;
- Module G: Obsessive-Compulsive Disorder;
- Module H: Posttraumatic Stress Disorder;
- Module N: Generalized Anxiety Disorder.

The MINI 7.0.2 will be collected at the Screening Visit and takes approximately 15 minutes to administer. The tool should be administered by the Investigator or a trained medical professional. Instructions and scales for the modules of the MINI which are to be used in this study are presented in Section 18.3.

8.1.6.2 Structured Clinical Interview-Positive and Negative Syndrome Scale (SCI-PANSS)

The PANSS is one of the most widely used measures of psychopathology of schizophrenia in clinical research, and is considered the 'gold standard' for measuring antipsychotic treatment [39]. It is a 30-item scale used to evaluate the presence, absence, and severity of Positive, Negative and General Psychopathology symptoms of schizophrenia. In this study, the PANSS will be used at Baseline in order to assess the stability and severity of subjects' disease. Each of the 30 items in the PANSS has a definition and a basis for rating, and all items are rated on a 7-point scale (1 = absent; 7 = extreme). Subjects' PANSS scores at Screening must be aligned with stable, mild to moderate disease based on values of ≤4 for individual items P1, P3, P4, P6, P7, and G14. The strengths of the PANSS include its structured interview, robust factor dimensions, reliability, the availability of detailed anchor points, and validity.

The PANSS is accompanied by a semi-structured interview, the SCI-PANSS, which will be used in this study at Screening to ensure that all content domains are covered during the interview session [40]. SCI-PANSS ratings are made after the completion of the interview, using additional reports of daily function from caregivers, family members and a review of available clinical

material as needed. Administration of the entire PANSS interview is between 45 and 50 minutes. In order to prevent subject fatigue during the interview, it is acceptable for subjects to take a short break during an assessment if needed, and then resume completion of the assessment.

The SCI-PANSS will be administered by the Investigator or a delegate trained in PANSS methodology. The core principles for the use of the PANSS, which ensure maximum reliability and inter-rater validity, should be followed in the administration of this assessment [39]. The PANSS is to be conducted at the Screening Visit and should be collected as outlined in the SCI-PANSS booklet, seen in Section 18.4.

8.1.6.3 Clinical Global Impression – Severity (CGI-S)

The CGI is widely used by clinicians in clinical studies in order to assess a subject's global functioning both prior to and after initiating treatment with a study medication [41]. It is comprised of two one-item measures; the CGI-S measures the severity of a subject's psychopathology, and the CGI-Improvement captures changes from Baseline after treatment initiation and includes an efficacy index [41, 42]. As efficacy is not assessed in this study, solely the CGI-S will be used to assess subject stability at Screening, enrollment and throughout the study.

The CGI-S consists of a single 7-point rating score of illness severity, to be completed by a clinician [41, 42]. Raters select one response based on the following question, "Considering your total clinical experience with this particular population, how mentally ill is your subject at this time?". The CGI-S has been demonstrated as a valid and user-friendly alternative to longer assessments, including the PANSS, and can be used to identify subjects in remission [43]. Scores are as follows:

1. Normal, not ill at all
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most severely ill subjects

Subjects at Screening must have a stability score of less than or equal to 4 (moderately ill) to be eligible for the study. The CGI-S will also be administered to all subjects at multiple time points throughout the study, as specified in the SOE (Section 18.1.1 and Section 18.1.2), to monitor stability and may also be administered at the discretion of the Investigator. The scale and guidelines for its administration are found in Section 18.5.

8.1.6.4 Assessment of Suicidal Ideation and Behavior – Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview-based rating scale intended to systematically assess suicidal ideation and suicidal behavior. This scale has is recognized internationally as the 'gold standard' for risk assessments in clinical studies due to its simplicity, evidence-supported validity, efficiency, and effectiveness [44]. Two versions of the C-SSRS will be utilized in this study to ensure subject safety; Baseline/Screening and Since Last Visit assessments.

At the Screening Visit, the Baseline/Screening version will be used to asses study eligibility criteria and Baseline suicidal ideation and behavior. Subjects who have made a suicide attempt within the last 2 years and subjects who, in the Investigator's judgment, pose a significant suicide risk are excluded from study participation. Subjects who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (i.e., "Yes" answers on items 4 or 5 of the C-SSRS) are also to be excluded.

Each subsequent assessment will utilize the Since Last Visit version of the C-SSRS. Subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior based on this assessment must be evaluated by a licensed and qualified mental health professional (MHP) skilled in the evaluation of suicidality in the subjects by virtue of training or experience (e.g., a psychiatrist or, licensed PhD level clinical psychologist) who will determine if it is safe for the subject to continue in the study. Specific criteria that indicate a need for such an assessment are:

- Scores reflecting suicidal ideation associated with actual intent and/or plan in the past year; i.e., a "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent";
- Subject response of "YES" to any behavioral question of the C-SSRS during a study (as compared to the previous assessment with the C-SSRS);
- In the Investigator's judgment, a risk assessment or exclusion is warranted.

Subjects who meet the above criteria must have additional assessments and have their suicidality managed appropriately by the Investigator together with the clinician/MHP (or the Investigator alone if the Investigator is a qualified mental health professional). Depending on the specifics of the situation as assessed by the Investigator and/or clinician/MHP, the subject may be discontinued from the study.

Other possible suicidality AEs or other clinical observations may, based on the judgment of the Investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS and available information; including information from Baseline/ Screening, and the clinician/MHP assessment. With the positive response to any question on the C-SSRS, the Investigator should determine whether an AE has occurred.

The C-SSRS should be collected at times specified in the SOE (Section 18.1.1 and Section 18.1.2) by an appropriately trained site staff member, as well as at any time during the study at the discretion of the Investigator. Section 18.6 presents both C-SSRS scales.

8.1.6.5 Extrapyramidal Symptoms – Extrapyramidal Symptom Rating Scale (ESRS)

Antipsychotics are a well-recognized treatment of schizophrenia, but their use is often associated with drug-induced EPS or drug-induced movement disorders (DIMD). Therefore, the ESRS will be used at Baseline and throughout the study in order to assess the severity of and monitor extrapyramidal symptoms. The ESRS was developed to assess four types of drug-induced movement disorders [45, 46]: Parkinsonism, akathisia, dystonia, and TD. The ESRS consists of several components:

- a questionnaire of EPS or DIMD;
- an examination of Parkinsonism and akathisia;
- an examination of dystonia;
- an examination of dyskinesia;
- CGI-S scales of TD, Parkinsonism, dystonia, and akathisia.

The ESRS has been validated and is widely used in clinical research on antipsychotics and to differentiate drug induced EPS and symptoms of schizophrenia [46]. It has been demonstrated to be a sensitive and specific scale [46], and that ESRS measurement of drug-induced EPS is valid and discriminative from psychiatric symptoms as measured by the PANSS [47].

Administration of the ESRS takes approximately 10-15 minutes and should be conducted by medical professionals trained on the use of the scale. The ESRS should be administered at Baseline and throughout the study as specified in the SOE (Section 18.1.1 and Section 18.1.2). ESRS examination procedures and the scale are presented in Section 18.8.

In cases of marked and clinically significant changes in EPS, the Investigator will use best clinical judgment on which treatment to consider in managing these symptoms.

8.1.7 Fecal Samples for Occult Blood

A fecal specimen will be tested at Screening for the presence of fecal occult blood, and results will be documented for all participants. A positive fecal occult blood test at Screening in subjects will be exclusionary. For enrolled subjects, fecal samples will be tested for the presence of fecal occult blood on Days 1, 7, 14, and 21, and the EOS visit.

8.1.8 General Physical Examination and Directed Physical Examination

A general physical examination will be performed at Screening, Day -2 and the EOS visit. This examination will consist, at a minimum, of a check of general appearance; auscultation of the heart, lungs, and abdomen; palpation of the abdomen; abbreviated neurological examination; and examination of other organ systems in accordance with institutional practice. Body weight is to be measured as part of the general physical examination.

Directed physical examinations will be performed on other days as indicated in the SOE (Section 18.1.1 and Section 18.1.2). This examination will consist, at a minimum, of a check of general appearance; auscultation of the heart, lungs and abdomen; and palpation of the abdomen. In addition, other organ systems may be examined at the discretion of the qualified medical professional performing the examination and as guided by interview of the subject.

Any new clinically significant abnormality detected during physical examinations and considered an AE will be captured on the AE eCRF page.

8.1.9 Vital Signs

Vital signs include measurement of systolic and diastolic blood pressure, pulse, and respiratory rate as well as body temperature. Vital signs are to be measured at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Vital signs may be measured at additional time points at the Investigator's discretion.

8.1.10 Electrocardiograms

Standard 12-lead ECGs will be performed at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2), according to the site Standard Operating Procedures, and ECG parameters will be collected in source documentation. ECGs are to be performed with the subject in a supine position for at least 5 minutes. All ECGs must be evaluated by a qualified physician for the presence of abnormalities, and findings should be classified as normal, abnormal not clinically significant or abnormal clinically significant. Additional ECGs may be performed at the discretion of the Investigator.

8.1.11 CYP2D6 Genotyping

Risperidone is primarily metabolized by CYP2D6 and genetic testing for CYP2D6 will be conducted at Screening to determine metabolizer status. To reduce the inter-subject variability in exposure of risperidone and 9-hydroxyrisperidone, subjects identified as poor metabolizers will be excluded from the study. Approximately 7 mL (minimum 3 mL) of whole blood will be obtained at Screening for CYP2D6 genetic testing.

8.1.12 Screening Serology

Blood is to be collected for serology testing including hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), and HIV, during Screening.

8.1.13 Safety Laboratory Assessments

Safety laboratory assessments will include the following parameters:

- Clinical chemistry panel
  - blood urea nitrogen (BUN) should be calculated from urea
  - includes liver function tests
  - HbA1c will be performed at Screening only
- Hematology panel
  - includes complete blood count (CBC) with differential
- Coagulation tests
- Urinalysis to be performed at Screening only, unless for pregnancy test or at Investigator discretion

Safety laboratory assessments will be performed throughout the study at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Safety Laboratory Assessments are to be reviewed by the Investigator or delegate within 24 hours of available results and prior to discharge of the subject from the inpatient unit.

For a complete list of assessments and further details relating to the collection and handling of laboratory specimens, please refer to the Laboratory Instruction Manual.

8.1.14 Prolactin

Blood samples for prolactin will be collected at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2).

8.1.15 Pregnancy Testing

Pregnancy testing in females of childbearing potential is to be performed at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Pregnancy testing is to be repeated any time pregnancy is suspected. At Screening, a serum pregnancy test is to be performed. At all time points thereafter, a urine pregnancy test may be performed.

Subjects with a positive pregnancy test during Screening are not eligible for study participation. After starting study drug, study drug is to be discontinued immediately for any subject with a positive pregnancy test, and pregnancies are to be reported and followed as described in Section 8.2.8.

8.1.16 Compliance Laboratory Assessments

Subjects will undergo testing to confirm the absence of alcohol or substance abuse at Screening, upon admission to the unit, and at any time during the study as warranted by the Investigator or study staff. In accordance with the exclusion criteria (Section 6.3) any individual who has a test

reflecting recent use of excessive alcohol or illicit substances at Screening must not be enrolled in the study.

Compliance Laboratory Assessments will include breath testing for alcohol use and urine testing for illicit substances (drugs of abuse). Analytes for the urine drug test will be specified in the Laboratory Instruction Manual.

8.2 Adverse Events and Serious Adverse Events

According to the International Conference on Harmonization (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting dated 27 October 1994, an AE is defined as follows:

8.2.1 Definition of an Adverse Event

Any untoward medical occurrence in a participation or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This definition includes onset of illness, injuries, and/or exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (i.e., through the End-of-Study visit) or terminates the study early (whichever comes first). AEs occurring after the informed consent form (ICF) is signed but prior to receiving study drug/product will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study drug will be analyzed separately from “treatment-emergent” AEs (AEs occurring after administration of study drugs) unless there is a change in severity or frequency of AEs persisting after the subject is dosed. AEs present on the first day of treatment that worsen in intensity or frequency during the treatment or post treatment periods should be reported and recorded as AEs.

Unchanged chronic conditions are not AEs and should not be recorded on the AE pages of the eCRF. These medical conditions should be documented on the appropriate page of the eCRF (medical history or physical examination). The Investigator will actively solicit this information from the subject and assess the event in terms of severity and relationship to the study treatment regimen.

Every effort should be made by the Investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page.

8.2.2 Serious Adverse Events

An AE occurring should be classified as "Serious" if it meets one of the following criteria:

1. It results in death (i.e., the AE caused or led to death).
2. It is life threatening (i.e., the AE placed the subject at immediate risk of death). This classification does not apply to an AE that hypothetically might cause death if it is more severe.
3. It requires or prolongs inpatient hospitalization (i.e., the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay). Hospitalizations for elective medical or surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion.
4. Persistent or significant disability or incapacity (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions).
5. It is a congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy).
6. It does not meet any of the above criteria but could jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.

8.2.3 Collection of Adverse Events

To prompt reporting of AEs, simple unbiased questions should be used as the initial questions at all evaluation points during the study. Whether considered related or not, all AEs are to be recorded on the eCRF page and monitored until resolution or through the end of the study.

8.2.4 Evaluation and Classification of Adverse Events

Both serious and non-serious AEs should be graded with respect to severity on the following 3-point scale and reported, in detail, on the appropriate eCRF page:

Mild: Discomfort noticed, but no disruption of normal daily activities; event usually requires no intervention.

Moderate: Discomfort sufficient to reduce or affect normal daily activities; even may require intervention.

Severe: Incapacitating, with inability to perform normal daily activities; event usually requires treatment or other intervention. Subject may not be able to continue in the study.

8.2.5 Relationship to Study Drug (Intervention)

The Investigator should evaluate the relationship of each AE to the study treatment regimen, using the following criteria:

Unrelated: Another cause of the AE is more plausible; a clinically plausible temporal sequence is inconsistent with the onset of the AE and administration of the study drug; or a causal relationship is considered biologically impossible.

Possibly related: There is a clinically plausible time sequence between onset of the AE and administration of the study drug, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. "Possibly Related" should be used when the study drug is one of several biologically plausible AE causes.

Related: The AE is clearly related to administration of the study drug.

The relationship of the study drug to an AE will be determined by the Investigator or qualified delegate.

All AEs, regardless of severity, will be monitored until resolution or until the Investigator assesses them as chronic or stable. All subjects experiencing AEs whether considered associated with the use of the study drug or not must be monitored until symptoms subside or until the Investigator determines the AE is chronic and stable and does not warrant further follow-up, or until death, in which case a full pathologist's report should be supplied, if possible.

8.2.6 Time Period and Frequency for Event Assessment and Follow-up

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented accordingly to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset, offset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until the EOS Visit. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.7 Procedures for Recording and Reporting Adverse Events

Adverse events suspected or confirmed as meeting the definition of SAE should be reported to the Lyndra Medical representative, site CRA and contract research organization (CRO) Safety Officer within 24 hours. Contact details for each will be provided in the Safety Reporting Plan.

8.2.7.1 Recording Adverse Events

All findings regarding AEs must be reported on an Adverse Events eCRF and on the SAE Reporting Form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must also be reported in the subject's source document.

To improve the quality and precision of AE data, Investigators should observe the following guidelines: laboratory, vital sign, ECG and physical examination abnormalities that are defined as clinically significant that meet the definition of an AE, are to be recorded on the AE eCRF page.

8.2.7.2 Recording and Reporting Serious Adverse Events

Specific instructions and contact details for collecting and reporting SAEs to the Sponsor will be provided to the Investigator and site staff. All SAEs are also to be documented on the Adverse Events eCRF. Any medication or other therapeutic measures used to treat the SAE will be recorded on the appropriate eCRF(s) in addition to the outcome of the SAE.

After receipt of the initial report, representatives of the Sponsor or its designee will contact the Investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the Investigator in accordance with institutional policy/regulatory requirements or within 24 hours of their knowledge of the event. Adequate documentation of this notification must be provided to the Sponsor.

The Sponsor or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse drug reactions (also known as SUSARs) to the Regulatory Authority and, where applicable, the IRB. If a SUSAR or other safety signal relating to use of the study drugs in another research related activity is reported to the Sponsor or its designee, the Sponsor will communicate this information to the Investigator and the Investigator will be responsible for submitting this information, where applicable, to the IRB and other relevant authorities.

8.2.7.3 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period but considered to be caused by the study drug must be reported according to the procedures specified above (Section 8.2.7) and in the Safety Reporting Plan. These SAEs will be processed by the Sponsor or a designee during the study, until the last subject enrolled in the study completes the last study visit. After that point, the Lyndra Medical Monitor should be contacted with any suspected or possibly drug related SAE experienced by an individual participating in this study.

8.2.8 Reporting of Pregnancies

To ensure subjects' safety, each pregnancy in a subject which occurs during the study (from administration of study drug through the EOS) must be reported to the Sponsor within 24 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data, inclusive of initial reporting and follow-up information regarding the course of the pregnancy and the outcome, must be recorded on a Pregnancy Reporting Form and reported to the Sponsor. Instructions and contact details for submitting the Pregnancy Reporting Forms will be provided to the Investigator in the Safety Reporting Plan.

Any pregnancy outcome meeting the definition of a SAE (Section 8.2.2) must also be reported on the SAE Reporting Form.

8.3 Gastrointestinal Imaging (X-ray)

Abdominal X-rays are to be performed in all subjects where specified in the SOE (Section 18.1.1 and Section 18.1.2). Refer to the Study Imaging Manual for details regarding the procedures for abdominal X-ray.

8.4 Pharmacokinetics

At each time point specified in the SOE (Section 18.1.1 and Section 18.1.2), 2 mL of blood for PK evaluation will be drawn into a designated and labelled collection tube and processed for storage and shipment, as described in the Laboratory Instruction Manual. The windows around sample collection at each time point, as designated in the SOE, are to be observed.

Analysis of risperidone and 9-hydroxyrisperidone will be performed using a validated assay. Time and date of the PK assessment will be recorded on the eCRF for each blood sample.

Refer to the Laboratory Instruction Manual for further details.

8.5 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations as no authorized deviations are permitted. If the Investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB and health authorities it cannot be implemented.

Pregnancy during the study is a protocol deviation (Section 8.2.8).

A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Protocol deviations may be defined as exclusionary from the analysis according to protocol objectives and endpoints. Prior to the final analysis of the study data, subjects with exclusionary protocol deviations will be identified and specified for each analysis set and documented. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g., early termination.

9 STATISTICS AND DATA MANAGEMENT

9.1 General Procedures

A statistical analysis plan (SAP), providing details about the specific planned analyses and potential hypothesis tests, will be prepared and approved prior to study database lock. Both descriptive and inferential statistical methods may be used to fully explore the preliminary data. In addition, post hoc analyses may be performed that are not described in the SAP but will be described fully in the CSR where presented.

Summary statistics will be presented by dose group, dose period, and overall. Unless otherwise stated, categorical data will be presented using frequency counts and percentages and continuous data will be presented by number of subjects reporting (n), means, standard deviations (SD), median, minimum, and maximum. Geometric means and coefficient of variations (%CV) will be presented in addition for PK data.

9.2 Data Management

Data management will be performed in accordance with clinical standards.

AEs and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v22.0 or a more recent version) and the World Health Organization Drug Dictionary Enhanced (WHO DDE) Drug Reference List (2018), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and hematology data (and other safety laboratory data) will be collected by a central laboratory and stored electronically in their clinical pathology system. All laboratory data that are transferred will be reconciled, queried, and answered by the site laboratory and clinical staff before the database can be closed. The database will be locked when all criteria listed in the Data Management Plan are met. Further details are addressed in the Data Management Plan.

SAS 9.4 or higher (SAS Institute Inc., Cary NC USA) will be used for generating individual data listings, summary tables and associated figures and for performing statistical analyses.

9.3 Sample Size

This study is exploratory in nature and therefore not designed to test hypotheses.

The sample size of 32 (24 assigned to LYN-005 and 8 assigned to IR risperidone) is driven by clinical rather than statistical considerations for providing data in the evaluation of the endpoints.

9.4 Statistical Methods

9.4.1 Analysis Sets

The following analysis sets will be defined:

Enrolled Set: The Enrolled Set is defined as all subjects who are enrolled in the study and admitted to the research unit on Day -2. The Enrolled Set will be the primary set used for disposition, demographic and baseline characteristic data reporting.

Safety Set: The Safety Set is defined as all enrolled subjects who are randomized to study drug (LYN-005 14mg/28mg or IR Risperidone 2mg/4mg) and receive at least one dose of randomized study drug. Subjects will be reported according to the treatment received. The Safety Set will be the primary safety analysis population.

PK Set: The PK Set is defined as all enrolled subjects who receive a dose of LYN 005 and have least 1 post-dose quantifiable (or evaluable) PK concentration data.

Additional analysis sets, if identified, will be specified in the SAP.

9.4.2 Statistical Methods

Safety endpoint data will be descriptive in nature and summarized by dose group, dose period and overall. Listings will also be presented. The Safety Set will be the primary population for analysis unless otherwise stated. Plasma concentration data for risperidone and 9-hydroxyrisperidone separately and combined as active moiety will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration-time data obtained will be performed using appropriate non-compartmental analysis to obtain estimates of the standard PK parameters.

The PK of LYN-005 relative to IR at 2 dose levels will be determined.

There are no pharmacodynamic endpoints in this study.

9.4.3 Analysis of Safety - Analysis of Adverse Events

This analysis applies to all AEs occurring during the study, judged either as related, possibly related, or not related to study drug by the Investigator, recorded on the AE eCRF, with a start date on or after the date of dose of randomized study drug (i.e., TEAEs). AEs starting prior to administration of randomized study drug (non-treatment emergent AEs) will be listed for subjects in the Enrolled Set. The original verbatim terms used by Investigators to identify AE in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

Analyses of TEAEs will be summarized by dose group, dose period, and overall. Events will also be included in subject listing by dose group and dose period.

Further details may be found in the SAP.

9.4.4 Analyses of Pharmacokinetics

PK concentrations will be summarized descriptively for both IR risperidone and LYN-005. PK parameters will also be presented by dose group, and plots of concentration-time data and C_{max} and AUC will be provided. Further analyses to assess PK levels in LYN-005 relative to IR risperidone will be explored and detailed in the SAP.

9.4.5 Demographic and Baseline Characteristics

Descriptive statistics will be summarized for the Enrolled Set. Demographic and baseline characteristic data includes age, gender, ethnic group/race, height, weight, BMI at enrollment will be calculated.

9.5 Assessment of Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Protocol deviations may be defined as exclusionary from the analysis according to protocol objectives and endpoints. Prior to the final analysis of the study data, all protocol deviations will be reviewed by the Sponsor Medical representatives. Subjects with exclusionary protocol deviations will be identified, specified, and documented. Protocol deviations will be listed.

9.6 Safety Reviews

There is a planned safety review by the Investigator and Medical Monitor on interim blinded PK data after PK data through Day 14 are available from 12 subjects. Blinded safety data will also be reviewed at this interim look and will include adverse events, laboratory data, suicidality, and illness severity. Additionally, the PI or Sponsor may request an ad hoc review of safety information, e.g., serious adverse events, at any time during the study.

9.7 Data Entry and Management

In this study, all requested data will be entered onto eCRFs in a timely manner after each assessment by the Investigator and/or the Investigator's dedicated site staff. Data entered onto eCRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA, 1997) [48]. The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor or delegate prior to activation for data entry by sites. The Investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Additional data collection forms (e.g., Pregnancy and SAE Reporting Forms) will be provided to the site by the Sponsor or delegate, should a pregnancy or SAE occur. Instructions on how to complete and archive these forms will be provided to the Investigator by the Sponsor or delegate prior to the start of the study.

9.8 Data Clarification

As part of the conduct of the study, the Sponsor may have questions about the data entered by the site, referred to as queries. The Clinical Research Associates and Data Management are the only parties that can generate a query, and they will generate queries on behalf of any other data reviewer with "read only" access to the EDC. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed eCRF, the Investigator must confirm and endorse the changes.

9.9 Data Protection

The Sponsor respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, Good Clinical Practices, the relevant ICH guidelines, the ethical principles that have their origins in the Declaration of Helsinki, and in accordance with the applicable regulatory requirements in the country where this study will be executed. As required by the Declaration of Helsinki; the study protocol, amendments, and, Informed Consent Form/Subject Information Sheet will be reviewed and approved by the study center's IRB.

10.2 Sponsor Medical Monitor

The Sponsor's Medical Monitor will be available to the Investigator for discussion of any safety events or findings. The Investigator and Lyndra Medical Monitor may review AE listings on a weekly basis to evaluate any trends until each subject reaches Day 35. Additionally, the Lyndra Medical Monitor may be engaged at an ad hoc basis at any time to review SAEs, any events that may trigger pausing or halting the study and will review the safety data for the final reporting of the study data.

10.3 Investigator and Institutional Review Board Responsibilities

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. Properly constituted IRB is defined in ICH Guideline for Good Clinical Practice [49]. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to the Sponsor or delegate before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor (or representative) monitors, auditors, other designated agents of the Sponsor, IRB, and regulatory authorities, as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

At the site level, the Investigator must ensure that any person(s) assisting with the study are adequately trained and informed about the protocol, the investigational product(s), and their study-related duties and functions, including study-related medical decisions and medical care of subjects experiencing any AE related to the study. Additional responsibilities include maintaining a list of appropriately qualified persons to whom s/he has delegated significant study-related duties, and ensuring that s/he has the capability, time and staffing to recruit the required number of suitable subjects within the recruitment period and properly conduct and complete the study within the agreed study period. When required, and if permission is given by the subject, the Investigator will ensure that the subject's primary healthcare provider is informed of the individual's participation in the study.

The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in staff, change of telephone number[s]). In addition, the Investigator or delegate Investigator, should document and explain any deviation from the approved protocol. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Sponsor for agreement, thereafter to the IRB for review and approval/favorable opinion, and if applicable, to the regulatory authority(ies).

10.4 Subject Information and Informed Consent

The informed consent and subject information sheets used for this study will meet requirements for subject information, as outlined ICH Guideline E6 and the Declaration of Helsinki.

Prior to the start of the study, the proposed ICF must be jointly agreed upon by the site and Sponsor or its delegate prior to submission to the IRB and a copy of the approved version must be provided to the Sponsor or delegate after IRB approval.

Eligible subjects may only be included in the study after providing written informed consent or assent. Before the start of the study, the Investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB. This review and approval will be documented and stored with other study documents. The Investigator or delegate must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject. The subject be allowed ample time to ask about the details of the study and to decide as to whether or not to participate in the study. The subject must sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted.

The informed consent process may be conducted up to 5 weeks prior to enrollment on Day -2.

Men and women of childbearing potential should be reminded of the requirement to use a highly effective method of contraception throughout the duration of the study, which should be recorded in the source documentation. Women of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that to participate in the study, they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study.

11 RECORDS MANAGEMENT

11.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The documents that will serve as source documents will be agreed between the Sponsor or its delegate and Investigator or delegate and specified in the source document agreement prior to subject enrollment.

In addition, source documentation must include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of AEs, documentation of prior/concomitant medication/drugs, study drug receipt/dispensing/return records, study drug administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to his or her own medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an AE, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the AE eCRF.

11.2 Study Files and Record Retention

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential Documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12 AUDITING AND MONITORING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated CRO standard operating procedures and applicable regulatory requirements (e.g., TGA and ICH guidelines).

Prior to enrollment of the first study healthy volunteer, the Sponsor or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. Electronic CRFs supplied by the Sponsor or delegate must be completed for each enrolled subject and limited data for all screened subjects who have swallowing questionnaire and imaging data available. Data and documents for all enrolled subjects will be checked by the Sponsor and/or monitor.

Prior to enrollment of the first study volunteer, the Sponsor or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how remote and/or on-site monitoring, including clinical specimen reconciliation, will be performed for the study. Study progress will be monitored by the Sponsor or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents, and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), Good Clinical Practice (GCP) and applicable regulatory requirements.

Contact details for the Sponsor or its designee involved in study monitoring will be provided to the Investigator in the Clinical Monitoring Plan. Study data recorded on eCRFs will be verified by checking the eCRF entries against source documents to ensure data completeness and accuracy as required by study protocol.

Data verification may also be performed through remote and/or centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the Investigator Site File, pharmacy records, and Informed Consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the Clinical Monitoring Plan, except in case of emergency.

The Investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification, and copying, as required by regulations, by officials of the regulatory health authorities and/or IRBs. The Investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

13 AMENDMENTS

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

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

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

14 STUDY REPORT, PUBLICATIONS, DATA POSTING

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

The Sponsor assures that the key design elements of this protocol will be posted in compliance with current regulations. The Sponsor also assures that key results of this clinical study will be posted within the required time frame from the end of study as defined in Section 5.4.

15 STUDY DISCONTINUATION

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

16 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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18 APPENDICES

18.1 Schedules of Events

18.1.1 Schedule of Events LYN-005-C-004: Screening and LYN-005 Doses 1 and 2

Visit Name		Screening Visit	Run-In (10 days)[o]	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient Visits
Subject Status		Outpatient		Inpatient Stay 1											
Study Day		- 21 to -14	-13 to -3	-2	-1	1[a]	2	3	4	5	6	7	8	9	10-13
Study Event	**Section**														
Study Treatment LYN-005 (N=24)															
Oral antipsychotic	4.1.1	X													
IR risperidone run-in[b]	4.1.2		X	X	X										
Randomization	4.1.4					X									
00EL placebo	6.3.3					X	X	X	X	X	X	X	X	X	X
LYN-005	6.3.3					X							X		
Study Treatment IR (00EL) risperidone (N=8)															
Oral antipsychotic	4.1.1	X													
IR risperidone run-in	4.1.2		X	X	X										
Randomization	4.1.4					X									
00EL placebo	6.3.3					X							X		
00EL risperidone	6.3.3					X	X	X	X	X	X	X	X	X	X
Screening and Safety Assessments															
Informed Consent[c]	8.1.1	X													
PILL-5 Questionnaire	8.1.2	X													
H. Pylori breath test	8.1.3	X													
Medical History	8.1.4	X													
MINI	8.1.6.1	X													
PANSS	8.1.6.2	X													

Visit Name		Screening Visit	Run-In (10 days)[o]	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient Visits
Subject Status		Outpatient		Inpatient Stay 1											
Study Day		- 21 to -14	-13 to -3	-2	-1	1[a]	2	3	4	5	6	7	8	9	10-13
CGI-S	8.1.6.3	X				X						X		X	
C-SSRS	8.1.6.4	X				X						X		X	
ESRS	8.1.6.5	X				X						X		X	
Fecal Occult Blood	8.1.7	X				X						X			
Physical Examination[d]	8.1.8	X		X	X	X							X		X
Vital Signs [e]	8.1.9	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram [f]	8.1.10	X	X	X	X	X			X				X		
CYP2D6 Genotype	8.1.11	X													
Serology Assessments [g]	8.1.12	X													
Safety Laboratory Assessments [h]	8.1.13	X	X	X	X				X				X		
Prolactin	8.1.14	X				X							X		
Pregnancy Test [i]	8.1.15	X				X							X		
Compliance Lab Assessments	8.1.16	X	X	X											
Inclusion/ Exclusion Criteria	5.1, 5.2	X		X											
Acid Reflux Symptom Severity Scale	8.1.5	X													
Solicitation of AEs	8.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GI Imaging (On Study)															
Abdominal X-ray	8.3											X			
Pharmacokinetic Assessments (see Note)[j]															
Blood Sample/PK	8.4			S1[k]	S2[l]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S4[n]	S3[m]	S3[m]

Visit Name	Screening Visit	Run-In (10 days)[o]	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient Visits
Subject Status	**Outpatient**		**Inpatient Stay 1**											
Study Day	**- 21 to -14**	**-13 to -3**	**-2**	**-1**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10-13**

AEs = Adverse Events; CGI-S = Clinical Global Impression – Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = Cytochrome P450; ESRS = Extrapyramidal Symptom Rating Scale; GI = Gastrointestinal; PK = Pharmacokinetics; RSP = Risperidone; PANSS = Positive and Negative Syndrome Scale.

General Notes:

a. Prior to dosing with LYN-005 Days 1, 8, 15, and 22, vital signs, ECG, PE, safety laboratory tests, AEs, CGI-S, ESRS will be collected. After dosing, safety assessments will be performed, including vital signs, directed physical examination, adverse event, and concomitant medication collection.

b. Subjects must receive at least 5 IR risperidone doses during the Run-in period, 3 in the outpatient setting and 2 in the inpatient setting.

c. Consent form is signed prior to performing any study related procedures.

d. General physical examinations will occur at Screening and Days -2; all other exams will be directed physical examinations.

e. Vital signs will be collected prior to (-60 min) and 12 hours (±45 min) after IR risperidone dosing on Days -2 to Day -1 and on Day 1 at prior to dosing and 4, 8, 12, 24 and 36 hours post dose. The timing and addition of further assessments will occur at the Investigator's discretion.

f. Electrocardiograms should be collected 4 hours (±15 mins) after IR dosing on Day -1, prior to and 4 hours (±15 mins) after dosing with LYN-005 and additionally where indicated.

g. Serological laboratory tests are for Hepatitis B, and C and HIV.

h. All safety laboratory assessments include serum chemistry, hematology, and coagulation. Measurement of HbA1c concentration only occurs at Screening.

i. Required in women of childbearing potential only.

j. Schedule for Pharmacokinetic (PK) collection:

k. S1: Date and time of last dose is to be recorded, and PK samples to be collected upon arrival at unit, 12 pm and 6 pm (±30 min) on Day -2, prior to administration of half the regimen of daily IR risperidone in the evening (i.e. either 1 or 2 mg).

l. S2: On the morning of Day -1, a dose of IR risperidone (2 or 4 mg based on dose allocation) will be administered to each subject after fasting with PK samples collected prior to and at 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 min), 16 h (±30 min), and 24 h (±30 min) after dosing. (The 24-hour post-dose sample is equivalent to the LYN-005 pre-dose sample.)

m. S3: PK samples to be collected just prior to and following LYN-005 administration or 00EL placebo Day 1 at 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 min) post dose and every 12 hours (±30) thereafter through Day 7, and again on Day 9 and on the morning of Day 10.

n. S4: On Day 8, a PK sample will be taken prior to the administration of LYN-005 administration or 00EL placebo and at hours 4 and 8 (±15 min).

o. Assessments during the run-in period (Days -13 to -3) may occur at any timepoint/visit during this period, at Investigator discretion.

18.1.2 Schedule of Events LYN-005-C-004: LYN-005 Dose 3 through Study Completion

Visit Name		LYN-005 Dose 3						Resume Prior APD		EOS[a]
Subject Status		Inpatient Stay 2			Outpatient					
Study Day		14[b]	15	16	17	18	21	22	23	35
Window		-	-	-	-	+1	±1	±1	±1	±1
Study Event	**Section**									
Study Treatment: LYN-005 (N=24)										
Oral antipsychotic	4.1.1							X	X	X
IR risperidone run-in	4.1.2									
Randomization	4.1.4									
00EL placebo	6.3.3	X	X	X	X	X	X			
LYN-005	6.3.3		X							
Study Treatment: IR (00EL) risperidone (N=8)										
Oral antipsychotic	4.1.1							X	X	X
IR risperidone run-in	4.1.2									
Randomization	4.1.4									
00EL placebo	6.3.3		X							
00EL risperidone	6.3.3	X	X	X	X	X	X			
Safety Assessment										
Informed Consent	8.1.1									
Medical History	8.1.2									
PILL-5 Questionnaire	8.1.3									
H. Pylori breath test	8.1.4									
MINI	8.1.6.1									
PANSS	8.1.6.2									
CGI-S	8.1.6.3		X				X			X
C-SSRS	8.1.6.4		X				X			X
ESRS	8.1.6.5		X				X			X

Visit Name		LYN-005 Dose 3						Resume Prior APD		EOS[a]
Subject Status		Inpatient Stay 2			Outpatient					
Study Day		14[b]	15	16	17	18	21	22	23	35
Window		-	-	-	-	+1	±1	±1	±1	±1
Study Event	**Section**									
Fecal Occult Blood	8.1.7	X					X			X
Physical Examination[c]	8.1.8		X		X				X	X
Vital Signs	8.1.9		X	X	X	X	X	X	X	X
Electrocardiogram[d]	8.1.10		X		X			X		
CYP2D6 Genotype	8.1.11									
Serology Assessments	8.1.12									
Safety Laboratory Assessments [e]	8.1.13		X	X						X
Prolactin	8.1.14		X				X			X
Pregnancy Test [f]	8.1.15		X							
Compliance Laboratory Assessments	8.1.16				X					
Inclusion/ Exclusion Criteria	5.1, 5.2									
Solicitation of AEs	8.2.3	X	X	X	X	X	X	X	X	X
Concomitant Medications	6.5	X	X	X	X	X	X	X	X	X
GI Imaging (on study)										
Abdominal X-ray	8.3	X					X			X
Pharmacokinetics Assessments (see Note)[g]										
Blood Sample/PK	8.4	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]		

AEs = Adverse Events; CGI-S = Clinical Global Impression – Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = Cytochrome P450; ESRS = Extrapyramidal Symptom Rating Scale; GI = Gastrointestinal; PK = Pharmacokinetics; RSP = Risperidone; PANSS = Positive and Negative Syndrome Scale.

General Notes:

a. Final outpatient clinic visit will occur on Day 35 (EOS Visit).

b. Subjects will return to clinic on the evening of Day 14 to prepare for dosing on the morning of Day 15.

c. General physical examinations will occur on Day 35; all other examinations will be directed physical examinations.

d. 4 hours (±15 mins) after IR dosing on Day -1, prior to and 4 hours (±15 mins) after dosing with LYN-005 and additionally where indicated.

e. All safety laboratory assessments include serum chemistry, hematology, and coagulation. Measurement of HbA1c concentration only occurs at Screening.

Visit Name		LYN-005 Dose 3						Resume Prior APD		EOS[a]
Subject Status		Inpatient Stay 2			Outpatient					
Study Day		14[b]	15	16	17	18	21	22	23	35
Window		-	-	-	-	+1	±1	±1	±1	±1
Study Event	Section									

f. Required in women of childbearing potential only.

g. Schedule for Pharmacokinetic (PK) collection:

h. S5: On Day 14, the subject will return to the clinic to prepare for an inpatient stay through Day 16. A PK sample will be collected upon arrival in the inpatient unit on Day 14. On Day 15, PK samples will be collected pre-dose and at 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 mi), and 24 h (±30 min) (i.e., Day 16). Single samples also are to be collected on Days 17, 18, 21, and 22; on these study days, the sample is to be collected at the same time of day as the 24-hour post-dose sample on Day 16.

18.2 PILL-5 Questionnaire

The italicized text below is the questionnaire, which is to be administered to the individual during the Screening process.

The individual should complete this questionnaire independently and should answer all questions. If the subject has not experienced pill swallowing in the past week, they should answer for a previous week where they have taken oral medications. After the individual has provided his/her answers, the total score is achieved by adding together the numerical value from each question. Subjects with a PILL-5 questionnaire score of 5 or greater are to be excluded.

These are statements that many people have used to describe their problems swallowing pills. Please circle the response that indicates how frequently you had the same experience in the past week. If you do not have any problem swallowing pills, please circle zero (0) in response to these statements.

Please circle the response that indicates how frequently you experience these symptoms.

	Never	***Almost Never***	***Sometimes***	***Almost Always***	***Always***
1. Pills stick in my throat	0	1	2	3	4
2. Pills stick in my chest	0	1	2	3	4
3. I have a fear of swallowing pills	0	1	2	3	4
4. My problem swallowing pills interferes with my ability to take medication	0	1	2	3	4
5. I can't take my pills without crushing, coating, or using other forms of assistance	0	1	2	3	4

18.3 Mini International Neuropsychiatric Interview (MINI) version 7.0.2

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	ICD 10 CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	F32 x	☐
		Past	☐	F32 x	☐
		Recurrent	☐	F33 x	☐
B	SUICIDALITY	Current (Past Month)	☐		☐
		L fet me attempt	☐	☐ Low ☐ Moderate ☐ H gh	☐
	SUICIDE BEHAVIOR DISORDER	Current	☐	(n Past Year)	☐
		In ear y rem ss on	☐	(1 2 Years Ago)	☐
C	MANIC EPISODE	Current	☐		
		Past	☐		
	HYPOMANIC EPISODE	Current	☐		
		Past	☐	☐ Not Exp ored	
	BIPOLAR I DISORDER	Current	☐	F31 0 F31 76	☐
		Past	☐	F31 0 F31 76	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31 2/31 5/F31 64	☐
		Past	☐	F31 2/31 5/F31 64	☐
	BIPOLAR II DISORDER	Current	☐	F31 81	☐
		Past	☐	F31 81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31 89	☐
		Past	☐	F31 89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41 0	☐
		L fet me	☐	F40 0	☐
E	AGORAPHOBIA	Current	☐	F40 00	☐
F	SOCIAL ANXIETY DISORDER (Soc a Phob a)	Current (Past Month)	☐	F40 10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42 2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43 10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10 10 - F10 21	☐
J	SUBSTANCE USE DISORDER (Non-a coho)	Past 12 Months	☐	F11 10 - F19 21	☐

K	ANY PSYCHOTIC DISORDER	Current	☐	F20 81 F29	☐
		L fet me	☐	F20 81 F29	☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F32 3/F33 3	☐
		Past	☐	F32 3/F33 3	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31 2/F31 5/F31 64	☐
		Past	☐	F31 2/F31 5/F31 64	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50 01/F50 02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50 2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50 81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41 1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	L fet me	☐	F60 2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAP TALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis or diagnoses is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any quest ons, suggest ons, need for a tra n ng sess on or nformat on about updates of the M.I.N.I., p ease contact:
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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day, for two weeks?	NO	YES
		F NO, CODE NO TO **A1b**: F **YES** ASK:		
	b	For the past two weeks, were you depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		F NO, CODE NO TO **A2b**: F **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
		➡ S **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 F **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMAT C **PAST** EP SODE, OTHERW SE
F **A1b** AND **A2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMAT C **PAST** EP SODE.

	Over that two-week period, when you felt depressed or uninterested: a	Past 2 Weeks		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? F **YES** TO E THER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
	F **YES**, ASK FOR EXAMPLES. LOOK FOR DELUS ONS OF FA LURE, OF NADEQUACY, OF RU N OR OF GU LT, OR OF NEED NG PUN SHMENT OR DELUS ONS OF D SEASE OR DEATH OR N H L ST C OR SOMAT C DELUS ONS. THE EXAMPLES ARE CONS STENT W TH A DELUS ONAL DEA. Current Ep sode ☐ No ☐ Yes Past Ep sode ☐ No ☐ Yes				
f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly think about death **(FEAR OF DYING DOES NOT COUNT HERE)**, or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? **IF YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4	Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest?

N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND S **A4** CODED **YES** FOR THAT T ME FRAME?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPEC FY F THE EP SODE S CURRENT AND / OR PAST.

F **A5** S CODED **YES,** CODE **YES** FOR RECURRENT.

NO **YES**

MAJOR DEPRESSIVE EPISODE

CURRENT ☐
PAST ☐
RECURRENT ☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

TH S QUEST ON S NOT A CR TER ON FOR B POLAR D SORDER, BUT S ASKED TO NCREASE THE CL N C AN'S V G LANCE ABOUT THE R SK FOR B POLAR D SORDER.

IF YES, PLEASE SPEC FY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' and so active or full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

F PAT ENT S PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'H GH' OR 'HYPER', CLAR FY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy or increased activity; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE **NO** TO **C1b**: **IF YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE **NO** TO **C2b**: **IF YES** ASK:

b Are you currently feeling persistently irritable? NO YES
➡

S **C1a** OR **C2a** CODED **YES**? NO YES

C3 F **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** EP SODE F RST AND THEN THE MOST SYMPTOMAT C **PAST** EP SODE, OTHERW SE
F **C1b** AND **C2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMAT C **PAST** EP SODE

WHEN EXPLOR NG THE CURRENT EP SODE, PREFACE EACH QUEST ON AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLOR NG THE PAST EP SODE, PREFACE EACH QUEST ON AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most irritable, did you:

	Current Episode		Past Episode	
a Feel that you could do things others couldn't do, or that you were an especially important person? **IF YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONS STENT W TH A DELUS ONAL DEA. Current Ep sode ☐ No ☐ Yes; Past Ep sode ☐ No ☐ Yes	NO	YES	NO	YES
b Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless? This increase in activity may be with or without a purpose.	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 SUMMARY: WHEN RAT NG CURRENT EP SODE: NO YES NO YES

F **C1b** S **NO,** ARE **4** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

F **C1b** S **YES**, ARE **3** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

WHEN RAT NG PAST EP SODE:

F **C1a** S **NO**, ARE **4** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

F **C1a** S **YES**, ARE **3** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

CODE **YES** ONLY F THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DUR NG THE SAME T ME PER OD.

RULE: ELAT ON/EXPANS VENESS REQU RES ONLY **3** OF THE **C3** SYMPTOMS, WH LE RR TABLE MOOD ALONE REQU RES **4** OF THE **C3** SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS TH S DURAT ON FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 consecutive days or less	☐	☐
b)	4, 5 or 6 consecutive days or more	☐	☐
c)	7 consecutive days or more	☐	☐

C5	Were you hospitalized for these problems?	NO	YES	NO	YES
	IF YES, C RCLE **YES** N MAN C EP SODE FOR THAT T ME FRAME AND GO TO **C7**.				
C6	Did these symptoms cause significant problems at home, at work, socially, in your relationships, at school or in some other important way?	NO	YES	NO	YES
C7	Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are?	NO	YES	NO	YES

ARE **C3 SUMMARY** AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOT C FEATURE N **K1** THROUGH **K8**) CODED **YES**?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPEC FY F THE EP SODE S CURRENT AND / OR PAST.

NO **YES**

MANIC EPISODE

CURRENT ☐

PAST ☐

IS **C3 SUMMARY** CODED **YES** AND ARE **C5** AND **C6** CODED **NO** AND **C7** CODED **YES**, AND S E THER **C4b** OR **C4c** CODED **YES**?

AND

S "RULE OUT ORGAN C CAUSE **(O2 SUMMARY)**" CODED **YES**?

AND

ARE **ALL** PSYCHOT C FEATURES N **K1** THROUGH **K8** CODED **NO**?

SPEC FY F THE EP SODE S CURRENT AND / OR PAST.

F **YES** TO CURRENT MAN C EP SODE, THEN CODE CURRENT HYPOMAN C EP SODE AS **NO**.

F **YES** TO PAST MAN C EP SODE, THEN CODE PAST HYPOMAN C EP SODE AS **NOT EXPLORED**.

HYPOMANIC EPISODE

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

ARE **C3 SUMMARY** AND **C4a** CODED **YES** AND S **C5** CODED **NO**?

SPEC FY F THE EP SODE S CURRENT AND / OR PAST.

F **YES** TO CURRENT MAN C EP SODE OR HYPOMAN C EP SODE, THEN CODE CURRENT HYPOMAN C SYMPTOMS AS **NO.**

F **YES** TO PAST MAN C EP SODE OR **YES** TO PAST HYPOMAN C EP SODE, THEN CODE PAST HYPOMAN C SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

C8

a) F MAN C EP SODE S POS T VE FOR E THER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) F MAN C OR HYPOMAN C EP SODE S POS T VE FOR E THER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting 4 days or more (**C4b**) in your lifetime (including the current episode)? NO YES

c) F THE PAST "HYPOMAN C SYMPTOMS" CATEGORY S CODED POS T VE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

D. PANIC DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, very frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make any significant change in your behavior because of the attacks (e.g., avoiding unfamiliar situations, or avoiding leaving your house or shopping alone, or doing things to avoid having a panic attack or visiting your doctor or the emergency room more frequently)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing or a smothering sensation?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or feel faint?	NO	YES
	i	Did you have hot flushes or chills?	NO	YES
	j	Did you have tingling or numbness in parts of your body?	NO	YES
	k	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	l	Did you fear that you were losing control or going crazy?	NO	YES
	m	Did you fear that you were dying?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**?	➡ NO	YES ***PANIC DISORDER LIFETIME***
D6		In the past month did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES ***PANIC DISORDER CURRENT***

S E THER **D5** OR **D6** CODED **YES**?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPEC FY F THE EP SODE S CURRENT AND / OR L FET ME.

NO	**YES**
PANIC DISORDER	
LIFETIME	☐
CURRENT	☐

E. AGORAPHOBIA

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult if you had a panic attack or panic-like or embarrassing symptoms, like: being in a crowd, or standing in a line (queue), being in an open space or when crossing a bridge, being in an enclosed space, when you are alone away from home, or alone at home, or traveling in a bus, train or car or using public transportation?	➡ NO	YES
	ARE **2** OR MORE OF THE ABOVE S TUAT ONS N **E1** CODED **YES**?	➡ NO	YES
E2	Do these situations almost always bring on fear or anxiety?	➡ NO	YES
E3	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
E4	Is this fear or anxiety excessive or out of proportion to the real danger in the situation?	➡ NO	YES
E5	Did this avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
E6	Did these symptoms cause significant distress or problems at home, at work, socially, at school or in some other important way?	➡ NO	YES

S **E6** CODED **YES**?

NO	**YES**
AGORAPHOBIA CURRENT	

F. SOCIAL ANXIETY DISORDER (Social Phobia)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	➡ NO	YES

EXAMPLES OF SUCH SOC AL S TUAT ONS TYP CALLY NCLUDE

- N T AT NG OR MA NTA N NG A CONVERSAT ON,
- PART C PAT NG N SMALL GROUPS,
- DAT NG,
- SPEAK NG TO AUTHOR TY F GURES,
- ATTEND NG PART ES,
- PUBL C SPEAK NG,
- EAT NG N FRONT OF OTHERS,
- PERFORM NG N FRONT OF OTHERS,
- UR NAT NG N A PUBL C WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	➡ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	➡ NO	YES

S **F6** CODED **YES**?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

NOTE TO CL N C AN: PLEASE SPEC FY F THE SUBJECT'S FEARS ARE RESTR CTED TO SPEAK NG OR PERFORM NG N PUBL C.

NO **YES**

SOCIAL ANXIETY DISORDER
(Social Phobia)
CURRENT

RESTRICTED TO PERFORMANCE SAD ONLY ☐

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

G1a	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** religious obsessions.)	NO YES ↓ SK P TO **G3a**
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? (DO NOT NCLUDE S MPLY EXCESS VE WORR ES ABOUT REAL L FE PROBLEMS. DO NOT NCLUDE OBSESS ONS D RECTLY RELATED TO HOARD NG, HA R PULL NG, SK N P CK NG, BODY DYSMORPH C D SORDER, EAT NG D SORDERS, SEXUAL DEV AT ONS, PATHOLOG CAL GAMBL NG, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PAT ENT MAY DER VE PLEASURE FROM THE ACT V TY AND MAY WANT TO RES ST T ONLY BECAUSE OF TS NEGAT VE CONSEQUENCES.)	NO YES ↓ SK P TO **G3a**
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES **obsessions**
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES **compulsions**

ARE (**G1a** AND **G1b** AND **G2**) OR (**G3a** AND **G3b**) CODED **YES**?

➡
NO YES

G4 In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?
(CHECK FOR ANY OBSESS VE-COMPULS VE SYMPTOMS START NG W TH N 3 WEEKS OF AN NFECT ON)

SPEC FY THE LEVEL OF NS GHT AND F THE EP SODE S T C-RELATED.

NO **YES**

O.C.D. CURRENT

INSIGHT:

- GOOD OR FAIR ☐
- POOR ☐
- ABSENT ☐
- DELUSIONAL ☐

- TIC-RELATED ☐

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury or sexual violence to you or someone else? EXAMPLES OF TRAUMAT C EVENTS NCLUDE: SER OUS ACC DENTS, SEXUAL OR PHYS CAL ASSAULT, A TERROR ST ATTACK, BE NG HELD HOSTAGE, K DNAPP NG, F RE, D SCOVER NG A BODY, WAR, OR NATURAL D SASTER, W TNESS NG THE V OLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A L FE-THREATEN NG LLNESS.	➡ NO	YES
H2	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	➡ NO	YES

H3	**In the past month:**		
a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event?	NO	YES
b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
	ARE **1** OR MORE **H3** ANSWERS CODED **YES**?	➡ NO	YES
H4	**In the past month:**		
a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
f	Did you feel detached or estranged from others?	NO	YES
g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
	ARE **2** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES

H5 **In the past month:**

a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
b	Were you more reckless or more self-destructive?	NO	YES
c	Were you more nervous or constantly on your guard?	NO	YES
d	Were you more easily startled?	NO	YES
e	Did you have more difficulty concentrating?	NO	YES
f	Did you have more difficulty sleeping?	NO	YES
	ARE **2** OR MORE **H5** ANSWERS CODED **YES**?	NO	YES
H6	Did all these problems start after the traumatic event and last for more than one month?	NO	YES

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

AND

S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPEC FY F THE COND T ON S ASSOC ATED W TH DEPERSONAL ZAT ON, DEREAL ZAT ON OR W TH DELAYED EXPRESS ON.

NO **YES**

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH

DEPERSONALIZATION ☐

DEREALIZATION ☐

DELAYED EXPRESSION ☐

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUEST ON ANSWERED POS T VELY. CODE **YES** ONLY F THE EXAMPLES CLEARLY SHOW A D STORT ON OF THOUGHT OR OF PERCEPT ON OR F THEY ARE NOT CULTURALLY APPROPR ATE. THE PURPOSE OF TH S MODULE S TO EXCLUDE PAT ENTS W TH PSYCHOT C D SORDERS. TH S MODULE NEEDS EXPER ENCE.

Now I am going to ask you about unusual experiences that some people have.

K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE:** ASK FOR EXAMPLES TO RULE OUT ACTUAL STALK NG.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CL N C AN: ASK FOR EXAMPLES AND D SCOUNT ANY THAT ARE NOT PSYCHOT C.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CL N C AN: ASK FOR EXAMPLES. ONLY CODE YES F THE EXAMPLES ARE CLEARLY DELUS ONAL DEAS NOT EXPLORED N QUEST ONS **K1** TO **K4**. FOR EXAMPLE, REL G OUS, DEATH, D SEASE OR SOMAT C DELUS ONS, DELUS ONS OF GRAND OS TY, JEALOUSY OR GU LT, OR OF FA LURE, NADEQUACY, RU N, OR DEST TUT ON, OR N H L ST C DELUS ONS.	NO	YES
	b	**IF YES:** do they currently consider your beliefs strange or unusual?	NO	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES
	b	**IF YES TO K6a:** have you heard sounds / voices in the past month?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CL N C AN: CHECK TO SEE F THESE ARE CULTURALLY NAPPROPR ATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 a D D THE PAT ENT EVER N THE PAST EXH B T D SORGAN ZED, NCOHERENT OR DERA LED SPEECH, OR MARKED LOOSEN NG OF ASSOC AT ONS? NO YES

K8 b S THE PAT ENT CURRENTLY EXH B T NG NCOHERENCE, D SORGAN ZED OR DERA LED SPEECH, OR MARKED LOOSEN NG OF ASSOC AT ONS? NO YES

K9 a D D THE PAT ENT EVER N THE PAST EXH B T D SORGAN ZED OR CATATON C BEHAV OR? NO YES

K9 b S THE PAT ENT CURRENTLY EXH B T NG D SORGAN ZED OR CATATON C BEHAV OR? NO YES

K10 a D D THE PAT ENT EVER N THE PAST HAVE NEGAT VE SYMPTOMS, E.G. S GN F CANT REDUCT ON OF EMOT ONAL EXPRESS ON OR AFFECT VE FLATTEN NG, POVERTY OF SPEECH (ALOG A) OR AN NAB L TY TO N T ATE OR PERS ST N GOAL-D RECTED ACT V T ES (AVOL T ON)? NO YES

K10 b ARE NEGAT VE SYMPTOMS OF SCH ZOPHREN A, E.G. S GN F CANT REDUCT ON OF EMOT ONAL EXPRESS ON OR AFFECT VE FLATTEN NG, POVERTY OF SPEECH (ALOG A) OR AN NAB L TY TO N T ATE OR PERS ST N GOAL-D RECTED ACT V T ES (AVOL T ON), PROM NENT DUR NG THE NTERV EW? NO YES

K11 a ARE **1** OR MORE « **a** » QUEST ONS FROM **K1a** TO **K7a**, CODED **YES**?

AND IS EITHER:

MAJOR DEPRESS VE EP SODE, (CURRENT, RECURRENT OR PAST)
OR
MAN C OR HYPOMAN C EP SODE, (CURRENT OR PAST) CODED **YES**?

AND

HOW LONG HAS THE MOOD EP SODE LASTED? _____
HOW LONG HAS THE PSYCHOT C EP SODE LASTED? _____
F SUCH A MOOD EP SODE S PRESENT, CODE **YES** TO **K11a** ONLY F THE MOOD D STURBANCE S PRESENT FOR THE MAJOR TY OF THE TOTAL DURAT ON OF THE ACT VE AND RES DUAL PER ODS OF THE PSYCHOT C SYMPTOMS. OTHERW SE CODE **NO**. NO YES
↳ **K13**

F **NO** TO **K11a** AND THE TOTAL DURAT ON OF THE MOOD EP SODE S **LESS THAN** THE TOTAL DURAT ON OF THE PSYCHOT C EP SODE, THEN C RCLE **NO** N BOTH 'MOOD D SORDER W TH PSYCHOT C FEATURES' D AGNOST C BOXES AND MOVE TO **K13**.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

F THE PAT ENT EVER HAD A PER OD OF AT LEAST **2 WEEKS** OF HAV NG THESE BEL EFS OR EXPER ENCE (PSYCHOT C SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/H GH/ RR TABLE, CODE **NO** TO TH S D SORDER.

F THE ANSWER S **NO** TO TH S D SORDER GROUP NG, ALSO C RCLE **NO** TO **K12** AND MOVE TO **K13**

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

LIFETIME

K12 a ARE **1** OR MORE « **b** » QUEST ONS FROM **K1b** TO **K7b** CODED **YES**?

AND IS EITHER:

MAJOR DEPRESS VE EP SODE (CURRENT)

OR

MAN C OR HYPOMAN C EP SODE (CURRENT) CODED **YES**?

F THE ANSWER S **YES** TO TH S D SORDER (L FET ME OR CURRENT), C RCLE **NO** TO **K13** AND **K14** AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

CURRENT

K13

ARE **1** OR MORE « **b** » QUEST ONS FROM **K1b** TO **K8b**, CODED **YES**?

AND

ARE **2** OR MORE « **b** » QUEST ONS FROM **K1b** TO **K10b**, CODED **YES**?

AND D D AT LEAST TWO OF THE PSYCHOT C SYMPTOMS OCCUR DUR NG THE SAME 1-MONTH PER OD?

AND

S "RULE OUT ORGAN C CAUSE **(O2 SUMMARY)**" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14

S **K13** CODED **YES**?

OR

(ARE **1** OR MORE « **a** » QUEST ONS FROM **K1a** TO **K8a**, CODED **YES**?

AND

ARE **2** OR MORE « **a** » QUEST ONS FROM **K1a** TO **K10a**, CODED **YES**

AND

D D AT LEAST **2** OF THE PSYCHOT C SYMPTOMS OCCUR DUR NG THE SAME 1-MONTH PER OD?)

AND

S "RULE OUT ORGAN C CAUSE **(O2 SUMMARY)**" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? N ENGL SH, F THE PAT ENT S UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASK NG (Do others think that you are a worrier or a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PAT ENT'S ANX ETY AND WORR ES RESTR CTED EXCLUS VELY TO, OR BETTER EXPLA NED BY, ANY D SORDER PR OR TO TH S PO NT?	NO	➡ YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOW NG, CODE **NO** F THE SYMPTOMS ARE CONF NED TO FEATURES OF ANY D SORDER EXPLORED PR OR TO TH S PO NT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES**?	➡ NO	YES
N4		Do these anxieties and worries significantly disrupt your ability to work, to function socially or in your relationships or in other important areas of your life or cause you significant distress? **AND** S "RULE OUT ORGAN C CAUSE **(O2 SUMMARY)**" CODED **YES**?	**NO**	**YES**

GENERALIZED ANXIETY DISORDER
CURRENT

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

F THE PAT ENT CODES POS T VE FOR ANY CURRENT D SORDER OR A MAJOR DEPRESS VE EP SODE OR A MAN C OR A HYPOMAN C EP SODE ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines or in withdrawal from any of these?	☐ No	☐ Yes	☐ Uncertain
O1b	Did you have any medical illness?	☐ No	☐ Yes	☐ Uncertain
O2	F **O1a** OR **O1b** S CODED **YES**, N THE CL N C AN'S JUDGMENT, S E THER L KELY TO BE A D RECT CAUSE OF THE PAT ENT'S D SORDER? F NECESSARY, ASK ADD T ONAL OPEN-ENDED QUEST ONS.	☐ No	☐ Yes	☐ Uncertain
O2 SUMMARY: HAS AN "ORGAN C" / MED CAL / DRUG RELATED CAUSE BEEN RULED OUT? F **O2** S **YES**, THEN **O2** SUMMARY S **NO**. F **O2** S **NO**, THEN **O2** SUMMARY S **YES**. OTHERW SE T S UNCERTA N.		☐ No	☐ Yes	☐ Uncertain

MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:

- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders

MODULE K:

1a	S **K11b** CODED **YES**?	NO	YES
1b	S **K12a** CODED **YES**?	NO	YES

MODULES A and C:		Current	Past
2 a	C RCLE **YES** F A DELUS ONAL DEA S DENT F ED N **A3e** OR N ANY PSYCHOT C FEATURE N **K1** THROUGH **K7**	YES	YES
b	C RCLE **YES** F A DELUS ONAL DEA S DENT F ED N **C3a** OR N ANY PSYCHOT C FEATURE N **K1** THROUGH **K7**	YES	YES

c S MAJOR DEPRESS VE EP SODE CODED **YES** (CURRENT OR PAST)?
AND
S MAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S HYPOMAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S "RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- F THE DEPRESS VE EP SODE S **CURRENT** OR **PAST** OR BOTH
- W TH PSYCHOT C FEATURES, CURRENT: F **1b** OR **2a** (CURRENT) = **YES**
  W TH PSYCHOT C FEATURES, PAST: F **1a** OR **2a** (PAST) = **YES**

MAJOR DEPRESSIVE DISORDER

	Current	Past
MDD	☐	☐

With Psychotic Features

Current	☐
Past	☐

d S MAN C EP SODE CODED **YES** (CURRENT OR PAST)?
AND
S **"**RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- F THE B POLAR D SORDER S **CURRENT** OR **PAST** OR BOTH
- W TH S NGLE MAN C EP SODE: F MAN C EP SODE (CURRENT OR PAST) = **YES**
  AND MAJOR DEPRESS VE EP SODE (CURRENT AND PAST) = **NO**
- W TH PSYCHOT C FEATURES, CURRENT: F **1b** OR **2a** (CURRENT) OR **2b** (CURRENT) = **YES**
  W TH PSYCHOT C FEATURES, PAST: F **1a** OR **2a** (PAST) OR **2b** (PAST) = **YES**
- F THE MOST RECENT EP SODE S MAN C, DEPRESSED, OR HYPOMAN C (MUTUALLY EXCLUS VE)
- F THE MOST RECENT MOOD EP SODE S W TH M XED, ANX OUS OR PSYCHOT C FEATURES

  HYPO/MAN C W TH M XED FEATURES = HYPO/MAN C + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED W TH M XED FEATURES = MAJOR DEPRESS VE EP SODE + AT LEAST **3** SYMPTOMS FROM **C3**

  W TH ANX OUS D STRESS = W TH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR I DISORDER

	Current	Past
Bipolar I Disorder	☐	☐
Single Manic Episode	☐	☐

With Psychotic Features
Current ☐
Past ☐

Most Recent Episode
Manic ☐
Depressed ☐
Hypomanic ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

e S MAJOR DEPRESS VE EP SODE CODED **YES** (CURRENT OR PAST)?
AND
S HYPOMAN C EP SODE CODED **YES** (CURRENT OR PAST)?
AND
S MAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S **"**RULE OUT ORGAN C CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- F THE B POLAR D SORDER S **CURRENT** OR **PAST** OR BOTH
- F THE MOST RECENT MOOD EP SODE S HYPOMAN C OR DEPRESSED (MUTUALLY EXCLUS VE)
- F THE MOST RECENT MOOD EP SODE S W TH M XED, ANX OUS OR PSYCHOT C FEATURES

  HYPOMAN C W TH M XED FEATURES = HYPOMAN C + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED W TH M XED FEATURES = MAJOR DEPRESS VE EP SODE + AT LEAST **3** SYMPTOMS FROM **C3**

  W TH ANX OUS D STRESS = W TH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR II DISORDER

	Current	Past
Bipolar II Disorder	☐	☐

Most Recent Episode
Hypomanic ☐
Depressed ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

f S MAJOR DEPRESS VE EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S MAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S **C4b** CODED **YES** FOR THE APPROPR ATE T ME FRAME?
AND
S **C8b** CODED **YES**?

OR

S MAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S HYPOMAN C EP SODE CODED **NO** (CURRENT AND PAST)?
AND
S **C4a** CODED **YES** FOR THE APPROPR ATE T ME FRAME?
AND
S **C8c** CODED **YES**?

SPEC FY F THE OTHER SPEC F ED B POLAR AND RELATED D SORDER S **CURRENT** OR **PAST** OR BOTH.

OTHER SPECIFIED BIPOLAR AND RELATED DISORDER

	Current	Past
Other Specified Bipolar and Related Disorder	☐	☐

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18.4 Structured Clinical Interview – Positive and Negative Syndrome Scale (SCI-PANSS)

SCI-PANSS

SCI–PANSS

Structured Clinical Interview – Positive and Negative Syndrome Scale

Lewis A. Opler, M.D., Ph.D.
Stanley R. Kay, Ph.D.
J.P. Lindenmayer, M.D., &
Abraham Fiszbein, M.D.

MHS

Structured Clinical Interview for the Positive and Negative Syndrome Scale

SCI-PANSS

L. A. Opler, M.D., Ph.D. S. R. Kay, Ph.D. J. P. Lindenmayer, M.D. A. Fiszbein, M.D.

Patient Name or ID: _____

Interviewer: _____ Date: _____ / _____ / _____

Data on "Lack of Spontaneity and Flow of Conversation" (N6), "Poor Rapport" (N3), and "Conceptual Disorganization" (P2)

Hi, I'm ... We're going to be spending the next 30 to 40 minutes talking about you and your reasons for being here. Maybe you can start out by telling me something about yourself and your background?

(Instruction to interviewer: Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on "Anxiety" (G2)

1. Have you been feeling worried or nervous in the past week? _____

   IF YES, skip to question 3. IF NO, continue.

2. Would you say that you're usually calm and relaxed? _____

   IF YES, skip to question 8. IF NO, continue.

3. What's been making you feel nervous (worried, not calm, not relaxed)? _____

4. Just how nervous (worried, etc.) have you been feeling? _____

5. Have you been shaking at times, or has your heart been racing? _____

6. Do you get into a state of panic? _____

7. Has your sleep, eating, or participation in activities been affected? _____

Data on "Delusions (General)" (P1) and "Unusual Thought Content" (G9)

8. Have things been going well for you? _____

9. Has anything been bothering you lately? _____

10. Can you tell me something about your thoughts on life and its purpose? _____

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11. Do you follow a particular philosophy (any special rules, teachings, or religious doctrine)? _____

12. Some people tell me they believe in the Devil; what do you think? _____

IF NO (i.e., he/she doesn't believe in the Devil), skip to question 14.
IF YES (i.e., he/she does believe), continue.

13. Can you tell me more about this? _____

14. Can you read other people's minds? _____

IF NO, skip to question 16. IF YES, continue.

15. How does that work? _____

16. Can others read your mind? _____

IF NO, skip to question 19. IF YES, continue.

17. How can they do that? _____

18. Is there any reason that someone would want to read your mind? _____

19. Who controls your thoughts? _____

Data on "Suspiciousness/Persecution" (P6) and "Poor Impulse Control" (GI4)

20. How do you spend your time these days? _____

21. Do you prefer to be alone? _____

22. Do you join in activities with others? _____

IF YES, skip to question 25. IF NO, continue.

23. Why not? ... Are you afraid of people, or do you dislike them? _____

IF NO, skip to question 26. IF YES, continue.

24. Can you explain? _____

Skip to question 26.

25. Tell me about it. _____

26. Do you have many friends? _____

IF YES, skip to question 30. IF NO, continue.

27. Just a few? _____

IF YES, skip to question 29. IF NO, continue.

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28. Any? .... Why? _____

Skip to question 32.

29. Why just a few friends? _____

30. Close friends? _____

IF YES, skip to question 32. IF NO, continue.

31. Why not? _____

32. Do you feel that you can trust most people? _____

IF YES, skip to question 34. IF NO, continue.

33. Why not? _____

34. Are there some people in particular who you don't trust? _____

IF NO to question 34 and YES to question 32, skip to question 41.

IF NO to question 34 and NO to question 32, skip to question 36.

IF YES to question 34, continue.

35. Can you tell me who they are? _____

36. Why don't you trust people (or name specific person)? _____

IF "DON'T KNOW" OR "DON'T WANT TO SAY," continue. Otherwise, skip to question 41.

37. Do you have a good reason not to trust ...?

_____

38. Is there something that .... did to you? _____

39. Perhaps something that ... might do to you now? _____

IF NO, skip to question 41. IF YES, continue.

40. Can you explain to me? _____

41. Do you get along well with others? _____

IF YES, skip to question 43. IF NO, continue.

42. What's the problem? _____

43. Do you have a quick temper? _____

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44. Do you get into fights? _____

IF NO, skip to question 48. IF YES, continue.

45. How do these fights start? _____

46. Tell me about these fights. _____

47. How often does this happen? _____

48. Do you sometimes lose control of yourself? _____

IF NO, skip to question 50. IF YES, continue.

49. What happens when you lose control of yourself? _____

50. Do you like most people? _____

IF YES, skip to question 52. IF NO, continue.

51. Why not? _____

52. Are there perhaps some people who don't like you? _____

IF NO, skip to question 54. IF YES, continue.

53. For what reason? _____

54. Do others talk about you behind your back? _____

IF NO, skip to question 57. IF YES, continue.

55. What do they say about you? _____

56. Why? _____

57. Does anyone ever spy on you or plot against you? _____

58. Do you sometimes feel in danger? _____

IF NO, skip to question 64. IF YES, continue.

59. Would you say that your life is in danger? _____

60. Is someone thinking of harming you or even perhaps thinking of killing you? _____

61. Have you gone to the police for help? _____

62. Do you sometimes take matters into your own hands or take action against those who might harm you?

_____

IF NO, skip to question 64. IF YES, continue.

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63. What have you done? _____

Data on "Hallucinatory Behavior" (P3) and associated delusions

64. Do you once in a while have strange or unusual experiences? _____

65. Sometimes people tell me that they can hear noises or voices inside their head that others can't hear. What about you? _____

IF YES, skip to question 68. IF NO, continue.

66. Do you sometimes receive personal communications from the radio or TV? _____

IF YES, skip to question 68. IF NO, continue.

67. From God or the Devil?: _____

IF NO, skip to question 83. IF YES, continue.

68. What do you hear? _____

69. Are these as clear and loud as my voice? _____

70. How often do you hear these voices, noises, messages, etc.? _____

71. Does this happen at a particular time of day or all the time? _____

IF HEARING NOISES ONLY, skip to question 80. IF HEARING VOICES, continue.

72. Can you recognize whose voices these are? _____

73. What do the voices say? _____

74. Are the voices good or bad? _____

75. Pleasant or unpleasant? _____

76. Do the voices interrupt your thinking or your activities? _____

77. Do they sometimes give you orders or instructions? _____

IF NO, skip to question 80. IF YES, continue.

78. For example? _____

79. Do you usually obey these orders (instructions)? _____

80. What do you make of these voices (or noises); where do they really come from? _____

81. Why do you have these experiences? _____

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82. Are these normal experiences? _____

83. Do ordinary things sometimes look strange or distorted to you? _____

84. Do you sometimes have "visions" or see things that others can't see? _____

IF NO, skip to question 88. IF YES, continue.

85. For example? _____

86. Do these visions seem very real or life-like? _____

87. How often do you have these experiences? _____

88. Do you sometimes smell things that are unusual or that others don't smell? _____

IF NO, skip to question 90. IF YES, continue.

89. Please explain. _____

90. Do you get any strange or unusual sensations from your body? _____

IF NO, skip to question 92. IF YES, continue.

91. Tell me about this. _____

Data on "Somatic Concern" (GI)

92. How have you been feeling in terms of your health? _____

IF OTHER THAN "GOOD," skip to question 94. IF "GOOD," continue.

93. Do you consider yourself to be in top health? _____

IF YES, skip to question 95. IF NO, continue.

94. What has been troubling you? _____

95. Do you have any medical illness or disease? _____

96. Has any part of your body been troubling you? _____

IF YES, skip to question 98. IF NO, continue.

97. How is your head? Your heart? Stomach? The rest of your body? _____

98. Could you explain? _____

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99. Has your head or body changed in shape or size? _____

IF NO, skip to question 102. IF YES, continue.

100. Please explain. _____

101. What is causing these changes? _____

Data on "Depression" (G6)

102. How has your mood been in the past week: mostly good, mostly bad? _____

IF "MOSTLY BAD," skip to question 104. IF "MOSTLY GOOD," continue.

103. Have there been times in the past week when you were feeling sad or unhappy? _____

IF NO, skip to question 114. IF YES, continue.

104. Is there something in particular that is making you sad? _____

105. How often do you feel sad? _____

106. Just how sad have you been feeling? _____

107. Have you been crying lately? _____

108. Has your mood in any way affected your sleep? _____

109. Has it affected your appetite? _____

110. Do you participate less in activities on account of your mood? _____

111. Have you had any thoughts of harming yourself? _____

IF NO, skip to question 114. IF YES, continue.

112. Any thoughts about ending your life? _____

IF NO, skip to question 114. IF YES, continue.

113. Have you attempted suicide? _____

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Data on "Guilt Feelings" (G3) and "Grandiosity" (P5)

114. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same? _____

IF "BETTER," skip to question 117.
IF "ABOUT THE SAME," skip to question 118.
IF "WORSE," continue.

115. Worse in what ways? _____

116. Just how do you feel about yourself? _____

Skip to question 120.

117. Better in what ways? _____

Skip to question 120.

118. Are you special in some ways? _____

IF NO, skip to question 120. IF YES, continue.

119. In what ways? _____

120. Would you consider yourself gifted? _____

121. Do you have talents or abilities that most people don't have? _____

IF NO, skip to question 123. IF YES, continue.

122. Please explain. _____

123. Do you have any special powers? _____

IF NO, skip to question 126. IF YES, continue.

124. What are these? _____

125. Where do these powers come from? _____

126. Do you have extrasensory perception (ESP), or can you read other people's minds? _____

127. Are you very wealthy? _____

IF NO, skip to question 129. IF YES, continue.

128. Explain please. _____

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129. Can you be considered to be very bright? _____

IF NO, skip to question 131. IF YES, continue.

130. Why would you say so? _____

131. Would you describe yourself as famous? _____

132. Would some people recognize you from TV, radio, or the newspaper? _____

IF NO, skip to question 134. IF YES, continue.

133. Can you tell me about it? _____

134. Are you a religious person? _____

IF NO, skip to question 140. IF YES, continue.

135. Are you close to God? _____

IF NO, skip to question 140. IF YES, continue.

136. Did God assign you some special role or purpose? _____

137. Can you be one of God's messengers or angels? _____

IF NO, skip to question 139. IF YES, continue.

138. What special powers do you have as God's messenger (angel)? _____

139. Do you perhaps consider yourself to be God? _____

140. Do you have some special mission in life? _____

IF NO, skip to question 143. IF YES, continue.

141. What is your mission? _____

142. Who assigned you to that mission? _____

143. Did you ever do something wrong — something you feel bad or guilty about? _____

IF NO, skip to question 149. IF YES, continue.

144. Just how much does that bother you now? _____

145. Do you feel that you deserve punishment for that? _____

IF NO, skip to question 149. IF YES, continue.

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146. What kind of punishment would you deserve? _____

147. Have you at times thought of punishing yourself? _____

IF NO, skip to question 149. IF YES, continue.

148. Have you ever acted on those thoughts of punishing yourself? _____

Data on "Disorientation" (GIO)

149. Can you tell me today's date (i.e., the day, month, and year)? _____

IF YES, skip to question 151. IF NO, continue.

150. Can you tell me what day of the week it is? _____

151. What is the name of the place that you are in now? _____

IF NOT HOSPITALIZED, skip to question 154. IF HOSPITALIZED, continue.

152. What ward are you on? _____

153. What is the address of where you're now staying? _____

IF ABLE TO TELL, skip to question 155. IF NOT ABLE TO TELL, continue.

154. Can you tell me your home address? _____

IF NOT HOSPITALIZED, skip to question 156. IF HOSPITALIZED, continue.

155. If someone had to reach you by phone, what number would that person call? _____

156. If someone had to reach you at home, what number would that person call? _____

157. What is the name of the doctor who is treating you? _____

IF NOT HOSPITALIZED, skip to question 159. IF HOSPITALIZED, continue.

158. Can you tell me who else is on the staff and what they do? _____

159. Do you know who is currently the president (prime minister, etc.)? _____

160. Who is our governor (premier, etc.)? _____

161. Who is the mayor (town supervisor, etc.) of this city (town, etc.)? _____

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Data on "Difficulty in Abstract Thinking" (N5)

I'm going to now say a pair of words, and I'd like you to tell me in what important way they're alike. Let's start, for example, with the words "apple" and "banana." How are they alike — what do they have in common? **IF THE RESPONSE IS THAT "THEY'RE BOTH FRUIT", THEN SAY:** Good. Now what about ...? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

IF AN ANSWER IS GIVEN THAT IS CONCRETE, TANGENTIAL, OR IDIOSYNCRATIC (E.G., "THEY BOTH HAVE SKINS," "YOU CAN EAT THEM," "THEY'RE SMALL," OR "MONKEYS LIKE THEM"), THEN SAY: OK, but they're both fruit. Now how about ... and ... : how are these alike? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

APPENDIX A

Items for Similarities in the evaluation of "Difficulty in Abstract Thinking"

Circle the Similarities Used

1. How are a ball and an orange alike?
2. Apple and banana ?
3. Pencil and pen?
4. Nickel and dime?

_____

5. Table and chair?
6. Tiger and elephant?
7. Hat and shirt?
8. Bus and train?

_____

9. Arm and leg?
10. Rose and tulip?
11. Uncle and cousin?
12. The sun and the moon?

_____

13. Painting and poem?
14. Hilltop and valley?
15. Air and water?
16. Peace and prosperity?

Note on Appendix A: Similarities are generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Similarities responses:

_____

_____

_____

_____

You've probably heard the expression, "Carrying a chip on the shoulder." What does that really mean? There's a very old saying, "Don't judge a book by its cover." What is the deeper meaning of this proverb? *(Select two other proverbs from the list in Appendix B at varying levels of difficulty.)*

APPENDIX B

Items for assessing PROVERB INTERPRETATION in the evaluation of "Difficulty in Abstract Thinking"

Circle the Proverbs Used

What does the saying mean:

1. "Plain as the nose on your face"
2. "Carrying a chip on your shoulder"
3. "Two heads are better than one"
4. "Too many cooks spoil the broth"

_____

5. "Don't judge a book by its cover"
6. One man's food is another man's poison"
7. "All that glitters is not gold"
8. "Don't cross the bridge until you come to it"

_____

9. "What's good for the goose is good for the gander"
10. "The grass always looks greener on the other side"
11. "Don't keep all your eggs in one basket"
12. "One swallow does not make a summer"

_____

13. "A stitch in time saves nine"
14. "A rolling stone gathers no moss"
15. "The acorn never falls far from the tree"
16. "People who live in glass houses should not throw stones at others"

Note on Appendix B: Proverb interpretation is generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Proverb responses:

_____

_____

_____

_____

Data on "Lack of Judgment and Insight" (G12)

162. How long have you been in the hospital (clinic, etc.)? _____

163. Why did you come to the hospital (clinic, etc.)? _____

164. Did you need to be in a hospital (clinic, etc.)? _____

IF YES, skip to question 167. IF NO, continue.

165. Did you have a problem that needed treatment? _____

IF NO, skip to question 169. IF YES, continue.

166. Would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

167. Why?....would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

168. Can you tell me about it and what it consisted of? _____

169. In your own opinion, do you need to be taking medicine? _____

IF YES, skip to question 171.
IF NO and <u>unmedicated</u>, skip to question 172.
IF NO and <u>medicated</u>, continue.

170. Why then are you taking medicines? _____

Skip to question 172.

171. Why?... Does the medicine help you in any way? _____

172. Do you at this time have any psychiatric or mental problems? _____

IF YES, skip to question 174. IF NO, continue.

173. For what reason are you at the hospital (clinic, etc.)? _____

Skip to question 175.

174. Please explain _____

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175. Just how serious are these problems? _____

IF UNHOSPITALIZED, skip to question 178.
IF HOSPITALIZED, continue.

176. Are you ready yet for discharge from the hospital? _____

177. Do you think you'll be taking medicine for your problems after discharge? _____

178. What are your future plans? _____

179. What about your longer-range goals? _____

Well, that's about all I have to ask of you now. Are there any questions that you might like to ask of me? Thank you for your cooperation.

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18.5 Clinical Global Impression – Severity Scale (CGI-S)

Clinical Global Impression (CGI)

Reference: **Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare**

Rating Clinician-rated

Administration time Varies with familiarity with patient

Main purpose To provide a global rating of illness severity, improvement and response to treatment

Population Adults

Commentary

Amongst the most widely used of extant brief assessment tools in psychiatry, the CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The Early Clinical Drug Evaluation Program (ECDEU) version of the CGI (reproduced here) is the most widely used format, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. Several alternative versions of the CGI have been developed, however, such as the FDA Clinicians' Interview-Based Impression of Change (CIBIC), which uses only information collected during the interview, not collateral. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer, provided that the clinician knows the patient well.

Scoring

The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately; the instrument does not yield a global score.

Versions

CGI for bipolar disorder (CGI-BD), FDA Clinicians' Interview-Based Impression of Change (CIBIC), Clinicians' Interview-Based Impression of Change-Plus (CIBIC+), NYU CIBIC+, Parke-Davis Pharmaceuticals Clinical Interview-Based Impression (CIBI); the CGI has been translated into most languages.

Additional references

Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 1993; 13(5):327–31.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73(3):159–71.

Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med 2003; 33(4):611–22.

Address for correspondence

Not applicable – the CGI is in the public domain.

Clinical Global Impression - Severity (CGI-S)

CGI-S is to be collected at Screening and throughout the study where indicated in Schedule of Events

1. Severity of illness

Considering your total clinical experience with this particular population, 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

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

18.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Note that there are two specific scales, e.g., Baseline, Since Last Visit, and differentiated by footers.

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 <u>some intent to act on such thoughts</u>, 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

	Most Severe	Most Severe
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. <u>Lifetime</u> - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*) <u>Past X Months</u> - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*)		
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	____	____

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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* _____

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

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SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Since Last Visit

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____ as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes	No
☐	☐

Total # of Attempts: _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes	No
☐	☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes	No
☐	☐

Total # of interrupted: _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes	No
☐	☐

Total # of aborted

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes	No
☐	☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes	No
☐	☐

Suicide:

Yes	No
☐	☐

Answer for Actual Attempts Only

Most Lethal Attempt Date:

Actual Lethality/Medical Damage:

Enter Code: _____

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

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).

Enter Code: _____

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

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18.7 Acid Reflux Severity Scale

The Acid Reflux Severity Scale (ARSS) [2] is as follows. Subjects with a history of moderate to severe Acid Reflux Disease or a score of ≥ 2 on the ARSS are not eligible for the study:

None = 0 no symptoms

Mild = 1 awareness of symptom, but easily tolerated

Moderate = 2 discomfort sufficient to cause interference with normal activities

Severe = 3 incapacitating, with inability to perform normal activities.

18.8 Extrapyramidal Symptom Rating Scale (ESRS)

Administration instructions below are excerpted from the article by Chouinard et al. 2005 with edits from the Erratum, 2006

Instruction 1: Patient is asked to remove his/her shoes, to remove anything from his/her mouth (except dentures) and to sit facing the examiner on a chair with no armrests.

The removal of shoes can be omitted if an assessment of lower extremity dyskinetic movements is not required. In clinical trials it is completed unless clinically inappropriate for the patient (often patients do not feel comfortable removing their shoes) or it can be delayed until the testing of postural stability. Removing food and gum from the mouth is necessary in order to assess bucco–labial, lingual and jaw movements. The armless chair is essential for detection of tremors, decreased spontaneous movements, dyskinesia and akathisia.

Instruction 2: Complete the questionnaire.

The questionnaire rates subjective DIMD, i.e., Parkinsonism, akathisia, dystonia, and dyskinesia, as reported by the patient and which are experienced at periods other than the time of examination during the last week. For demented patients or autistic children, a nurse or key relative may also provide information in relation to the questionnaire. The questionnaire permits the evaluator to spend time with the patient to observe spontaneous DIMD.

Instruction 3: Observe facial expressiveness, speech, akathisia, dystonia and dyskinesia while completing the questionnaire and while completing items 4, 5, and 6.

Items in the objective examination are assessed during the course of standard tests of neurological examination (there is no new procedure to be learned by the physician when the physician is the examiner).

Instruction 4: Patient is asked to extend both arms forward, with palms down and eyes closed.

This test of posture tremors along with observing the patient's tremors at rest and the copying of a spiral with each hand (Instruction 6) is part of an overall assessment of tremors, which includes rest, posture and action tremors. Eyes are kept closed so that the patient is unable to correct if there is a lateralized neurological lesion.

Instruction 5: The patient is asked to carry out pronation and supination of both hands as fast as possible and to perform rapid alternate movements of both wrists simultaneously. Repeat as necessary.

Both tests are useful in the evaluation of tardive dyskinesia, as well as in the rating of slowness and difficulty in initiating movement. For bradykinesia, these two tests were selected because the initiation of several repetitive movements can be observed and for one test simultaneous movements of both wrists permit the detection of impaired ability to perform simultaneous tests. The inability to stop a movement should also be observed. For TD, the

Table 1
Summary of the ESRS examination procedure

1. Patient is asked to remove their shoes (omitted if judged clinically inappropriate or when patient hesitates, or delayed after patient has walked (after # 7). The patient is asked to remove anything from their mouth (except dentures). The patient is asked to sit facing the examiner on a chair with no armrests.
2. Complete the questionnaire.
3. Observe facial expressiveness, speech and dyskinesia while completing the questionnaire and while completing items 4, 5, and 6 below.
4. Patient is asked to extend both arms forward, with palms down and eyes closed.
5. The patient is asked to carry out pronation and supination of both hands as fast as possible, and to perform rapid alternate movements of both wrists. Repeat as necessary.
6. While the patient sits facing the examiner on a chair with no armrests about 1 foot (approx. 30 cm) from a table with his upper body turned, the patient is asked to copy a spiral with each hand and to write the name of his town, province/state and country.
7. Patient is asked to walk a distance of 12 15 feet (4 5 m) away from, and then back towards the examiner. Repeat as necessary.
8. Patient is asked to stand erect with eyes open with feet slightly apart (1 2 cm). The examiner pushes the patient on each shoulder, the back and pushes the chest or pulls from the back while asking the patient to keep his balance.
9. Carry out the examination of the muscular tonus of the four limbs.

oral–facial region is observed while the patient is performing pronation–supination and alternate movement tests; these voluntary movements help to uncover buccal–labial–masticatory and lower extremity dyskinesias.

Instruction 6: While the patient sits facing the examiner on a chair with no armrests about 1 foot (approx. 30 cm) from a table with his/her upper body turned, the patient is asked to copy a spiral with each hand and to write the name of his town, province/state and country.

This test permits the assessment of action tremors through graphic oscillation, and dyskinetic movements may be unmasked or augmented when the patient completes Instruction 6, for the test is performed under some emotional tension and uses other voluntary muscle groups. In this regard, it is important to encourage the patient to concentrate on the task requested.

Instruction 7: Patient is asked to walk a distance of 12–15 feet (4–5 m) away from, and then back towards, the examiner. Repeat as necessary.

This permits the evaluator to rate gait and posture. Absence of or a decrease in unilateral or bilateral pendular moments is observed. Abnormalities of posture are also looked for: flexed head, stiff posture, stooped posture. TD and/or chronic dystonia of upper limbs and trunk are looked for while the patient is walking.

Instruction 8: Patient is asked to stand erect with eyes open and feet together or slightly apart (1–2 cm). The examiner pushes the patient gently but firmly (strongly if necessary) on each shoulder (for lateropulsion), the back (for anteropulsion), and pushes the chest or pulls from the back (for retropulsion) while asking the patient to keep his balance and resist. Preferably, the patient removes his/her shoes before the test.

This test evaluates postural stability. The examiner should be ready to catch the patient from falling especially if the patient has an obvious impairment of balance at rest before testing. For patients who are already unstable, the test is completed gently.

Instruction 9: Carry out the examination of the muscular tonus of the four limbs.

Both limbs are examined as a pair in order to observe differences between the left and right side. Patient is asked to relax. Both arms are simultaneously rotated to permit examination of shoulders and, subsequently, elbows and wrists. Left and right knees are then successively moved and a comparison between the two sides made. Examination of hips and ankles does not provide more sensitivity and can be disturbing to psychotic patients. As with IPD, proximal joints are the most affected and rigidity may be more present in one part and/or one side of the body.

4. Scoring instructions

4.1. Questionnaire for Parkinsonism, akathisia, dystonia and dyskinesia

For the subjective examination (subscale I of the ESRS) scoring is on a 4-point scale (0=Absent; 1=Mild, 2=Moderate, 3=Severe). The evaluator takes into account the verbal report of the patient on: 1) the frequency and duration of the symptom during the day; 2) the number of days the symptom was present during the last week; and, 3) the subjective evaluation of the intensity of the symptom by the patient. When rating subjective EPS, severity is assessed over the last 7 days. One inquires about how persistent symptoms have been on the most typical day in the past 7 days.

4.2. Examination: Parkinsonism and akathisia

Both tremors and rigidity (items 1 and 4) are scored on a 7-point item scale (0=none–6=severe) for each part of the body, which are scored as separate items. The ESRS and the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) rate each part of the body separately for tremors and rigidity, since, in both drug-induced Parkinsonism and IPD, the symptoms can be seen initially in one limb and when it progresses it may involve several limbs, thus increasing the number of items in each scale, but permitting the rating of severity in each part of the body involved.

Ratings for tremors are made taking into account two axes: the amplitude of the movement and the number of times with which it is observed during the

interview. Assessment of tremors includes rest, posture and action tremors. Ratings of the other items of Parkinsonism and akathisia are recorded on a 7-point item scale (0=absent–6=most severe) with anchor points.

One difficulty in the rating of abnormal movements was to include both the amplitude of the abnormal movement (the higher the amplitude, the more severe the disorder) and the frequency that an abnormal movement is observed (the more frequent, the greater the severity). Thus, it appeared necessary to rate hyperkinetic disorders, tremors and dyskinesia, on a two-axis dimension to take into account that a small amplitude tremor seen frequently is as pathological as a larger amplitude tremor seen less frequently.

4.3. Examination: dystonia

Both acute and chronic dystonic movements are scored on a 7-point item scale (0=absent–6=most severe). Each body part is rated separately including right upper limb, left upper limb, right lower limb, left lower limb, head, jaw, tongue, lips, face, trunk and other (any other area).

4.4. Examination: dyskinesia

Dyskinetic movements at each site (tongue, jaw, bucco–labial, trunk, upper and lower extremities, and others {any other area including face}) are evaluated as individual items. They are rated similarly to tremors. Involuntary dyskinetic movements are repetitive, although not rhythmic and not oscillating along an axis, and their amplitude is usually greater with a low frequency cycle/s. Consequently we applied the same logic of a two-axis scale of amplitude and frequency as in the rating of tremors.

5. ESRS total and subtotal scores

5.1. ESRS Parkinsonism and akathisia scores in the era of classical antipsychotics

The score for Parkinsonism (including akathisia), ranges from 0 to 102 (17 items), and is based on all items of the Parkinsonism examination (subscale II): tremor (0–48), gait and posture (0–6), postural stability (0–6), rigidity (0–24), expressive automatic movements (0–6), bradykinesia (0–6), akathisia (0–6). In clinical trials, when establishing presence of Parkinsonism to initiate an antiParkinsonian medication, a score of 3 or greater is required on at least one of the above listed items including the 8 items of tremor or the 4 items of rigidity. When establishing the presence versus absence of Parkinsonism, a score of 2 on 2 items or a score of 3 or greater on one item is required to establish the presence.

Subscores: Two subscores were formed using the objective examination of Parkinsonism: a hypokinesia factor, ranging from 0 to 42, calculated as the sum of items: gait and posture (0–6), rigidity (0–24), expressive automatic movements (0–6), and bradykinesia (0–6); and a hyperkinesia factor, ranging from 0 to 54, calculated as the sum of items: tremor (0–48) and akathisia (0–6).

5.2. ESRS Parkinsonism and akathisia scores in the era of atypical antipsychotics

The Parkinsonism score, ranging from 0 to 96 (16 items), and the 2 factors (hypokinesia (0–42) and hyperkinesia (0–49) used now are similar to the previous ones (described in Section 5.1) minus one item: akathisia (0–6). The score for akathisia is separated from the Parkinsonism score and is based on the combined score of subjective akathisia (item 6 of the questionnaire) and objective akathisia (item 7 of the Parkinsonism/Akathisia objective examination). When establishing presence versus absence of akathisia, a total score of 3 or greater on the 2 items is required for presence.

5.3. Dystonia scores

The score for dystonia ranges from 0 to 60 (10 items), and is formed by including both acute and chronic dystonia, based on the dystonia examination (Subscale III). When establishing presence versus absence of dystonia, a score of 3 or greater on at least one item, or a score of 2 on 2 items is required to indicate presence of dystonia.

5.4. Dyskinesia and subtotal scores

Score for TD, ranging from 0 to 42, is based on the sum of all seven items in the TD objective examination. When scoring presence versus absence of TD, a score of 3 or greater on at least one item or a score of 2 on 2 items is required to indicate presence of TD. For tardive dyskinesia, scores for each item can be analyzed separately. A buccal–lingual–masticatory (BLM) subtotal, ranging from 0 to 18, is obtained from the sum of items 1, 2 and 3, and an extremities subtotal, ranging from 0 to 12, by adding the score for items 5 and 6.

5.5. ESRS total and subtotal scores for clinical trials and inter-rater reliability certification

For clinical trials, a total score for DIMD or EPS is formed based on all 41 items of the ESRS. It includes the 7 items of Subscale I (questionnaire), 17 items of Subscale II (Parkinsonism/Akathisia), 10 items of Part III (dystonia), and 7 items of Part IV (dyskinesia). For inter-rater reliability certification, the ESRS 41 item total score also includes the 4 CGI-S's and thus becomes ESRS 45 item total.

5.6. Clinical global impression of severity (CGI-S)

The clinical global impression of severity (CGI-S) of Parkinsonism, akathisia, dystonia, and tardive dyskinesia are rated according to results of the subjective questionnaire, examination subscales, and the evaluator's clinical experience by applying an 8 point rating (0: absent; 1: borderline; 2: very mild; 3: mild; 4: moderate; 5: moderately severe; 6: marked; 7: severe; 8: extremely severe). The 4 CGI-S's are analyzed as separate items.

Appendix A. ESRS Manual and scoring sheet

Extrapyramidal symptom rating scale (ESRS) (Chouinard) © 1979

In case of doubt score the lesser severity.

I. QUESTIONNAIRE : Parkinsonism, Akathisia, Dystonia and Dyskinesia. *In this questionnaire, take into account the verbal report of the patient on the following 1) the duration of the symptom during the day; 2) the number of days where the symptom was present during the last week; and, 3) the evaluation of the intensity of the symptom by the patient.*

Enquire into the status of each symptom and rate accordingly

	Absent	Mild	Moderate	Severe	
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	0	1	2	3	⌊⌋
2. Difficulty walking or with balance					
3. Stiffness, stiff posture	0	1	2	3	⌊⌋
4. Restless, nervous, unable to keep still	0	1	2	3	⌊⌋
	0	1	2	3	⌊⌋
5. Tremors, shaking					
6. Oculogyric crisis, abnormal sustained posture	0	1	2	3	⌊⌋
7. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips, face, extremities or trunk	0	1	2	3	⌊⌋
	0	1	2	3	⌊⌋

II. EXAMINATION: PARKINSONISM AND AKATHISIA

Items based on physical examinations for Parkinsonism.

	Occasional	Frequent	Constant or almost so				
1. Tremor							
None:	0			Right upper limb			⌊⌋
Borderline:	1			Left upper limb			⌊⌋
Small amplitude:	2	3	4	Right lower limb			⌊⌋
Moderate amplitude:	3	4	5	Left lower limb			⌊⌋
Large amplitude:	4	5	6	Head	⌊⌋	Jaw/Chin	⌊⌋
				Tongue	⌊⌋	Lips	⌊⌋
2. Bradykinesia	0:	normal					
	1:	global impression of slowness in movements					
	2:	definite slowness in movements					
	3:	very mild difficulty in initiating movements					⌊⌋
	4:	mild to moderate difficulty in initiating movements					
	5:	difficulty in starting or stopping any movement, or freezing on initiating voluntary act					
	6:	rare voluntary movement, almost completely immobile					
3. Gait & posture	0:	normal					
	1:	mild decrease of pendular arm movement					
	2:	moderate decrease of pendular arm movement, normal steps					
	3:	no pendular arm movement, head flexed, steps more or less normal					⌊⌋

	4:	stiff posture (neck, back) small step (shuffling gait)		
	5:	more marked, festination or freezing on turning		
	6:	triple flexion, barely able to walk		
4. Postural stability	0:	normal		
	1:	hesitation when pushed but no retropulsion		
	2:	retropulsion but recovers unaided		
	3:	exaggerated retropulsion without falling		⌊⌋
	4:	absence of postural response would fall if not caught by examiner		
	5:	unstable while standing, even without pushing		
	6:	unable to stand without assistance		⌊⌋
5. Rigidity	0:	normal muscle tone	Right upper limb	⌊⌋
	1:	very mild, barely perceptible	Left upper limb	⌊⌋
	2:	mild (some resistance to passive movements)	Right lower limb	⌊⌋
	3:	moderate (definite difficulty to move the limb)	Left lower limb	⌊⌋
	4:	moderately severe (moderate resistance but still easy to move limb)		
	5:	severe (marked resistance with definite difficulty to move the limb)		
	6:	extremely severe (limb nearly frozen)		

Items based on overall observation during examination for Parkinsonism.

6 . Expressive automatic movements (Facial mask / speech)	0:	normal	
	1:	very mild decrease in facial expressiveness	
	2:	mild decrease in facial expressiveness	
	3:	rare spontaneous smile, decrease blinking, voice slightly monotonous	⌊⌋
	4:	no spontaneous smile, staring gaze, low monotonous speech, mumbling	
	5:	marked facial mask, unable to frown, slurred speech	
	6:	extremely severe facial mask with unintelligible speech	
7 . Akathisia	0:	absent	
	1:	looks restless, nervous, impatient, uncomfortable	
	2:	needs to move at least one extremity	
	3:	often needs to move one extremity or to change position	⌊⌋

4:	moves one extremity almost constantly if sitting, or stamps feet while standing
5:	unable to sit down for more than a short period of time
6:	moves or walks constantly

III. EXAMINATION: DYSTONIA

Based on examination and observation

Acute torsion, and non acute or chronic or tardive dystonia

0:	absent	Right upper limb			⌊⌋
1:	very mild	Left upper limb			⌊⌋
2:	mild	Right lower limb			⌊⌋
3:	moderate	Left lower limb			⌊⌋
4:	moderately severe	Head	⌊⌋	Jaw/Chin	⌊⌋
5:	severe	Tongue	⌊⌋	Lips	⌊⌋
6:	extremely severe	Eyes	⌊⌋	Trunk	⌊⌋

IV. EXAMINATION: DYSKINETIC MOVEMENT

Based on examination and observation

		Occasional*	Frequent**	Constant or almost so	
1. Lingual movements (slow lateral or torsion movement of tongue)					
none:	0				
borderline:	1				
clearly present, within oral cavity:		2	3	4	
with occasional partial protrusion:		3	4	5	
with complete protusion:		4	5	6	⌊⌋
2. Jaw movements (lateral movement, chewing, biting clenching)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude: but without mouth opening:		3	4	5	
large amplitude: with mouth opening:		4	5	6	⌊⌋
3. Bucco-labial movements (puckering, pouting, smacking, etc.)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude, forward movement of lips:		3	4	5	
large amplitude; marked, noisy smacking of lips:		4	5	6	⌊⌋

4. Truncal movements (involuntary rocking, twisting, pelvic gyrations)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude:		3	4	5	
greater amplitude:		4			⌊⌋
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)			5	6	
none:	0				
borderline:	1				
clearly present, small amplitude, movement of one limb:		2	3	4	
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs:		3	4	5	
greater amplitude, movement involving two limbs:		4	5	6	⌊⌋
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)					
none:	0				
borderline:	1				
clearly present, small amplitude, movement of one limb:		2	3	4	
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs:		3	4	5	
greater amplitude, movement involving two limbs:		4	5	6	⌊⌋
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude:		3	4	5	
greater amplitude:		4	5	6	⌊⌋

Specify……..……..

* when activated or rarely spontaneous;

** frequently spontaneous and present when activated

V. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA

Considering your clinical experience, how severe is the dyskinesia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VI. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM

Considering your clinical experience, how severe is the parkinsonism at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSTONIA

Considering your clinical experience, how severe is the dystonia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VIII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF AKATHISIA

Considering your clinical experience, how severe is the akathisia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

Clinical Research Protocol

DRUG:	Risperidone
STUDY NUMBER(S):	LYN-005-C-004
PROTOCOL(S) TITLE:	A Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder
IND NUMBER:	143074
SPONSOR:	Lyndra® Therapeutics Inc, (US); hereafter referred to as Lyndra
ORIGINAL PROTOCOL DATE:	11 June 2020
VERSION NUMBER:	1.0
PROTOCOL VERSION DATE:	11 June 2020

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1 PROTOCOL SUMMARY

1.1 Study Synopsis

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
Title:	A Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder
Phase:	Phase 2
Rationale:	Lyndra is developing an oral, extended release (ER) formulation of risperidone (LYN-005) presented in a capsule dosage form with the intent of reducing the frequency of dosing orally-administered medications to once weekly or less and thereby improving the management of schizophrenia. Current treatment options for schizophrenia consist of acute symptom management for psychosis as well as efforts to prevent relapse and improve access to supportive treatments. Antipsychotic drug therapy is effective in most subjects in managing and stabilizing schizophrenia symptoms. Despite the benefits from treatment, approximately 75% of diagnosed subjects will experience a relapse, generally within two years, and the majority of subjects will experience multiple relapses over the course of the illness [1]. A major known risk factor leading to relapse is non-adherence with antipsychotic drug therapy [1]. In addition to improving adherence, an extended release oral risperidone may offer more consistent plasma levels of the pharmacologically active forms of risperidone, reducing both inter-subject and intra-subject variability. The target population for the Lyndra formulation (LYN-005) is subjects with schizophrenia who require maintenance treatment with risperidone and who have demonstrated tolerability of immediate release (IR) risperidone. An oral once weekly form of risperidone would offer a treatment opportunity facilitating greater clinician and subject contact and which could be integrated into a variety of community psychiatric treatment models, without need for specialized administration spaces or training. Once weekly dosing is anticipated to be highly convenient for both subjects and caregivers and provides certainty of dosing with only weekly supervision. Further, an oral extended release formulation, if demonstrated to be effective at achieving therapeutic systemic drug levels, could offer an opportunity to initiate a long-acting treatment earlier in the disease course, potentially prior to discharge from hospitalization. Study LYN-005-C-004 will evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple dose administration of the ER formulation at two dose levels of LYN-005 relative to IR risperidone.

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
OBJECTIVES	
Primary Objectives:	• To determine the safety and tolerability of risperidone extended release capsules (LYN-005) administered as repeat weekly doses compared to IR risperidone tablets at 2 dose levels; • To characterize the PK of risperidone, active metabolite 9-hydroxyrisperidone and active moiety (risperidone and 9-hydroxyrisperidone combined) after repeat weekly doses of LYN-005 ER capsules relative to IR risperidone tablets at 2 dose levels.
Secondary Objectives:	• To assess the exposure to risperidone, 9-hydroxyrisperidone and active moiety during the switch from IR risperidone to LYN-005.
Exploratory Objectives:	• To model the PK of risperidone, 9-hydroxyrisperidone and active moiety when administered as a LYN-005 extended-release capsule.
ENDPOINTS	
Primary Endpoints:	• Incidence of treatment emergent adverse events (TEAEs). • Risperidone, 9-hydroxyrisperidone, and active moiety PK after oral administration of LYN-005 capsules and IR risperidone to include, as possible and appropriate, C_{max}, C_{min}, T_{max}, Kel, $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-168)}$ and $AUC_{(0-\infty)}$.
Secondary Endpoints:	• Exposure to risperidone, 9-hydroxyrisperidone and active moiety as assessed from C_{max}, T_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ after switching from IR risperidone to LYN-005.
Exploratory Endpoints:	• PK modelling of risperidone, 9-hydroxyrisperidone, and active moiety exposure.
METHODOLOGY	
Study Duration:	Up to 55 days
Study Design:	LYN-005-C-004 is a blinded, multiple-dose, randomized, parallel group, safety, tolerability and PK study of LYN-005 in subjects with a primary diagnosis of schizophrenia or schizoaffective disorder in general good health. Eligible subjects must be clinically stable and receiving a therapeutic dose of an approved oral antipsychotic drug for a minimum of 6 weeks at the time of Screening. Enrolled subjects will be evaluated under steady-state conditions on commercially-available IR risperidone tablets and then assigned in blinded fashion either to LYN-005 weekly or continued encapsulated IR risperidone daily for 3 weeks to attain (or continue) steady-state exposure.

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
	A total of 32 subjects will participate in this study. Subjects will be randomized to LYN-005 plus IR risperidone matched placebo OR LYN-005 matched placebo or IR risperidone as follows: • Arm 1: LYN-005 (14 or 28 mg weekly) plus IR risperidone matched placebo (N=24). • Arm 2: LYN-005 matched placebo plus IR risperidone (2 or 4 mg/day) (N=8). Per above, in order to maintain the blind, all subjects will either receive LYN-005 and IR risperidone-matched placebo or LYN-005 matched placebo and IR risperidone, as follows: Arm 1: • LYN-005: Size 00EL capsules containing LYN-005 stellate; the 14mg dose of LYN-005 contains 3 active arms containing risperidone, and 3 inactive arms and he 28 mg dose of LYN-005 contains 6 active arms containing risperidone. AND • IR Risperidone Matched Placebo: Orange capsule-shaped tablets containing inactive ingredient. Arm 2: • LYN-005 Matched Placebo: Size 00EL capsules containing inactive ingredient with no stellate. AND • IR Risperidone: Risperidone 2 mg (orange) capsule-shaped tablets. Although treatment assignment is blinded; the dose level is not blinded. The dose of LYN-005 (14 or 28 mg)/IR risperidone (2 or 4 mg/day) administered will be based on the subject's current antipsychotic medication dose. Across both arms, a minimum of 8 subjects are to be enrolled at each dose level (LYN-005 14 mg/IR risperidone 2 mg/day [low dose] and LYN-005 28 mg/IR risperidone 4 mg/day [high dose]); thus, if 16 subjects receiving the low dose have been enrolled, all remaining subjects must be enrolled at the high dose level and vice versa. All administrations of LYN-005/matched placebo will be supervised. Complete PK evaluations will be performed after each LYN-005 dose, as designated in the Schedules of Events (Section 18.1.1 and Section 18.1.2) and over 24 hours at steady-state for IR risperidone at the beginning of the study.

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
	LYN-005 will be evaluated in subjects who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of schizophrenia or schizoaffective disorder of at least 2 years, who have already been stabilized on an oral antipsychotic medication for a minimum of 6 weeks at the time of Screening with no psychiatric hospitalizations for relapse in the past 6 months. Subjects who are prescribed an antipsychotic agent other than risperidone or a dose of risperidone outside the range are also eligible for study participation if they are a) able to tolerate risperidone and b) be completed switched to 2 or 4 mg daily oral risperidone for a minimum of 2 weeks prior to the first dose of LYN-005/placebo on Day 1 (see Section 6.3.1). Eligible subjects must be clinically stable (i.e., mildly or moderately ill psychiatrically), with a low risk of relapse and otherwise healthy without history of significant gastrointestinal (GI) diseases. Guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. In the event of worsening of schizophrenia symptoms while receiving risperidone during the study, another medication can be administered at the discretion of the Principal Investigator (PI), with notification of the Study Medical Monitor. Risperidone is primarily metabolized by cytochrome P450 (CYP) 2D6 and genetic testing for CYP2D6 will be conducted at Screening to determine metabolizer status. To reduce the inter-subject variability in exposure, subjects identified as poor metabolizers (PMs) will be excluded from the study.
Study Conduct	Subjects will be screened for study eligibility between Days -21 and -14. Subjects who are initially determined to be eligible, based on Screening assessments, will then participate in a 10-day IR risperidone run-in period, during which adherence with study treatment will be assessed. Subjects who remain eligible for the study will enter the inpatient unit on Day -2. After admittance to the inpatient unit and prior to the first LYN-005/matched placebo administration, samples for determination of IR risperidone PK will be collected from Days -2 to -1. Over the course of the study, subjects are to receive 3 doses of LYN-005/matched placebo, per their random assignment, 1 each on Days 1, 8, and 15, all on an inpatient basis. All subjects will also receive IR risperidone or matched placebo, again per their random assignment, from Days 1 to 21. Overall, during study participation, subjects will be housed in the inpatient unit twice, from Days -2 to 9 (Inpatient Stay 1) and then again from Days 14 to 16 (Inpatient Stay 2). Subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled. In between each inpatient stay, subjects will have study assessments performed on an outpatient basis daily from Days 10, 11, 12, and 13. After discharge from Inpatient Stay 2, subjects will again have assessments performed on an outpatient basis on Days 17, 18, 21, 22, and 23. An End of Study (EOS) visit will be conducted on Day 35. During study participation, guidelines will be in place for the use of recommended medications for agitation, anxiety, and insomnia. Rescue administration of an agent other than risperidone or paliperidone in the event of worsening of schizophrenia symptoms during the study can be administered at the discretion of the PI, with notification of the Study Medical Monitor. Extrapyramidal symptoms will be monitored throughout the study at regular intervals using the Extrapyramidal Symptom Rating Scale (ESRS). Severity of schizophrenia

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
	symptoms will be monitored throughout the study at regular intervals using the CGI-S scale. Concomitant medications, adverse events (AEs), safety laboratory tests, and vital signs will be assessed throughout the study, as per the Schedule of Events (Section 18.1.1 and Section 18.1.2).
Schedule of Events	The Schedules of Events are presented in Section 18.1.1 and Section 18.1.2.
SUBJECT POPULATION	
Number of Subjects:	Approximately 32 subjects of whom 24 will receive LYN-005 will be enrolled in the study. Subjects who discontinue prematurely may be replaced at the Sponsor's discretion.
Target Population:	Male and female subjects between the ages of 18 to 50 years of age, inclusive, with schizophrenia or schizoaffective disorder, as defined by DSM-5 criteria.
Entry Criteria	***Inclusion criteria:*** Eligibility for this study is met if each one of the following inclusion criteria is satisfied at Screening (or at baseline when specified): 1. Male or female aged ≥18 and ≤50 years. 2. Current diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria as confirmed by the MINI 7.0.2. 3. The following psychiatric criteria are to be used to determine subject eligibility: • Duration of diagnosis of schizophrenia or schizoaffective disorder of ≥2 years. • Outpatient; not hospitalized for worsening of schizophrenia within the last 6 months (partial hospitalization for social management within this time period is acceptable). • Medically stable over the last month and psychiatrically stable without significant symptom exacerbation over the last 3 months. 4. Stabilized on an oral antipsychotic medication (single agent) for a minimum of 6 weeks at the time of Screening. 5. On a stable dosage of all permitted non-antipsychotic medications (except for medication to be used on an as-needed basis) for at least 1 month prior to the Screening visit and for the duration of the study. 6. CGI-S score of ≤4 (moderately ill). 7. PANSS score of ≤80 points. 8. Body mass index (BMI) of ≥18 kg/m^2 and ≤35 kg/m^2. 9. Able to read and understand study procedures and provide written informed consent before the initiation of any protocol-specific procedures. 10. Willing to comply with all protocol-specified procedures and availability for the duration of the study.

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Investigational Product	LYN-005: Risperidone extended release capsule
	11. Subject has identified a caregiver or personal contact with whom the subject communicates with at least once a week. ***Exclusion Criteria:*** Subject will not be considered eligible to participate in this study if any one of the following exclusion criteria is satisfied at Screening (or at baseline when specified): 1. Subjects with known clinically significant esophageal or GI disease, including but not limited to: a. Known strictures such as esophageal web, pyloric stenosis, or small intestinal stricture, or subjects with high risk of stricture, e.g., Crohn's disease. b. Diagnosis of a condition known to elevate or lower gastric pH, e.g., achlorhydria or hypochlorhydria. c. Prior small or large bowel obstructions or varices. d. Prior abdominal or upper gastrointestinal surgery (prior uncomplicated laparoscopic procedures including appendectomy or colectomy). e. History of dysphagia or aspiration in the last 5 years. f. History of an esophageal motility disorder or undergoing treatment for a gastric motility disorder. g. Multiple episodes of abdominal pain within 3 months of Screening. h. Subjects who experience moderate or severe dysmenorrhea or menorrhagia (with use of pain medication) within 3 months of Screening. i. History of moderate to severe Acid Reflux Disease or a score of ≥2 on the Acid Reflux Severity Scale (ARSS) [2], indicating moderate to severe symptoms. The ARSS scale is as follows: None = 0 no symptoms Mild = 1 awareness of symptom, but easily tolerated Moderate = 2 discomfort sufficient to cause interference with normal activities Severe = 3 incapacitating, with inability to perform normal activities. 2. Subjects with PILL-5 questionnaire score of 5 or greater.

	3. Medical history or current diagnoses indicating the presence of any of the below conditions: a. Presence of an uncontrolled, unstable, clinically significant medical condition could that could put the subject at risk because of participation in the study, interfere with the subject's ability to participate in the study or influence the interpretation of safety or PK evaluations. b. History of a major cardiovascular event (myocardial infarction, cardiac surgery or revascularization, unstable angina, stroke, or transient ischemic attack) or a hospitalization for heart failure with 6 months of Screening. c. Any clinically significant illness, medical or surgical procedure or trauma within 4 weeks of Screening. d. Known immunocompromised status, including individuals who have undergone organ transplantation, on immunosuppression for an immune mediated disease, or are positive for human immunodeficiency virus (HIV). e. Subjects with a positive test for active hepatitis B or C at Screening. Subjects with successfully treated hepatitis B infection which has been resolved for greater than 1 year or successfully treated hepatitis C infection will not be excluded. f. Subjects who have donated more than 250 mL of blood within 30 days of Screening. g. Subjects who have difficulties with venipuncture/cannulation, including difficulty accessing veins for blood sampling and/or history of coagulopathy or endocarditis. h. Subjects with a current DSM-5 diagnosis of major depressive episode panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder on the MINI 7.0.2 or in the judgment of the Investigator. (Note that individuals with depression secondary to schizoaffective disorder are eligible). i. Suicidal ideation associated with actual intent and a method or plan in the past 6 months, as measured by the C-SSRS (i.e., "Yes" answers on items 4 or 5) at Screening or having made a suicide attempt within the last 2 years. j. Known or suspected (non-febrile) seizure disorder. k. History of neuroleptic malignant syndrome. l. Current or history of clinically significant tardive dyskinesia.

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	m. Known or suspected diagnosis of intellectual disability or organic brain disorder or other diagnosis that is primarily responsible for current symptoms and functional impairment. n. Medically non-adherent in the management of their schizophrenia/schizoaffective disorder. 4. Use of the below medications/treatments in the 2 weeks before enrollment, including: a. Proton pump inhibitors and H2 blockers. b. Prokinetic agents. c. Medications that may interfere with the absorption, metabolism, or excretion of risperidone, e.g.,: i. Drugs metabolized via CYP3A4 pathway, such as macrolide antibiotics and azole antifungals)Moderate or strong CYP3A4 p-glycoprotein (P-gp) enzyme inducers and inhibitors (carbamazepine, phenytoin, rifampicin, phenobarbital, itraconazole, verapamil). ii. Moderate or strong CYP2D6 inhibitors (e.g., fluoxetine, fluoxetine combinations, paroxetine), or quinidine. d. Concomitant medications, natural remedies, supplements or vitamins which are associated with changes to gastric motility or pH. Use of antacids is permissible, except within 2 hours of dosing with LYN-005. e. Benzodiazepines; except lorazepam, diazepam and oxazepam, which are acceptable if for the treatment of depression, anxiety or insomnia. f. Use of more than one antidepressant; or if on just one, a change in dose within 6 weeks of Screening. g. Depot antipsychotic use within 9 months of Screening. h. Electroconvulsive therapy within 3 months of Screening. 5. Subjects with clinically significant abnormal safety (e.g. physical examination, vital sign) or safety laboratory assessments, specifically: a. Presence of a clinically significant abnormal laboratory result on blood or urine safety tests at Screening. b. Anemia (hemoglobin below lower limit of normal reference range) at Screening.

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	c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN) and total bilirubin ≥1.5 × ULN. d. Moderate or severe renal insufficiency at Screening (glomerular filtration rate <60 mL/min, as determined using the Cockcroft-Gault formula). e. Heart rate of <50 beats per minute (bpm) at Screening. f. Systolic blood pressure ≥150 and/or diastolic blood pressure ≥100 mmHg at Screening. g. HbA1c ≥7.0% at Screening. h. Positive fecal occult blood test at Screening in subjects who are >45 years unless they have had a normal colonoscopy within the past 5 years. i. Clinically significant prolactin elevation (≥200 ng/mL for females; ≥100 ng/mL for males). 6. Subjects with the below specified patterns of substance use at Screening: a. Fulfillment of the DSM-5 criteria for moderate or severe substance use disorder (excluding nicotine and caffeine) within 6 months of Screening. b. History of alcohol consumption exceeding moderate use; in males exceeding 21 units per week and in females exceeding 14 units per week (1 unit = 360 ml beer, 25 mL of 40% spirit or a 125 mL glass of wine) over the past month. Subjects are not permitted to consume alcohol during the inpatient stay nor 12 hours before any clinic visit while outpatient. c. Positive ethanol breathalyzer. d. Positive urine drug screen for substances of abuse other than cannabis. e. Heavy nicotine use (consumption of >40 cigarettes or >36 mg of nicotine from other sources [e.g., vaping products] daily) or daily use of smokeless tobacco. 7. Subjects of reproductive potential who are (hetero) sexually active but unwilling to use acceptable means of contraception through the EOS. For clarity, subjects who are at least 1 year post-menopausal are not of reproductive potential. Acceptable means of contraception include: a. Subjects who have been surgically sterilized.

Name of Sponsor	Lyndra Therapeutics Inc.
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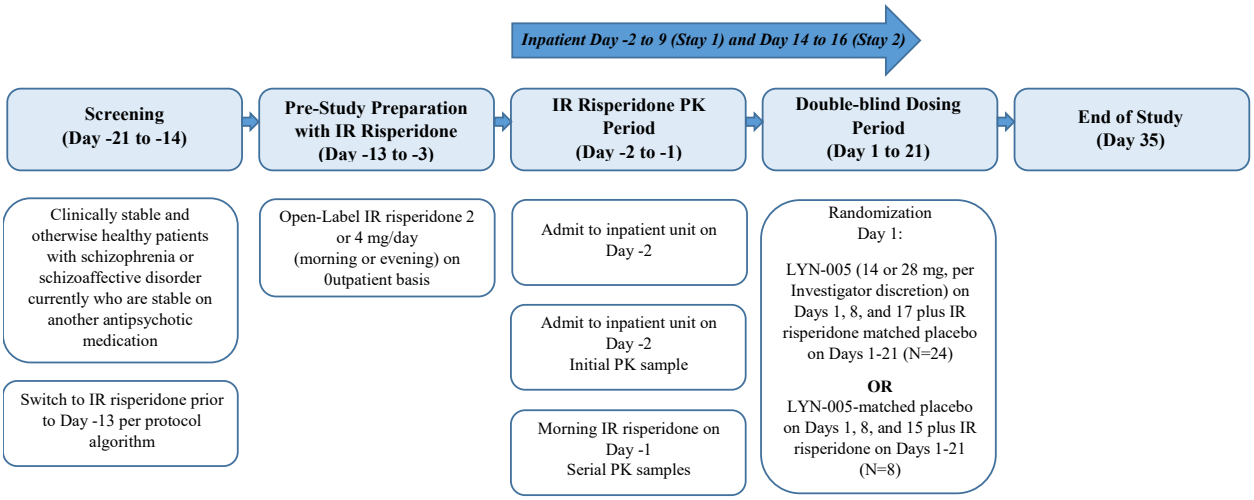
	b. Females of reproductive potential: diaphragm, injectable, oral/patch contraceptives for a minimum of 6 weeks, contraceptive sponge, implant, or intrauterine device in use prior to enrollment. c. Males: condom in combination with any of the above means of contraception. d. All subjects: abstinence may be an acceptable means of contraception as long as the individual consents to initiate immediate use of double barrier protection for the duration of the study should (hetero) sexual intercourse occur. 8. Subjects who are nursing or who have positive or indeterminate pregnancy tests at either Screening (serum test) or enrollment (urine test). 9. Use of any experimental agent within 1 month or 5 half-lives of Screening, whichever is longer. 10. Subjects who are employees or immediate family members of employees of the site, Sponsor or study-related vendors. 11. History of a serious allergic or hypersensitivity reaction to risperidone or LYN-005 excipients (refer to Investigator's Brochure). 12. Subjects with history of X-ray, computed tomography (CT) scan or angiogram of the abdomen within one year of Screening. 13. Subjects with CYP2D6 poor or underdetermined metabolizer status based on genetic testing.
STATISTICAL METHODS AND ANALYSIS	
Sample Size	The sample size of 32 (24 assigned to LYN-005 and 8 assigned to IR risperidone) is driven by clinical rather than statistical considerations for providing data in the evaluation of the endpoints.
Pharmacokinetics and Pharmacodynamics	Plasma concentration data for risperidone and 9-hydroxyrisperidone separately and combined as active moiety will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration-time data obtained will be performed using appropriate non-compartmental analysis to obtain estimates of the standard PK parameters. The pharmacokinetics of LYN-005 relative to IR at 2 dose levels will be determined. There are no pharmacodynamic endpoints in this study.
Safety	Safety data will be summarized by dose group, study period and overall.

Name of Sponsor	Lyndra Therapeutics Inc.
Investigational Product	LYN-005: Risperidone extended release capsule
Planned Analyses	There is a planned safety review by the Investigator and Medical Monitor on interim blinded PK through Day 14 from 12 subjects. Blinded safety data will also be reviewed at this time and will include adverse events, laboratory data, suicidality, and illness severity. Additionally, the PI or Sponsor may request an ad hoc review of safety information, e.g., serious adverse events, at any time during the study.

1.2 Study Schematic



1.3 List of Abbreviations

Abbreviation	Term
AE	Adverse event
AECI	Adverse events of clinical interest
ALT	Alanine aminotransferase
APD	Antipsychotic drug
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC_{0-168}	Area under the concentration versus time curve, time zero to 168 hours
AUC_{0-24}	Area under the concentration versus time curve, time zero to 24 hours
$AUC_{0-\infty}$	Area under the concentration versus time curve: time zero to infinity
AUC_{0-t}	Area under the concentration versus time curve: time zero to t (time point to be specified)
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximal observed concentration
C_{min}	Minimum observed concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DIMD	Drug-induced movement disorders
DIP	Drug-induced parkinsonism
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive therapy
EDC	Electronic Data Capture
EL	Extra Long
EOS	End of Study
EPS	Extrapyramidal symptoms
ER	Extended release
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
h	hour or hours
HbA1C	Glycated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody

Abbreviation	Term
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Council for Harmonization
ID	Identifier
ID	Identifier
IR	Immediate release
IRB	Institutional Review Board
Kel	First order elimination rate constant
LYN-005	Lyndra Extended Release Capsule containing risperidone
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional
MINI	Mini International Neuropsychiatric Interview version 7.0.2
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PK	Pharmacokinetic (adj.) *or* pharmacokinetics (singular noun)
QTcF	Corrected QT interval, Fridericia's correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMC	Safety Monitoring Committee
SOE	Schedule of Events
SUSAR	Serious unexpected suspected adverse reaction
TD	Tardive dyskinesia
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WHODDE	World Health Organization Drug Dictionary Enhanced

2 INTRODUCTION AND RATIONALE

2.1 Impact of Schizophrenia and Schizoaffective Disorder

Schizophrenia and schizoaffective disorder are chronic and debilitating psychiatric illnesses which have a massive global burden. There are millions of adults in the United States alone living with schizophrenia. The estimated prevalence rate of schizophrenia is around 0.5% in the United States (US) [3] and globally rates can be even higher, to above 1% [4]. In 2013, the total societal costs of schizophrenia were estimated at $155 billion in the US, with emergency room care alone estimated at $2.6 billion reflecting an emphasis on acute care for patients with schizophrenia [5]. When non-direct healthcare costs, such as lost productivity of patients and their caregivers are taken into account, schizophrenia could total up to 3% of the total healthcare budget of western countries [6].

Many patients suffer from lifelong persistent psychiatric symptoms and cognitive effects, which result in reduced quality of life and significant socio-economic impacts [7]. Approximately 75% of all patients diagnosed with schizophrenia will experience a relapse, generally within two years, and most will experience multiple relapses over the course of the illness [1]. Relapse associated with psychotic exacerbation can increase the risk of patients harming themselves or others and it can have potential negative effects on their relationships, education and work [8]. Furthermore, relapse can lead to long-term disability and an increased burden of health care needs in these patients [1, 9]. There are many factors that contribute to the risk of relapse, including patient-related, treatment-related, lifestyle, and disease-related factors such as an earlier onset of disease, severity at Baseline, lower social functioning, or substance abuse [10]. However, it is widely acknowledged that improving access to antipsychotic drug (APD) treatment for patients experiencing symptom exacerbation is critical to reduce relapses [1, 11, 12], and that non-adherence to APD treatment is the most frequently cited risk factor for relapse [10].

2.2 Role of Adherence

It is estimated that as many as half of all patients in developed countries are not taking their medications properly, and the level may be even higher in developing countries according to the World Health Organization (WHO) [13]. The collective impact to patients of not taking or not appropriately taking one's medicines is profound, leading to disease under-treatment, treatment resistance, drug toxicity, and other adverse outcomes.

> "Poor adherence to long-term therapies severely compromises the effectiveness of treatment making this a critical issue in population health both from the perspective of quality of life and of health economics. Interventions aimed at improving adherence would provide a significant positive return on investment through primary prevention (of risk factors) and secondary prevention of adverse health outcomes." [13]

In schizophrenia, non-adherence to APD treatment is common. A study of pharmacy records between 1998 and 1999 demonstrated medication possession ratios under 80% in almost 40% of patients prescribed APDs, with adherence fluctuating over time such that more than 60% of

patients experienced periods of significant nonadherence over a four-year period [14]. Few studies have assessed APD non-adherence directly via random blood drug sampling, but one such study showed rates of poor adherence were even higher, at 58% [15]. The associated treatment costs, disease progression and risk of relapse associated with poor control of disease, especially in relation to non-adherence to APD treatment, have been extensively studied.

Dosing frequency is the primary regimen factor that has been shown to influence adherence, where greater dosing frequency is associated with poorer outcomes [16]. A meta-analysis of all available randomized controlled studies of oral once daily versus oral once weekly therapy has demonstrated a consistent improved adherence by patients to their treatment across studies with a odds ratio of weekly therapy versus daily therapy of approximately 1.9 [17]. These data indicate that once weekly oral therapy for chronic disease could offer improved adherence as compared to daily oral therapy. In some analyses, the magnitude of the benefit of once weekly therapy versus once daily therapy expands over time, demonstrating substantial differences in the persistence to chronic therapy after two years [18].

2.3 Therapeutic Approach

The treatment of schizophrenia begins with acute symptom management for those who are in crisis and is followed by relapse prevention and access to supportive treatments. APD therapy is effective in most patients with schizophrenia or schizoaffective disorder in managing and stabilizing their symptoms. However, in order to avoid symptom exacerbation, continuous treatment with antipsychotic medication is recommended. Longer term (e.g., >6 months) and abrupt discontinuation with APD therapy has been associated with an increased risk of relapse [19-22].

The etiology of relapse in patients with schizophrenia or schizoaffective disorder is complex and multifaceted. Although some patients may never experience recurrence after their first episode, some patients on uninterrupted maintenance therapy may still experience changes in symptomology and relapse, which may require a change in treatment. It is essential that any intervention including treatment with an antipsychotic medication is appropriate and efficacious [23]. Selecting the correct medication for maintenance therapy is critical, and is largely driven by individual factors including symptomology (positive and negative symptoms), response to treatment, relapse risk profile as determined by a clinician, as well as by patient preference [24]. Among the second-generation atypical antipsychotics, risperidone is considered one of, if not the most, effective agent and is the most commonly prescribed agent in patients with schizophrenia. Numerous studies have shown the effectiveness of this medication, particularly with longer acting formulations [8, 25, 26], which is also related to the demonstrated improved medication adherence to these formulations of APDs [14]. For example, clinically stable patients with schizophrenia or schizoaffective disorder who switched to a long acting depot formulation of risperidone (RISPERDAL CONSTA), have demonstrated greater occurrence of sustained remission compared to patients on quetiapine [26]. PERSERIS is another once-monthly risperidone injection approved for the treatment of schizophrenia [27].

Lyndra Therapeutics is developing oral, extended release therapies with the intention to change how people take medicines to sustain therapeutic outcomes and benefits. Lyndra is targeting

therapeutic areas such as schizophrenia as well as Alzheimer's disease and transplant rejection where the replacement of daily (or more frequently), medication doses with weekly doses would improve pharmacologic consistency as well as medication adherence and lead to better health outcomes.

2.4 Study Rationale

Discussions with practicing psychiatrists and key opinion leaders around the world have identified a high level of interest and desire for a once-weekly oral therapeutic option. Lyndra's objective is to meet this need by offering long-acting oral once-weekly formulations of approved antipsychotic drugs to clinicians and patients. The development of an oral, extended release formulation of risperidone provides an alternative to bi-weekly intramuscular depot delivery of risperidone or daily oral risperidone. Lyndra's aim is to reduce the frequency of daily dosing to once weekly or less to help improve the management of this chronic debilitating illness. The target population for the Lyndra formulation (LYN-005) is subjects with schizophrenia already stabilized on US Food and Drug Administration-approved APDs and requiring maintenance therapy.

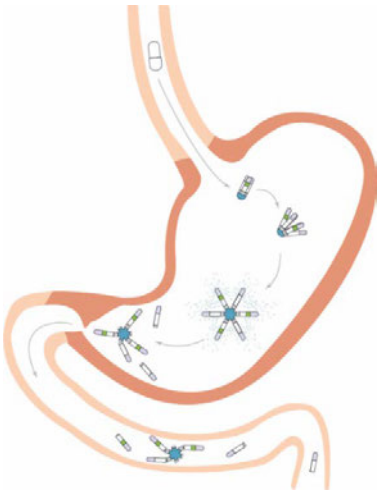
This study will evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple doses of LYN-005, a once-weekly, 14 and 28 mg extended release capsule of risperidone in otherwise healthy subjects with schizophrenia or schizoaffective disorder. Following a thorough review of the literature, it was determined subjects already taking risperidone may be a safer population for evaluating LYN-005 than healthy volunteers. Healthy volunteers who are naïve to risperidone or other second-generation antipsychotic agents may experience significant adverse events (AEs) due to D2 receptor antagonist activity when administered multiple doses at therapeutic levels [28]. Early clinical pharmacology studies with risperidone and other atypical antipsychotics involving healthy volunteers did observe dose-related AEs and laboratory changes (including hyperprolactinemia). The risk of side effects including extrapyramidal symptoms (EPS) such as drug-induced parkinsonism (DIP) and tardive dyskinesia (TD), the latter which can be permanent in some individuals [29], and possible AEs such as weight gain, anticholinergic effects, hyperprolactinemia and sexual impairment [30, 31] were considered unduly high. There is precedence for conducting early studies in patients rather than healthy volunteers for extended-release injectable risperidone products in the US with RISPERDAL CONSTA [32] and PERSERIS [27] due to these unnecessary risks to healthy volunteers.

2.5 Lyndra Extended Release Capsule

The LYN-005 (risperidone) extended release capsule is designed with modular components that serve specific functions for safe delivery of the formulation to the stomach. The components include a controlled release formulation and a capsule in which it is contained until the capsule disintegrates and the formulation opens in the stomach. The capsule is coated to promote transit through the esophagus without opening and thereafter, opening at gastric pH. [redacted]

[redacted]

Figure 2-2: Overview of Mechanism of Action



Colors for illustrative purposes only

When the coated capsule reaches the gastric environment (Figure 2-2), the exposure to acid causes dissolution of the acid-soluble (reverse enteric) coating, allowing the capsule to disintegrate and the formulation to unfold. The formulation opens into a configuration designed for retention within the stomach for a certain duration (i.e., gastric residence). Thereafter the formulation releases drug in a controlled and linear fashion, followed by safe exit and passage out of the stomach, transits through the intestinal tract until the formulation is excreted like other non-soluble materials. The design features by which the ER capsule achieves these targets are described in further detail in the current Lyndra Technology Background document.

2.6 Active Ingredient – Risperidone

Risperidone is an established second-generation antipsychotic belonging to the class of antipsychotic agents, the benzisoxazole-derivatives. Risperidone is a selective monoaminergic antagonist with a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors with no affinity for cholinergic receptors. The antipsychotic activity of risperidone is attributed to both risperidone and its active metabolite 9-hydroxyrisperidone, considered together as the active moiety of risperidone. The mechanism of action in improving positive symptoms of

schizophrenia is considered related to central dopamine D2 receptor antagonism. The balance of 5-HT2 to D2 receptor binding is thought to reduce extrapyramidal side effect liability from dopamine antagonism and extend the therapeutic activity to reducing negative and affective symptoms of schizophrenia.

Risperidone is primarily metabolized by cytochrome P450 (CYP) 2D6 to 9-hydroxyrisperidone which has two enantiomers with similar pharmacological activity to risperidone. Risperidone and 9-hydroxyrisperidone together form the pharmacologically active moiety that is similar in extensive and poor metabolizers; approximately 24 hours. The elimination half-life of risperidone alone is approximately 3 hours in extensive metabolizers and 17-20 hours in poor metabolizers. Clinical studies do not suggest that poor and extensive metabolizers have different rates of adverse effects, and risperidone is generally well-tolerated [33].

2.7 Benefits/Risks

The LYN-005 extended release (ER) capsule is a novel investigational formulation of risperidone designed to provide sustained oral drug delivery over 1 week, further described in the Investigator's Brochure. It is being developed for patients with schizophrenia whose tolerability and symptom management have already been established with oral administration of immediate release (IR) risperidone. The oral dose range considered effective in maintaining clinical stability of psychiatric symptoms from schizophrenia following acute therapy is 2 to 6 mg daily or 14 to 42 mg per week.

This study will evaluate 3 oral doses of once-weekly risperidone using the LYN-005 ER capsule at doses of 14 and 28 mg, designed to release the equivalent of 2 or 4 mg risperidone daily over 7 days. The study will be conducted in clinically stable subjects diagnosed with schizophrenia or schizoaffective disorder receiving a therapeutic dose of an APD for at least 6 weeks prior to Screening. Subjects will be in general good physical health who are mildly or moderately psychiatrically ill but clinically stable for at least 3 months prior to Screening and no hospitalization due to worsening of schizophrenia within the prior 6 months.

LYN-005 risperidone extended release capsule development has been informed by the results of previous clinical studies. The Sponsor has adopted several risk mitigation measures to protect subjects participating in Lyndra studies, described in the following subsections.

2.7.1 Risks Associated with Active Ingredient

Reference is made to the current LYN-005 Investigator's Brochure, Section 6.3, which includes reference material for marketed risperidone products and potential risks associated with risperidone.

2.7.2 Risks Associated with Extended Release Capsule

Although measures have been put into place to minimize risks to participants in the study, the following risks may occur with dosing with LYN-005 ER:

- Capsule dysphagia or aspiration.
- Esophageal capsular opening with formulation release and/or lodging in the esophagus.
- Irritation or injury to the mucosa of the gastrointestinal tract associated with passage of a partially or fully intact formulation.
- Rectal bleeding or rectal retention of formulation components that may require digital extraction.
- Obstipation, obstruction or perforation of the gastrointestinal tract.
- Shortened or prolonged gastrointestinal retention of the formulation, which may warrant additional assessments, including imaging.
- Abdominal events such as abdominal pain, discomfort, bloating, or nausea.

2.7.3 Risks Associated with Study Related Procedures

The following additional risks may occur associated with study-related procedures:

- X-Rays: detection of underlying anatomic abnormality or previously unknown health condition, injury from radiation exposure.
- Detection of unknown disease necessitating further evaluation and follow-up.
- Blood sampling: excessive bleeding, bruising, presyncope/syncope, nerve damage, or infection at the venipuncture site.
- Electrocardiogram (ECG) tracing: irritation or rash of the skin due to the use of adhesive leads.

2.7.4 Benefits/Risks Conclusions

There are no direct benefits to the subjects in this study. Subjects will be housed in the inpatient unit for 2 inpatient periods, totaling 11 days, for the evaluation of LYN-005, allowing daily monitoring for AEs or changes in symptomatology that might require treatment. APD dosing during the inpatient portion of the study will be supervised by the study site to ensure compliance with therapy and control of symptoms. Following discharge from the site, in addition to follow-up study center visits, subjects will be contacted periodically to help ensure medication compliance during the outpatient phase of the study.

There is risk of AEs from risperidone; to minimize this risk, doses are limited to the low to mid-range.

There is a possibility that the screening and evaluation tools employed in this study may suggest or detect a previously unknown health condition that may warrant additional investigation by the individual's general practitioner and in the case of positive human immunodeficiency virus (HIV) results, notification of health authorities in accordance with local and national requirements.

Detailed information for potential benefits and risk for LYN-005 (risperidone) extended release capsules may be found in the current LYN-005 Investigator's Brochure, Section 6.3.

3 STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives along with the associated endpoints are summarized in Table 3-1.

Table 3-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary:	
• To determine the safety and tolerability of risperidone extended release capsules (LYN-005) administered as repeat weekly doses compared to IR risperidone tablets at 2 dose levels;	• Incidence of treatment emergent adverse events (TEAEs).
• To characterize the PK of risperidone, active metabolite 9-hydroxyrisperidone and active moiety (risperidone and 9-hydroxyrisperidone combined) after repeat weekly doses of LYN-005 ER capsules relative to IR risperidone tablets at 2 dose levels.	• Risperidone, 9-hydroxyrisperidone, and active moiety PK after oral administration of LYN-005 capsules and IR risperidone to include, as possible and appropriate, C_{max}, C_{min}, T_{max}, Kel, $AUC_{(0-24)}$, $AUC_{(0-t)}$, $AUC_{(0-168)}$ and $AUC_{(0-\infty)}$.
Secondary:	
• To assess the exposure to risperidone, 9-hydroxyrisperidone and active moiety during the switch from IR risperidone to LYN-005.	• Exposure to risperidone, 9-hydroxyrisperidone and active moiety as assessed from C_{max}, T_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ after switching from IR risperidone to LYN-005.
Exploratory:	
• To model the PK of risperidone, 9-hydroxyrisperidone and active moiety when administered as a LYN-005 extended-release capsule.	• PK modelling of risperidone, 9-hydroxyrisperidone, and active moiety exposure.

4 STUDY PLAN

4.1 Study Design

LYN-005-C-004 is a blinded, multiple-dose, randomized, parallel group, safety, tolerability and PK study of LYN-005 in subjects with a primary diagnosis of schizophrenia or schizoaffective disorder in general good health. Eligible subjects must be clinically stable and receiving a therapeutic dose of an approved oral antipsychotic drug for a minimum of 6 weeks at the time of Screening. Enrolled subjects will be evaluated under steady-state conditions on commercially-available IR risperidone tablets and then assigned in blinded fashion either to LYN-005 weekly or continued encapsulated IR risperidone daily for 3 weeks to attain (or continue) steady-state exposure.

A total of 32 subjects will participate in this study. Subjects will be randomized to LYN-005 plus IR risperidone matched placebo OR LYN-005 matched placebo or IR risperidone as follows:

- Arm 1: LYN-005 (14 or 28 mg weekly) plus IR risperidone matched placebo (N=24).
- Arm 2: LYN-005 matched placebo plus IR risperidone (2 or 4 mg/day) (N=8).

Per above, in order to maintain the blind, all subjects will either receive LYN-005 and IR risperidone-matched placebo or LYN-005-matched placebo and IR risperidone, as follows:

Arm 1:

- LYN-005: Size 00EL capsules containing LYN-005 stellate; the 14mg dose of LYN-005 contains 3 active arms containing risperidone, and 3 inactive arms and he 28 mg dose of LYN-005 contains 6 active arms containing risperidone.

  AND

- IR Risperidone Matched Placebo: Orange capsule-shaped tablets containing inactive ingredient.

Arm 2:

- LYN-005 Matched Placebo: Size 00EL capsules containing inactive ingredient with no stellate.

  AND

- IR Risperidone: Risperidone 2 mg (orange) capsule-shaped tablets.

Although treatment assignment is blinded; the dose level is not blinded. The dose of LYN-005 (14 or 28 mg)/IR risperidone (2 or 4 mg/day) administered will be based on the subject's current antipsychotic medication dose. Across both arms, a minimum of 8 subjects are to be enrolled at each dose level (LYN-005 14 mg/IR risperidone 2 mg/day [low dose] and LYN-005 28 mg/IR risperidone 4 mg/day [high dose]); thus, if 16 subjects receiving the low dose have been enrolled, all remaining subjects must be enrolled at the high dose level and vice versa.

All administrations of LYN-005 will be supervised. Complete PK evaluations will be performed after each LYN-005 dose, as designated in the Schedules of Events (SOE) (Section 18.1.1 and Section 18.1.2) and over 24 hours at steady-state for IR risperidone at the beginning of the study.

LYN-005 will be evaluated in subjects who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of schizophrenia or schizoaffective disorder of at least 2 years, who have already been stabilized on an oral antipsychotic medication for a minimum of 6 weeks at the time of screening with no psychiatric hospitalizations for relapse in the past 6 months. Subjects who are prescribed an antipsychotic agent other than risperidone or a dose of risperidone outside the range are also eligible for study participation if they are a) able to tolerate risperidone and b) be completed switched to 2 or 4 mg daily oral risperidone for a minimum of 2 weeks prior to the first dose of LYN-005/placebo on Day 1 (see Section 6.3.1).

Eligible subjects must be clinically stable (i.e., mildly or moderately ill psychiatrically), with a low risk of relapse and otherwise healthy without history of significant GI diseases. Guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. In the event of worsening of schizophrenia symptoms while receiving risperidone during the study, another medication can be administered at the discretion of the Principal Investigator (PI), with notification of Lyndra's Medical Monitor.

Subjects will be screened for study eligibility between Days -21 and -14. Subjects who are initially determined to be eligible, based on initial Screening assessments, will then participate in a 10-day IR risperidone run-in period, during which adherence with study treatment will be assessed. Subjects who remain eligible for the study will enter the inpatient unit on Day -2. After admittance to the inpatient unit and prior to the first LYN-005/matched placebo administration, samples for determination of IR risperidone PK will be collected from Days -2 to -1.

Over the course of the study, subjects are to receive 3 doses of LYN-005/matched placebo, per their random assignment, 1 each on Days 1, 8, and 15, all on an inpatient basis. All subjects also will receive IR risperidone or matched placebo, again per their random assignment, from Days 1 to 21.

Overall, during study participation, subjects will be housed in the inpatient unit twice, from Days -2 to 9 (Inpatient Stay 1) and then again from Days 14 to 16 (Inpatient Stay 2). Subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled. In between each inpatient stay, subjects will have study assessments performed on an outpatient basis daily from Days 10, 11, 12, and 13. After discharge from Inpatient Stay 2, subjects will again have assessments performed on an outpatient basis on Days 17, 18, 21, 22, and 23. An End of Study (EOS) visit will be conducted on Day 35.

During study participation, guidelines will be in place for the use of recommended rescue medications for agitation, anxiety, and insomnia. Rescue administration of an agent other than risperidone or paliperidone in the event of worsening of schizophrenia symptoms during the study can be administered at the discretion of the PI, with notification of Lyndra's Medical Monitor. Extrapyramidal symptoms will be monitored throughout the study at regular intervals

using the Extrapyramidal Symptom Rating Scale (ESRS). Severity of schizophrenia/schizoaffective disorder symptoms will be monitored throughout the study at regular intervals using the Clinical Global Impression-Severity (CGI-S) scale. Concomitant medications, AEs, safety laboratory tests, and vital signs will be assessed throughout the study, as per the SOE (Section 18.1.1 and Section 18.1.2).

Details regarding each study period follow.

4.1.1 Screening Period (Day -21 to Day -14):

All screening procedures will be performed on an outpatient basis. Prior to any screening procedures, the subject or designated representative must provide written informed consent. Male and female subjects between 18 to 50 years of age who have a diagnosis of schizophrenia or schizoaffective disorder, as defined by DSM-5 criteria and as confirmed by the Mini International Neuropsychiatric Interview (MINI) version 7.0.2. The MINI will also be used to exclude comorbid psychiatric diagnoses. Further eligibility requirements will include a CGI-S score of ≤4 (moderately ill). Subjects must have been medically stable within the last month, and stable in their psychiatric illness on a stable antipsychotic treatment regimen and without significant symptom exacerbation over the last 3 months. Additionally, subjects must be receiving outpatient treatment and not have been hospitalized for worsening schizophrenia in the last 6 months (hospitalization for social management within this time is acceptable). Subjects should have a Positive and Negative Syndrome Scale (PANSS) score aligned with stable and mild-moderate disease (i.e., ≤80 points).

An assessment of pill swallowing will be assessed with a questionnaire, PILL-5, where a score of 4 or below is regarded as “normal” pill swallowing. Additional screening measures to confirm general good health will be performed as described in the SOE (Section 18.1.1).

To be eligible for this study, subjects must either have been stable on a therapeutic dose of an oral IR risperidone between 2 and 8 mg/day or been on a stable dose of another antipsychotic medication (single agent) for a minimum of 6 weeks. As shown in Figure 6-1, subjects already receiving 2 to 4 mg IR risperidone will transition to 2 mg daily administration by Day -13 to complete the run-in. Subjects on a daily dose of approximately 4 mg to 8 mg IR risperidone will be placed in a cohort based on clinical judgement of the Investigator and fully transitioned to this dose by Day -13 and remain at this dose during the run-in.

Subjects who currently are on antipsychotic medications other than IR risperidone are also eligible for the study and are to be switched to either 2 or 4 mg/day IR risperidone based on the clinical judgement of the Investigator are to begin the transition to IR risperidone starting on Day -13; by Day -13, these subjects should only be receiving 2 or 4 mg IR daily during the run-in. To improve toleration and management of symptoms during the transition to risperidone run-in, short-term changes to the daily risperidone dose during the run-in may be considered in consultation with the PI. A home or clinic visit may also be considered at the discretion of the PI in order to assure subject stability.

4.1.2 Pre-study Preparation with IR Risperidone

All subjects who are eligible for study participation at the end of Screening will receive a medication log for use Days -13 through -3 to record the timing and dose of their IR risperidone during the run-in period. IR Risperidone must be taken once a day and at approximately the same time of day (morning or evening) on Days -13 to -3. Guidelines for switching antipsychotic medication to risperidone 2 or 4 mg/day prior to Day -13 are provided in Figure 6-1 in Section 6.3.1.

Eligible subjects will be contacted daily on Days -13 to -3 prior to admission to the study unit on Day -2 to ensure medication adherence and check on safety, concomitant medications, and AEs. The subject must be adherent (self-report) with risperidone administration for 5 consecutive days prior to Day -3 to be eligible for enrollment into the study. Additional days may be added to the pre-study preparation to ensure 5 consecutive days of medication adherence prior to Day -3. Subjects who confirm medication adherence will be prepared by the site regarding the arrangements for subject arrival at the study unit the next day (Day -2) and the subsequent 10-night stay. Subjects will be instructed on Day -3 to take their risperidone dose at the normal time and to not bring risperidone tablets to the unit on Day -2.

4.1.3 IR Risperidone PK Period

Subjects will be admitted to the study unit on Day -2.

Medication adherence for IR risperidone based on the medication log should be assessed upon arrival to the unit on Day -2, and subjects who are non-adherent are not to be admitted to the inpatient unit at that time. The site should confirm the dose and time of last IR risperidone for subjects who remain eligible to begin the inpatient phase of the study, and a blood sample collected for PK analysis.

Subjects who are switching from evening to morning dosing will be given half the regimen of daily oral risperidone in the evening of Day -2 (i.e., either 1 or 2 mg risperidone) to minimize overlapping exposure. This dose should be given after the evening (6 pm) PK sample has been collected. Morning administration of the full dose of IR risperidone, 2 or 4 mg respectively, must begin by Day -1 for all subjects.

Patients will receive IR risperidone on Day -1, as described in Section 6.3.2, with PK samples collected thereafter.

4.1.4 Randomization (Day 1)

Subjects who successfully complete the admission procedures will be randomized on Day 1 in a 3:1 ratio to LYN-005 or IR risperidone, as follows:

- LYN-005: Subjects randomly assigned to LYN-005 ER will receive a single LYN-005 ER capsule (14 or 28 mg) taken once-weekly (on Days 1, 8, and 15) plus dummy IR risperidone-matched placebo daily though Day 21.

- IR Risperidone: Subjects randomly assigned to IR risperidone will receive a single weekly dummy capsule (placebo capsule representing LYN-005, but containing no stellate) taken once-weekly (On Days 1, 8, and 15) plus IR risperidone (2 or 4 mg/day) daily though Day 21.

Subjects will be split into 2 groups based on their IR risperidone run-in dose prior to randomization. Subjects receiving 2 mg/day IR risperidone will be randomized to receive either 14 mg/week LYN-005 or continued 2 mg/day IR risperidone and those receiving 4 mg/day IR risperidone will be randomized to receive either 28 mg/week LYN-005 or continue with 4 mg/day risperidone, respectively. Although treatment assignment is blinded; the dose level is not blinded. Within each treatment arm, a minimum of 8 subjects are to be enrolled at each dose level; thus, if 16 subjects have been enrolled at a given dose level, all remaining subjects must be enrolled at the other dose level.

4.1.5 Double-blind Dosing Period (Days 1 to 21)

During the LYN-005 dosing period, subjects are to receive 3 doses of LYN-005 or matched placebo, one each on Days 1, 8, and 15. Following an overnight fast, subjects are to consume a light breakfast over 30 minutes or less, with the meal started 30 minutes prior to study drug administration. Subjects also will receive IR risperidone Study assessments are to be performed before and after each dose per the Schedule of Events (Section 18.1.1 and Section 18.1.2).

Subjects will remain in the inpatient unit until Day 9 for continued safety monitoring. On Day 9, the Investigator will perform study assessments to confirm the subject is eligible to leave the inpatient unit and continue outpatient treatment with study drug.

After discharge from the inpatient unit on Day 9, subjects will be followed on an outpatient basis from Days 10 to 13 via safety calls until their return to the unit on Day 14. During this period, subjects will continue taking their daily dummy or IR risperidone as prescribed.

In the evening of Day 14, subjects will return to the clinic for Inpatient Period 2 in advance of the third LYN-005/matched placebo administration on Day 15. AEs and concomitant medications will be assessed upon arrival.

On the morning of Day 15, a pre-dose PK-sample will be collected, and as on Days 1 and 8, subjects will be administered either the third dose of LYN-005/matched placebo. PK samples will be collected and safety assessments performed as per the SOE (Section 18.1.1 and Section 18.1.2). Subjects are to remain in the unit for a minimum of 8 hours for observation prior to discharge on Day 16.

On Days 16 through 21, subjects will continue taking their daily IR risperidone or matched placebo as outpatients, as per their random treatment assignment.

4.1.6 End of Study Visit (Day 35)

On Day 35, subjects will be asked to return to the clinic for follow-up assessments, as per the SOE (Section 18.1.2). Thereafter, additional follow-up telephone calls may occur as warranted if there are ongoing AEs at the time of the EOS Visit.

4.2 Blinding Procedures

Subjects and site and Sponsor personnel associated with study conduct will be blinded to treatment assignment.

During the conduct of the study, the blind should only be broken on an individual subject basis in the event of an emergency where it is necessary for the Investigator to know which treatment the subject is receiving before the subject can be treated. The code may also be broken if someone not in the study uses study drug (e.g., if a child in the subject's household takes study drug, the blind may be broken to determine treatment for the child).

When it is necessary to break the blind, the Investigator may unblind the treatment immediately (i.e., without prior notice to the Medical Monitor, sponsor, or other) via the Interactive Response Technology system, but must notify the IRB per local regulations and Sponsor as soon as possible, preferably by telephone and then in writing, regarding the necessity of code breaking.

If the code is broken for a subject, this must be documented in the electronic case report form (eCRF) and source documents, together with the reasons for breaking the code.

4.3 Justification of Dose Selection

The justification for dose selection is based on the target oral dose range for risperidone ranging from 2 to 8 mg/day in subjects with schizophrenia and schizoaffective disorder [33]. These doses would be expected to correspond to therapeutically equivalent weekly doses of 14 to 56 mg risperidone using LYN-005. Accordingly, for this study, 14 and 28 mg LYN-005 ER capsule formulations of risperidone will be evaluated.

LYN-005 containing 14 and 28 mg risperidone is expected to deliver comparable exposures to risperidone active moiety concentrations associated with 2 mg/day and 4 mg/day, respectively, given orally as an immediate release formulation over 1 week. Given the metabolism of risperidone to the equipotent metabolite, 9-hydroxyrisperidone, and due to the exposure differences between poor and extensive metabolizers, it was decided to exclude poor metabolizers to minimize study variability.

5 SUBJECT POPULATION

5.1 Inclusion Criteria

To be eligible to participate in the study, subjects must meet ALL of the following inclusion criteria at Screening (or at enrollment when specified):

1. Male or female aged ≥18 and ≤50 years.

2. Current diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria as confirmed by the MINI 7.0.2.

3. The following psychiatric criteria are to be used to determine subject eligibility:

    - Duration of diagnosis of schizophrenia or schizoaffective disorder of ≥2 years.

    - Outpatient; not hospitalized for worsening of schizophrenia within the last 6 months (partial hospitalization for social management within this time period is acceptable).

    - Medically stable over the last month and psychiatrically stable without significant symptom exacerbation over the last 3 months.

4. Stabilized on an oral antipsychotic medication (single agent) for a minimum of 6 weeks at the time of Screening.

5. On a stable dosage of all permitted non-antipsychotic medications (except for medication to be used on an as-needed basis) for at least 1 month prior to the Screening visit and for the duration of the study.

6. CGI-S score of ≤4 (moderately ill).

7. PANSS score of ≤80 points.

8. Body mass index (BMI) of ≥18 kg/m^2 and ≤35 kg/m^2.

9. Able to read and understand study procedures and provide written informed consent before the initiation of any protocol-specific procedures.

10. Willing to comply with all protocol-specified procedures and availability for the duration of the study.

11. Subject has identified a caregiver or personal contact with whom the subject communicates with at least once a week.

5.2 Exclusion Criteria

In order to be eligible to participate in the study, subjects must meet NONE of the following exclusion criteria at Screening (or at enrollment when specified):

1. Subjects with known clinically significant esophageal or GI disease, including but not limited to:

    a. Known strictures such as esophageal web, pyloric stenosis, or small intestinal stricture, or subjects with high risk of stricture, e.g., Crohn's disease.

    b. Diagnosis of a condition known to elevate or lower gastric pH, e.g., achlorhydria or hypochlorhydria.

    c. Prior small or large bowel obstructions or varices.

    d. Prior abdominal or upper gastrointestinal surgery (prior uncomplicated laparoscopic procedures including appendectomy or colectomy).

    e. History of dysphagia or aspiration in the last 5 years.

    f. History of an esophageal motility disorder or undergoing treatment for a gastric motility disorder.

    g. Multiple episodes of abdominal pain within 3 months of Screening.

    h. Subjects who experience moderate or severe dysmenorrhea or menorrhagia (with use of pain medication) within 3 months of Screening.

    i. History of moderate to severe Acid Reflux Disease or a score of ≥2 on the Acid Reflux Severity Scale (ARSS) [2], indicating moderate to severe symptoms. The ARSS scale is as follows:

        None = 0 no symptoms

        Mild = 1 awareness of symptom, but easily tolerated

        Moderate = 2 discomfort sufficient to cause interference with normal activities

        Severe = 3 incapacitating, with inability to perform normal activities.

2. Subjects with PILL-5 questionnaire score of 5 or greater.

3. Medical history or current diagnoses indicating the presence of any of the below conditions:

    a. Presence of an uncontrolled, unstable, clinically significant medical condition could that could put the subject at risk because of participation in the study, interfere with the subject's ability to participate in the study or influence the interpretation of safety or PK evaluations.

b. History of a major cardiovascular event (myocardial infarction, cardiac surgery or revascularization, unstable angina, stroke, or transient ischemic attack) or a hospitalization for heart failure with 6 months of Screening.

c. Any clinically significant illness, medical or surgical procedure or trauma within 4 weeks of Screening.

d. Known immunocompromised status, including individuals who have undergone organ transplantation, on immunosuppression for an immune mediated disease, or are positive for HIV.

e. Subjects with a positive test for active hepatitis B or C at Screening. Subjects with successfully treated hepatitis B infection which has been resolved for greater than 1 year or successfully treated hepatitis C infection will not be excluded.

f. Subjects who have donated more than 250 mL of blood within 30 days of Screening.

g. Subjects who have difficulties with venipuncture/cannulation, including difficulty accessing veins for blood sampling and/or history of coagulopathy or endocarditis.

h. Subjects with a current DSM-5 diagnosis of major depressive episode panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder on the MINI 7.0.2 or in the judgment of the Investigator. (Note that individuals with depression secondary to schizoaffective disorder are eligible).

i. Suicidal ideation associated with actual intent and a method or plan in the past 6 months, as measured by the C-SSRS (i.e., “Yes” answers on items 4 or 5) at Screening or having made a suicide attempt within the last 2 years.

j. Known or suspected (non-febrile) seizure disorder.

k. History of neuroleptic malignant syndrome.

l. Current or history of clinically significant tardive dyskinesia.

m. Known or suspected diagnosis of intellectual disability or organic brain disorder or other diagnosis that is primarily responsible for current symptoms and functional impairment.

n. Medically non-adherent in the management of their schizophrenia/schizoaffective disorder.

4. Use of the below medications/treatments in the 2 weeks before enrollment, including:

   a. Proton pump inhibitors and H2 blockers.

   b. Prokinetic agents.

c. Medications that may interfere with the absorption, metabolism, or excretion of risperidone, e.g.,:

   i. Drugs metabolized via CYP3A4 pathway, such as macrolide antibiotics and azole antifungals)Moderate or strong CYP3A4 p-glycoprotein (P-gp) enzyme inducers and inhibitors (carbamazepine, phenytoin, rifampicin, phenobarbital, itraconazole, verapamil).

   ii. Moderate or strong CYP2D6 inhibitors (e.g., fluoxetine, fluoxetine combinations, paroxetine), or quinidine.

d. Concomitant medications, natural remedies, supplements or vitamins which are associated with changes to gastric motility or pH. Use of antacids is permissible, except within 2 hours of dosing with LYN-005.

e. Benzodiazepines; except lorazepam, diazepam and oxazepam, which are acceptable if for the treatment of depression, anxiety or insomnia.

f. Use of more than one antidepressant; or if on just one, a change in dose within 6 weeks of Screening.

g. Depot antipsychotic use within 9 months of Screening.

h. Electroconvulsive therapy within 3 months of Screening.

5. Subjects with clinically significant abnormal safety (e.g. physical examination, vital sign) or safety laboratory assessments, specifically:

   a. Presence of a clinically significant abnormal laboratory result on blood or urine safety tests at Screening.

   b. Anemia (hemoglobin below lower limit of normal reference range) at Screening.

   c. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN) and total bilirubin ≥1.5 × ULN.

   d. Moderate or severe renal insufficiency at Screening (glomerular filtration rate <60 mL/min, as determined using the Cockcroft-Gault formula).

   e. Heart rate of <50 beats per minute (bpm) at Screening.

   f. Systolic blood pressure ≥150 and/or diastolic blood pressure ≥100 mmHg at Screening.

   g. HbA1c ≥7.0% at Screening.

   h. Positive fecal occult blood test at Screening in subjects who are >45 years unless they have had a normal colonoscopy within the past 5 years.

i. Clinically significant prolactin elevation (≥200 ng/mL for females; ≥100 ng/mL for males).

6. Subjects with the below specified patterns of substance use at Screening:

   a. Fulfillment of the DSM-5 criteria for moderate or severe substance use disorder (excluding nicotine and caffeine) within 6 months of Screening.

   b. History of alcohol consumption exceeding moderate use; in males exceeding 21 units per week and in females exceeding 14 units per week (1 unit = 360 ml beer, 25 mL of 40% spirit or a 125 mL glass of wine) over the past month. Subjects are not permitted to consume alcohol during the inpatient stay nor 12 hours before any clinic visit while outpatient.

   c. Positive ethanol breathalyzer.

   d. Positive urine drug screen for substances of abuse other than cannabis.

   e. Heavy nicotine use (consumption of >40 cigarettes or >36 mg of nicotine from other sources [e.g., vaping products] daily) or daily use of smokeless tobacco.

7. Subjects of reproductive potential who are (hetero) sexually active but unwilling to use acceptable means of contraception through the EOS. For clarity, subjects who are at least 1 year post-menopausal are not of reproductive potential. Acceptable means of contraception include:

   a. Subjects who have been surgically sterilized.

   b. Females of reproductive potential: diaphragm, injectable, oral/patch contraceptives for a minimum of 6 weeks, contraceptive sponge, implant, or intrauterine device in use prior to enrollment.

   c. Males: condom in combination with any of the above means of contraception.

   d. All subjects: abstinence may be an acceptable means of contraception as long as the individual consents to initiate immediate use of double barrier protection for the duration of the study should (hetero) sexual intercourse occur.

8. Subjects who are nursing or who have positive or indeterminate pregnancy tests at either Screening (serum test) or enrollment (urine test).

9. Use of any experimental agent within 1 month or 5 half-lives of Screening, whichever is longer.

10. Subjects who are employees or immediate family members of employees of the site, Sponsor or study-related vendors.

11. History of a serious allergic or hypersensitivity reaction to risperidone or LYN-005 excipients (refer to Investigator's Brochure).

12. Subjects with history of X-ray, computed tomography (CT) scan or angiogram of the abdomen within one year of Screening.

13. Subjects with CYP2D6 poor or underdetermined metabolizer status based on genetic testing.

5.3 Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical study but who do not meet inclusion/exclusion criteria and hence are not subsequently enrolled in the study. (For the purposes of this study, subjects who are admitted to the inpatient unit on Day -2 will be considered enrolled.) A minimal set of screen failure information is required to be captured to ensure transparent reporting of screen failure subjects and to respond to queries from Regulatory Authorities. Information to be captured on screen failure subjects includes demography, screen failure details including any inclusion/exclusion criteria that were not met, the primary reason and the relevant data (e.g., laboratory, medical historical details) that support the determination. Where applicable, potential subjects may be rescreened to reassess eligibility. These subjects should be assigned the same subject numbers as for the initial screening.

Subjects who consent to participate in the clinical study, meet eligibility criteria but are not enrolled will be referred to as Alternates (not screen failures) and may be considered for future enrollment.

5.4 Discharge Instructions at End of Study or Early Termination Visit

The site will facilitate a review with the study subject of the planned schedule for when information relating to their study information (e.g., study results, treatment assignments) will be available. The site will also discuss how information relating to their participation in the study will be shared with their healthcare provider, if they choose to share this information, and with the relevant health authorities in the event of a positive HIV or hepatitis result.

5.5 Study Completion

The site will complete the Study Termination eCRF page and this will mark the completion of the individual's participation in the study.

The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the Study Termination eCRF page.

6 STUDY DRUG MANAGEMENT

6.1 Description of Study Drugs

The term 'study drug' refers to those drugs provided by the Sponsor, which will be evaluated as part of the study objectives.

6.1.1 LYN-005 ER

The Lyndra ER product, LYN-005, contains risperidone 14 or 28 mg. The LYN-005 (risperidone) ER capsule is designed with modular components to ensure the safe and controlled administration of risperidone in the GI tract over several days. Drug is contained only within the [redacted] drug layers, which provide controlled drug release based on hydration. Refer to the Investigator's Brochure for additional details.

Lyndra will provide LYN-005 14 and 28 mg capsules and matched placebo.

6.1.2 IR Risperidone

RISPERDAL® (risperidone) is an atypical antipsychotic agent. Lyndra will provide risperidone 2 mg (orange) capsule-shaped tablets and matched placebo.

6.2 Storage

All drugs associated with this study (study drugs) are to be stored separately from other drugs and medications in a secure location under appropriate storage conditions with temperature monitoring. All drugs associated with this study must be checked for expiration or retest date prior to use. Expired drugs or those beyond their retest date must not be administered to subjects.

The Investigator or designee will be responsible for oversight of the administration of drug to subjects enrolled in the study according to the procedures stipulated in this study protocol. All drugs will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

6.2.1 LYN-005

LYN-005 is to be stored at 15 to 25ºC (59° to 77°F). The capsules are to be handled in a manner to avoid squeezing or crushing.

6.2.2 IR Risperidone

IR risperidone tablets should be stored at controlled room temperature 15° to 25°C (59° to 77°F) and protected from light and moisture.

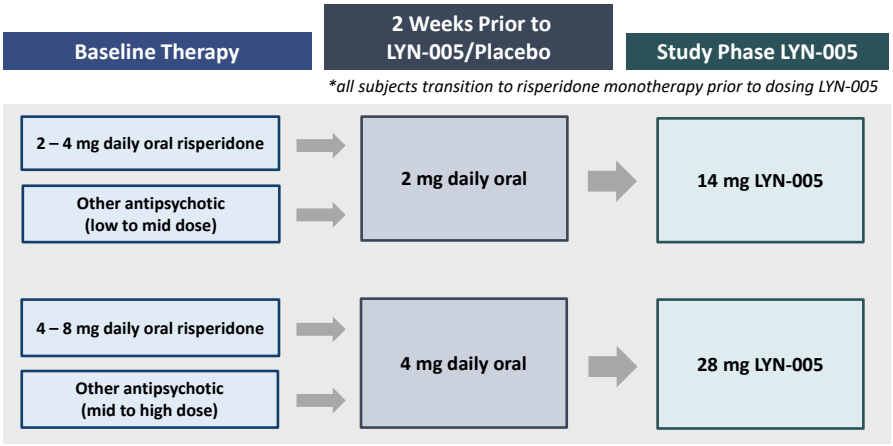
6.3 Dosing and Administration

6.3.1 Run-in Preparation with IR Risperidone

All subjects must take IR risperidone once a day and at approximately the same time of day (morning or evening) on Days -13 to -3.

Subjects who are receiving antipsychotic medications must switch to either 2 or 4 mg/day IR risperidone based on the clinical judgement of the Investigator are to begin the transition to IR risperidone starting on Day -13; by Day -13, these subjects should only be receiving 2 or 4 mg IR daily. Guidelines for switching antipsychotic medication to risperidone 2 or 4 mg/day prior to Day -13 are provided in Figure 6-1.

Figure 6-1: IR Risperidone Switch and Dosing Guidelines



6.3.2 IR Risperidone PK Period

Morning administration of the full dose of IR risperidone, 2 or 4 mg respectively, must begin by Day -1 for all subjects.

Subjects who must switch from evening to morning dosing will be given half the regimen of daily oral risperidone in the evening of Day -2 (i.e., either 1 or 2 mg risperidone) to minimize overlapping exposure. This dose should be given after the evening (6 pm) PK sample has been collected.

On Day -1, following an overnight fast, subjects will consume a light breakfast over 30 minutes or less, with the mean started 30 minutes prior to study drug administration. IR risperidone will be administered thereafter with 250 mL of water with the option for additional water (increments of 50 mL), as needed. Following risperidone administration, blood samples for PK will be obtained per the SOE (Section 18.1.1 and Section 18.1.2).

6.3.3 Blinded Treatment (LYN-005 or Placebo)

Subjects who successfully complete the admission procedures will be randomized on Day 1 in a 3:1 ratio to LYN-005 or IR risperidone, as follows:

- LYN-005: Subjects randomly assigned to LYN-005 ER will receive a single LYN-005 ER capsule (14 or 28 mg) taken once-weekly (on Days 1, 8, and 15) plus dummy IR risperidone-matched placebo daily though Day 21.

- IR Risperidone: Subjects randomly assigned to IR risperidone will receive a single weekly dummy capsule (placebo, representing LYN-005) taken once-weekly (On Days 1, 8, and 15) plus IR risperidone (2 or 4 mg/day) daily though Day 21.

6.3.3.1 LYN-005/Placebo Administration

LYN-005 capsules are to be taken orally following a light breakfast with approximately 250 mL of water immediately after capsule administration, while the subject is in a standing position. If the subject requests more fluid for swallowing, they may be given additional water in increments of 50 mL to chase. The volume of water consumed by the subject will be recorded in the eCRF. The subject is to remain upright after dosing for a total of at least 15 minutes. The subject must not bite or chew the capsule nor hold the capsule in the mouth prior to swallowing.

6.3.3.2 IR Risperidone/Placebo Administration

IR risperidone or matched placebo tablets are to be taken orally in the morning with 250 mL of water with the option for additional water (increments of 50 mL), as needed.

6.4 Accountability and Compliance

The United States Food and Drug Administration (FDA) requires accounting of all investigational treatment received by each study center. Records of treatment disposition required by federal law include the date received by the center, date administered, quantity administered, and the subject to whom study treatment was administered. The investigator is responsible for the accountability of all used and unused study treatment containers and unused study treatment.

Each study center is to use a study treatment accountability log to document study treatment disposition. All items on this form are to be completed in full. The area where study treatment accountability records are to be maintained is to be approved by the Sponsor or designee. The Clinical Research Associate (CRA) is to routinely review study treatment accountability records.

6.5 Prior and Concomitant Medications and Therapies

All medications, drugs and blood products taken or received by the subject within 3 months and any over-the-counter medications, natural supplements or vitamins taken within 4 weeks (28 days) prior to Day -2 are to be recorded on the Concomitant Medications eCRF. Similarly, any medication, drug, blood product, over-the-counter medication, herbal remedy taken by the

subject after study enrollment through EOS will also be recorded on the Concomitant Medications eCRF.

Subjects on medication who do not discontinue medications within 2 weeks of study dosing (unless otherwise specified in the Exclusion Criteria, Section 5.2) are not eligible for dosing with LYN-005 on Day 1.

During the study, the use of contraceptives (oral or other acceptable method) to prevent pregnancy in subjects of childbearing potential is required. Aside from contraceptives and necessary psychotropic medications, the use of other concomitant medications is generally discouraged during the study unless deemed appropriate by the Investigator to treat new or worsening medical conditions, including AEs. If pain relief is required during the study, the Investigator is encouraged to prescribe paracetamol.

Psychotherapy should not be started or stopped during a subject's participation in the study. It is acceptable for a subject already receiving psychotherapy to continue such therapy during study participation.

Concomitant medications include all medications (including drugs) taken by/administered to the subject at and after enrollment and must be documented on the Concomitant Medications eCRF. As a reminder: any change to medical history or onset of AEs must also be captured in the respective Medical History and Adverse Event eCRFs.

7 PAUSING AND STOPPING GUIDELINES AND SUBJECT DISCONTINUATION/ WITHDRAWAL

7.1 Pausing and Stopping Guidelines

Dosing of study subjects is to be **paused** if any of the following occurs:

- [redacted]

Under these circumstances, clinical study dosing would be **paused** to allow for the evaluation of potential underlying causes and treatment assignments. If a clinically significant injury (or risk thereof) is directly attributed to the [redacted], further study dosing will be **stopped**. Should study dosing resume, the study would remain observer blinded for subsequent subject dosing.

The study will be **stopped** if any subject experiences clinically significant injuries including:

- [redacted]

- Any confirmed trend identified by ongoing review of safety data suggesting unacceptable risk of clinically significant injury to subjects.

In addition, if a trend in the review of the safety data suggests the risk of a clinically significant injury for subjects participating in other clinical studies evaluating the modified release formulations, this information will be reviewed in a timely manner to understand the risks to these subjects.

7.2 Premature Withdrawal from Study

Subjects may withdraw at any time or be removed from the study at the discretion of the Investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the Investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The Investigator or Study Coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an AE.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The Investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal.

If a subject wishes to withdraw from the study after dosing with LYN-005 and before the last planned study visit, efforts should be made to obtain an X-ray in lieu of the scheduled X-rays for all subjects without fecal recovery or prior negative X-ray demonstrating GI exit of the formulation.

When a subject withdraws, or is withdrawn, from the study after dosing with any study drug, the procedures described for the EOS visit (Section 18.1.2) should be completed, if possible. If a subject withdraws or is withdrawn from the study after enrollment but before dosing with LYN-005, that subject would complete EOS visit procedures, excluding abdominal X-ray and would be considered a premature withdrawal.

8 STUDY ASSESSMENTS AND PROCEDURES

After signing informed consent, individual subject data will be collected from subjects throughout the duration of their study participation. All data collected will use deidentified subject identifiers such as Screening and enrollment/subject IDs.

This study utilizes eCRFs to collect study-related data for each subject. A qualified site staff member(s) is required to enter subject data in the eCRFs based on the medical information available in each subject's source record.

The study day and time each assessment will be performed relative to dosing is shown in the SOE (Section 18.1.1 and Section 18.1.2). However, when study assessments fall on the same time point, the site may arrange the order of procedures according to their usual practice.

8.1 Screening and Safety Assessments

8.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks, and potential benefits, and the requirements of the research to be able to make an informed decision.

Written informed consent following local IRB guidance must be obtained from each subject before conducting any study-specific procedure (i.e., all procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

Subjects who are unable to read must not be enrolled in the study.

8.1.2 PILL-5 Questionnaire

The PILL-5 Questionnaire is to be administered to subjects during Screening. Refer to Section 18.2 for details.

8.1.3 Breath Test for H. Pylori

Breath testing will be used at Screening to test for active *H. pylori* infection, and all results will be documented. Subjects will not be excluded on the basis of the rest results. Methods for evaluating the *H. pylori* breath test are described in the Laboratory Instruction Manual.

8.1.4 Medical and Psychiatric History

Medical and psychiatric history for the past 12 months will be assessed at Screening and may be reassessed o prior to dosing to determine if there are any clinically relevant updates. The assessment of medical history will include but will not be limited to any history that may be relevant to subject eligibility for study participation such as concomitant medications, previous

and ongoing illnesses or injuries, and duration of medical and psychiatric stability. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem. Relevant psychiatric history should include any psychiatric history relevant to the duration and understanding of diagnosis of mental illness and time of last hospitalization. The Investigator or delegate should update the medical and psychiatric history as needed while investigating treatment-emergent AEs.

8.1.5 Psychiatric and Extrapyramidal Symptom Assessment

The following table lists the typical times to complete the psychiatric and EPS assessments in this study by visit date. The longest completion time occurs at Screening, lasting ~1.5 hours for all assessments. Thereafter, the total time to complete the assessments is <30 minutes or less.

Table 8-1: Psychiatric and EPS Assessment Timing and Durations

Assessment Scale	Assessment Duration [Reference]	Screening	Day 7	Day 9	Day 15	Day 21	Day 35
PANSS	45 to 50 min [34]	√					
MINI	19 min [35]	√					
CGI-S	2 min [36] (after clinical interview)	√	√	√	√	√	√
C-SSRS	10 min [37]	√	√	√	√	√	√
ESRS	15 min [38]	√	√	√	√	√	√
Total Time		96 minutes	27 minutes	27 minutes	27 minutes	27 minutes	27 minutes

8.1.5.1 Mini International Neuropsychiatric Interview (MINI) version 7.0.2

The Mini International Neuropsychiatric Interview version 7.0.2 is a short, structured diagnostic interview that was developed to assess DSM-5 and ICD-10 psychiatric disorders. The MINI was developed for use in clinical and epidemiological studies as a short but accurate clinical assessment and has been validated against the Structured Clinical Interview for DSM diagnoses [35]. This study will utilize the MINI at Screening in order to ascertain inclusion and exclusion criteria. To assess the diagnosis of schizophrenia or schizoaffective disorder for study inclusion, the below modules of the MINI will be assessed:

- Module A: Major Depressive Episode;
- Module C: Manic and Hypomanic Episode;
- Module K: Psychotic Disorders and Mood Disorder with Psychotic Features.

Depression, mania, and hypomania are components of a diagnosis for schizophrenia/ schizoaffective disorder. However, recent major depressive episodes may be exclusionary at the discretion of the Investigator.

In addition to Modules A, C and K, several further modules of the MINI will be used to assess for excluded psychiatric conditions, as outlined in the study exclusion criteria:

- Module D: Panic Disorder;
- Module E: Agoraphobia;
- Module F: Social Anxiety Disorder;
- Module G: Obsessive-Compulsive Disorder;
- Module H: Posttraumatic Stress Disorder;
- Module N: Generalized Anxiety Disorder.

The MINI 7.0.2 will be collected at the Screening Visit and takes approximately 15 minutes to administer. The tool should be administered by the Investigator or a trained medical professional. Instructions and scales for the modules of the MINI which are to be used in this study are presented in Section 0.

8.1.5.2 Structured Clinical Interview-Positive and Negative Syndrome Scale (SCI-PANSS)

The PANSS is one of the most widely used measures of psychopathology of schizophrenia in clinical research, and is considered the 'gold standard' for measuring antipsychotic treatment [39]. It is a 30-item scale used to evaluate the presence, absence, and severity of Positive, Negative and General Psychopathology symptoms of schizophrenia. In this study, the PANSS will be used at Baseline in order to assess the stability and severity of subjects' disease. Each of the 30 items in the PANSS has a definition and a basis for rating, and all items are rated on a 7-point scale (1 = absent; 7 = extreme). Subjects' PANSS scores at Screening must be aligned with stable, mild to moderate disease based on values of ≤4 for individual items P1, P3, P4, P6, P7, and G14. The strengths of the PANSS include its structured interview, robust factor dimensions, reliability, the availability of detailed anchor points, and validity.

The PANSS is accompanied by a semi-structured interview, the SCI-PANSS, which will be used in this study at Screening to ensure that all content domains are covered during the interview session [40]. SCI-PANSS ratings are made after the completion of the interview, using additional reports of daily function from caregivers, family members and a review of available clinical material as needed. Administration of the entire PANSS interview is between 45 and 50 minutes. In order to prevent subject fatigue during the interview, it is acceptable for subjects to take a short break during an assessment if needed, and then resume completion of the assessment.

The SCI-PANSS will be administered by the Investigator or a delegate trained in PANSS methodology. The core principles for the use of the PANSS, which ensure maximum reliability and inter-rater validity, should be followed in the administration of this assessment [39]. The PANSS is to be conducted at the Screening Visit and should be collected as outlined in the SCI-PANSS booklet, seen in Section 18.4.

8.1.5.3 Clinical Global Impression – Severity (CGI-S)

The CGI is widely used by clinicians in clinical studies in order to assess a subject's global functioning both prior to and after initiating treatment with a study medication [41]. It is comprised of two one-item measures; the CGI-S measures the severity of a subject's psychopathology, and the CGI-Improvement captures changes from Baseline after treatment initiation and includes an efficacy index [41, 42]. As efficacy is not assessed in this study, solely the CGI-S will be used to assess subject stability at Screening, enrollment and throughout the study.

The CGI-S consists of a single 7-point rating score of illness severity, to be completed by a clinician [41, 42]. Raters select one response based on the following question, "Considering your total clinical experience with this particular population, how mentally ill is your subject at this time?". The CGI-S has been demonstrated as a valid and user-friendly alternative to longer assessments, including the PANSS, and can be used to identify subjects in remission [43]. Scores are as follows:

1. Normal, not ill at all
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most severely ill subjects

Subjects at Screening must have a stability score of less than or equal to 4 (moderately ill) to be eligible for the study. The CGI-S will also be administered to all subjects at multiple time points throughout the study, as specified in the SOE (Section 18.1.1 and Section 18.1.2), to monitor stability and may also be administered at the discretion of the Investigator. The scale and guidelines for its administration are found in Section 18.5.

8.1.5.4 Assessment of Suicidal Ideation and Behavior – Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview-based rating scale intended to systematically assess suicidal ideation and suicidal behavior. This scale has is recognized internationally as the 'gold standard' for risk assessments in clinical studies due to its simplicity, evidence-supported validity, efficiency, and effectiveness [44]. Two versions of the

C-SSRS will be utilized in this study to ensure subject safety; Baseline/Screening and Since Last Visit assessments.

At the Screening Visit, the Baseline/Screening version will be used to asses study eligibility criteria and Baseline suicidal ideation and behavior. Subjects who have made a suicide attempt within the last 2 years and subjects who, in the Investigator's judgment, pose a significant suicide risk are excluded from study participation. Subjects who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (i.e., "Yes" answers on items 4 or 5 of the C-SSRS) are also to be excluded.

Each subsequent assessment will utilize the Since Last Visit version of the C-SSRS. Subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior based on this assessment must be evaluated by a licensed and qualified mental health professional (MHP) skilled in the evaluation of suicidality in the subjects by virtue of training or experience (e.g., a psychiatrist or, licensed PhD level clinical psychologist) who will determine if it is safe for the subject to continue in the study. Specific criteria that indicate a need for such an assessment are:

- Scores reflecting suicidal ideation associated with actual intent and/or plan in the past year; i.e., a "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent";
- Subject response of "YES" to any behavioral question of the C-SSRS on more than one occasion during a study (as compared to the previous assessment with the C-SSRS);
- In the Investigator's judgment, a risk assessment or exclusion is warranted.

Subjects who meet the above criteria must have their suicidality managed appropriately by the Investigator together with the clinician/MHP (or the Investigator alone if the Investigator is a qualified mental health professional). Depending on the specifics of the situation as assessed by the Investigator and/or clinician/MHP, the subject may be discontinued from the study.

Other possible suicidality AEs or other clinical observations may, based on the judgment of the Investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS and available information; including information from Baseline/ Screening, and the clinician/MHP assessment. With the positive response to any question on the C-SSRS, the Investigator should determine whether an AE has occurred.

The C-SSRS should be collected at times specified in the SOE (Section 18.1.1 and Section 18.1.2) by an appropriately trained site staff member, as well as at any time during the study at the discretion of the Investigator. Section 18.6 presents both C-SSRS scales.

8.1.5.5 Extrapyramidal Symptoms – Extrapyramidal Symptom Rating Scale (ESRS)

Antipsychotics are a well-recognized treatment of schizophrenia, but their use is often associated with drug-induced EPS or drug-induced movement disorders (DIMD). Therefore, the ESRS will be used at Baseline and throughout the study in order to assess the severity of and monitor extrapyramidal symptoms. The ESRS was developed to assess four types of drug-induced

movement disorders [45, 46]: Parkinsonism, akathisia, dystonia, and TD. The ESRS consists of several components:

- a questionnaire of EPS or DIMD;
- an examination of Parkinsonism and akathisia;
- an examination of dystonia;
- an examination of dyskinesia;
- CGI-S scales of TD, Parkinsonism, dystonia, and akathisia.

The ESRS has been validated and is widely used in clinical research on antipsychotics and to differentiate drug induced EPS and symptoms of schizophrenia [46]. It has been demonstrated to be a sensitive and specific scale [46], and that ESRS measurement of drug-induced EPS is valid and discriminative from psychiatric symptoms as measured by the PANSS [47].

Administration of the ESRS takes approximately 10-15 minutes and should be conducted by medical professionals trained on the use of the scale. The ESRS should be administered at Baseline and throughout the study as specified in the SOE (Section 18.1.1 and Section 18.1.2). ESRS examination procedures and the scale are presented in Section 18.8.

In cases of marked and clinically significant changes in EPS, the Investigator will use best clinical judgment on which treatment to consider in managing these symptoms.

8.1.6 Screening Fecal Sample for Occult Blood

A fecal specimen will be tested at Screening for the presence of fecal occult blood, and results will be documented for all participants. Positive fecal occult blood test at Screening in subjects who are >45 years will be exclusionary unless the subjects have had a normal colonoscopy within the past 5 years.

8.1.7 General Physical Examination and Directed Physical Examination

A general physical examination will be performed at Screening, Day -2 and the EOS visit. This examination will consist, at a minimum, of a check of general appearance; auscultation of the heart, lungs, and abdomen; palpation of the abdomen; abbreviated neurological examination; and examination of other organ systems in accordance with institutional practice. Body weight is to be measured as part of the general physical examination.

Directed physical examinations will be performed on other days as indicated in the SOE (Section 18.1.1 and Section 18.1.2). This examination will consist, at a minimum, of a check of general appearance; auscultation of the heart, lungs and abdomen; and palpation of the abdomen. In addition, other organ systems may be examined at the discretion of the qualified medical professional performing the examination and as guided by interview of the subject.

Any new clinically significant abnormality detected during physical examinations and considered an AE will be captured on the AE eCRF page.

8.1.8 Vital Signs

Vital signs include measurement of systolic and diastolic blood pressure, pulse, and respiratory rate as well as body temperature. Vital signs are to be measured at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Vital signs may be measured at additional time points at the Investigator's discretion.

8.1.9 Electrocardiograms

Standard 12-lead ECGs will be performed at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2), according to the site Standard Operating Procedures, and ECG parameters will be collected in source documentation. ECGs are to be performed with the subject in a supine position for at least 5 minutes. All ECGs must be evaluated by a qualified physician for the presence of abnormalities, and findings should be classified as normal, abnormal not clinically significant or abnormal clinically significant. Additional ECGs may be performed at the discretion of the Investigator.

8.1.10 CYP2D6 Genotyping

Risperidone is primarily metabolized by CYP2D6 and genetic testing for CYP2D6 will be conducted at Screening to determine metabolizer status. To reduce the inter-subject variability in exposure of risperidone and 9-hydroxyrisperidone, subjects identified as poor metabolizers will be excluded from the study. Approximately 7 mL (minimum 3 mL) of whole blood will be obtained at Screening for CYP2D6 genetic testing.

8.1.11 Screening Serology

Blood is to be collected for serology testing including hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), and HIV, during Screening.

8.1.12 Safety Laboratory Assessments

Safety laboratory assessments will include the following parameters:

- Clinical chemistry panel
  - blood urea nitrogen (BUN) should be calculated from urea
  - includes liver function tests
  - HbA1c will be performed at Screening only
- Hematology panel
  - includes complete blood count (CBC) with differential
- Coagulation tests
- Urinalysis to be performed at Screening only, unless for pregnancy test or at Investigator discretion

Safety laboratory assessments will be performed throughout the study at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Safety Laboratory Assessments are to be reviewed by the Investigator or delegate within 24 hours of available results and prior to discharge of the subject from the inpatient unit.

For a complete list of assessments and further details relating to the collection and handling of laboratory specimens, please refer to the Laboratory Instruction Manual.

8.1.13 Prolactin

Blood samples for prolactin will be collected at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2).

8.1.14 Pregnancy Testing

Pregnancy testing in females of childbearing potential is to be performed at the time points indicated in the SOE (Section 18.1.1 and Section 18.1.2). Pregnancy testing is to be repeated any time pregnancy is suspected. At Screening, a serum pregnancy test is to be performed. At all time points thereafter, a urine pregnancy test may be performed.

Subjects with a positive pregnancy test during Screening are not eligible for study participation. After starting study drug, study drug is to be discontinued immediately for any subject with a positive pregnancy test, and pregnancies are to be reported and followed as described in Section 8.2.8.

8.1.15 Compliance Laboratory Assessments

Subjects will undergo testing to confirm the absence of alcohol or substance abuse at Screening, upon admission to the unit, and at any time during the study as warranted by the Investigator or study staff. In accordance with the exclusion criteria (Section 6.3) any individual who has a test reflecting recent use of excessive alcohol or illicit substances at Screening must not be enrolled in the study.

Compliance Laboratory Assessments will include breath testing for alcohol use and urine testing for illicit substances (drugs of abuse). Analytes for the urine drug test will be specified in the Laboratory Instruction Manual.

8.2 Adverse Events and Serious Adverse Events

According to the International Conference on Harmonization (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting dated 27 October 1994, an AE is defined as follows:

8.2.1 Definition of an Adverse Event

Any untoward medical occurrence in a participation or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This definition includes onset of illness, injuries, and/or exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period (i.e., through the End-of-Study visit) or terminates the study early (whichever comes first). AEs occurring after the informed consent form (ICF) is signed but prior to receiving study drug/product will be documented as an adverse event and recorded within source document. However, any AEs occurring prior to receipt of any study drug will be analyzed separately from "treatment-emergent" AEs (AEs occurring after administration of study drugs) unless there is a change in severity or frequency of AEs persisting after the subject is dosed. AEs present on the first day of treatment that worsen in intensity or frequency during the treatment or post treatment periods should be reported and recorded as AEs.

Unchanged chronic conditions are not AEs and should not be recorded on the AE pages of the eCRF. These medical conditions should be documented on the appropriate page of the eCRF (medical history or physical examination). The Investigator will actively solicit this information from the subject and assess the event in terms of severity and relationship to the study treatment regimen.

Every effort should be made by the Investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page.

8.2.2 Serious Adverse Events

An AE occurring should be classified as "Serious" if it meets one of the following criteria:

1. It results in death (i.e., the AE caused or led to death).
2. It is life threatening (i.e., the AE placed the subject at immediate risk of death). This classification does not apply to an AE that hypothetically might cause death if it is more severe.
3. It requires or prolongs inpatient hospitalization (i.e., the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay). Hospitalizations for elective medical or surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion.
4. Persistent or significant disability or incapacity (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions).
5. It is a congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy).
6. It does not meet any of the above criteria but could jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.

8.2.3 Collection of Adverse Events

To prompt reporting of AEs, simple unbiased questions should be used as the initial questions at all evaluation points during the study. Whether considered related or not, all AEs are to be recorded on the eCRF page and monitored until resolution or through the end of the study.

8.2.4 Evaluation and Classification of Adverse Events

Both serious and non-serious AEs should be graded with respect to severity on the following 3-point scale and reported, in detail, on the appropriate eCRF page:

Mild: Discomfort noticed, but no disruption of normal daily activities; event usually requires no intervention.

Moderate: Discomfort sufficient to reduce or affect normal daily activities; even may require intervention.

Severe: Incapacitating, with inability to perform normal daily activities; event usually requires treatment or other intervention. Subject may not be able to continue in the study.

8.2.5 Relationship to Study Drug (Intervention)

The Investigator should evaluate the relationship of each AE to the study treatment regimen, using the following criteria:

Unrelated: Another cause of the AE is more plausible; a clinically plausible temporal sequence is inconsistent with the onset of the AE and administration of the study drug; or a causal relationship is considered biologically impossible.

Possibly related: There is a clinically plausible time sequence between onset of the AE and administration of the study drug, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. "Possibly Related" should be used when the study drug is one of several biologically plausible AE causes.

Related: The AE is clearly related to administration of the study drug.

The relationship of the study drug to an AE will be determined by the Investigator or qualified delegate.

All AEs, regardless of severity, will be monitored until resolution or until the Investigator assesses them as chronic or stable. All subjects experiencing AEs whether considered associated with the use of the study drug or not must be monitored until symptoms subside or until the Investigator determines the AE is chronic and stable and does not warrant further follow-up, or until death, in which case a full pathologist's report should be supplied, if possible.

8.2.6 Time Period and Frequency for Event Assessment and Follow-up

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be

documented accordingly to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset, offset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until the EOS Visit. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.7 Procedures for Recording and Reporting Adverse Events

Adverse events suspected or confirmed as meeting the definition of SAE should be reported to the Lyndra Medical representative, site CRA and contract research organization (CRO) Safety Officer within 24 hours. Contact details for each will be provided in the Safety Reporting Plan.

8.2.7.1 Recording Adverse Events

All findings regarding AEs must be reported on an Adverse Events eCRF and on the SAE Reporting Form, if applicable, which is part of the Investigator Site File. All findings in subjects experiencing AEs must also be reported in the subject's source document.

To improve the quality and precision of AE data, Investigators should observe the following guidelines: laboratory, vital sign, ECG and physical examination abnormalities that are defined as clinically significant that meet the definition of an AE, are to be recorded on the AE eCRF page.

8.2.7.2 Recording and Reporting Serious Adverse Events

Specific instructions and contact details for collecting and reporting SAEs to the Sponsor will be provided to the Investigator and site staff. All SAEs are also to be documented on the Adverse Events eCRF. Any medication or other therapeutic measures used to treat the SAE will be recorded on the appropriate eCRF(s) in addition to the outcome of the SAE.

After receipt of the initial report, representatives of the Sponsor or its designee will contact the Investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the Investigator in accordance with institutional policy/regulatory requirements or within 24 hours of their knowledge of the event. Adequate documentation of this notification must be provided to the Sponsor.

The Sponsor or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse drug reactions (also known as SUSARs) to the Regulatory Authority and, where applicable, the IRB. If a SUSAR or other safety signal relating to use of the study drugs in another research related activity is reported to the Sponsor or its designee, the Sponsor will communicate this information to the Investigator and the Investigator will be responsible for submitting this information, where applicable, to the IRB and other relevant authorities.

8.2.7.3 Post-Study Events

Any suspected SAE that occurs outside of the protocol-specified follow-up period but considered to be caused by the study drug must be reported according to the procedures specified above (Section 8.2.7) and in the Safety Reporting Plan. These SAEs will be processed by the Sponsor or a designee during the study, until the last subject enrolled in the study completes the last study visit. After that point, the Lyndra Medical Monitor should be contacted with any suspected or possibly drug related SAE experienced by an individual participating in this study.

8.2.8 Reporting of Pregnancies

To ensure subjects' safety, each pregnancy in a subject which occurs during the study (from administration of study drug through the EOS) must be reported to the Sponsor within 24 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data, inclusive of initial reporting and follow-up information regarding the course of the pregnancy and the outcome, must be recorded on a Pregnancy Reporting Form and reported to the Sponsor. Instructions and contact details for submitting the Pregnancy Reporting Forms will be provided to the Investigator in the Safety Reporting Plan.

Any pregnancy outcome meeting the definition of a SAE (Section 8.2.2) must also be reported on the SAE Reporting Form.

8.3 Gastrointestinal Imaging (X-ray)

Abdominal X-rays are to be performed in all subjects where specified in the SOE (Section 18.1.1 and Section 18.1.2). Refer to the Study Imaging Manual for details regarding the procedures for abdominal X-ray.

8.4 Pharmacokinetics

At each time point specified in the SOE (Section 18.1.1 and Section 18.1.2), 2 mL of blood for PK evaluation will be drawn into a designated and labelled collection tube and processed for storage and shipment, as described in the Laboratory Instruction Manual. The windows around sample collection at each time point, as designated in the SOE, are to be observed.

Analysis of risperidone and 9-hydroxyrisperidone will be performed using a validated assay. Time and date of the PK assessment will be recorded on the eCRF for each blood sample.

Refer to the Laboratory Instruction Manual for further details.

8.5 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations as no authorized deviations are permitted. If the Investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB and health authorities it cannot be implemented.

Pregnancy during the study is a protocol deviation (Section 8.2.8).

A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Protocol deviations may be defined as exclusionary from the analysis according to protocol objectives and endpoints. Prior to the final analysis of the study data, subjects with exclusionary protocol deviations will be identified and specified for each analysis set and documented. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g., early termination.

9 STATISTICS AND DATA MANAGEMENT

9.1 General Procedures

A statistical analysis plan (SAP), providing details about the specific planned analyses and potential hypothesis tests, will be prepared and approved prior to study database lock. Both descriptive and inferential statistical methods may be used to fully explore the preliminary data. In addition, post hoc analyses may be performed that are not described in the SAP but will be described fully in the CSR where presented.

Summary statistics will be presented by dose group, dose period, and overall. Unless otherwise stated, categorical data will be presented using frequency counts and percentages and continuous data will be presented by number of subjects reporting (n), means, standard deviations (SD), median, minimum, and maximum. Geometric means and coefficient of variations (%CV) will be presented in addition for PK data.

9.2 Data Management

Data management will be performed in accordance with clinical standards.

AEs and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v22.0 or a more recent version) and the World Health Organization Drug Dictionary Enhanced (WHO DDE) Drug Reference List (2018), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and hematology data (and other safety laboratory data) will be collected by a central laboratory and stored electronically in their clinical pathology system. All laboratory data that are transferred will be reconciled, queried, and answered by the site laboratory and clinical staff before the database can be closed. The database will be locked when all criteria listed in the Data Management Plan are met. Further details are addressed in the Data Management Plan.

SAS 9.4 or higher (SAS Institute Inc., Cary NC USA) will be used for generating individual data listings, summary tables and associated figures and for performing statistical analyses.

9.3 Sample Size

This study is exploratory in nature and therefore not designed to test hypotheses.

The sample size of 32 (24 assigned to LYN-005 and 8 assigned to IR risperidone) is driven by clinical rather than statistical considerations for providing data in the evaluation of the endpoints.

9.4 Statistical Methods

9.4.1 Analysis Sets

The following analysis sets will be defined:

Enrolled Set: The Enrolled Set is defined as all subjects who are enrolled in the study and admitted to the research unit on Day -2. The Enrolled Set will be the primary set used for disposition, demographic and baseline characteristic data reporting.

Safety Set: The Safety Set is defined as all enrolled subjects who are randomized to study drug (LYN-005 14mg/28mg or IR Risperidone 2mg/4mg) and receive at least one dose of randomized study drug. Subjects will be reported according to the treatment received. The Safety Set will be the primary safety analysis population.

PK Set: The PK Set is defined as all enrolled subjects who receive a dose of LYN 005 and have least 1 post-dose quantifiable (or evaluable) PK concentration data. Additional analysis sets within the PK population, if identified, will be specified in the PK Analysis Plan.

Additional analysis sets, if identified, will be specified in the SAP.

9.4.2 Statistical Methods

Safety endpoint data will be descriptive in nature and summarized by dose group, dose period and overall. Listings will also be presented. The Safety Set will be the primary population for analysis unless otherwise stated. Plasma concentration data for risperidone and 9-hydroxyrisperidone separately and combined as active moiety will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration-time data obtained will be performed using appropriate non-compartmental analysis to obtain estimates of the standard PK parameters.

The PK of LYN-005 relative to IR at 2 dose levels will be determined.

There are no pharmacodynamic endpoints in this study.

9.4.3 Analysis of Safety - Analysis of Adverse Events

This analysis applies to all AEs occurring during the study, judged either as related, possibly related, or not related to study drug by the Investigator, recorded on the AE eCRF, with a start date on or after the date of dose of randomized study drug (i.e., TEAEs). AEs starting prior to administration of randomized study drug (non-treatment emergent AEs) will be listed for subjects in the Enrolled Set. The original verbatim terms used by Investigators to identify AE in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

Analyses of TEAEs will be summarized by dose group, dose period, and overall. Events will also be included in subject listing by dose group and dose period.

Further details may be found in the SAP.

9.4.4 Analyses of Pharmacokinetics

PK concentrations will be summarized descriptively for both IR risperidone and LYN-005. PK parameters will also be presented by dose group, that plots of concentration-time data and C_{max} and AUC will be provided. Further analyses to assess PK levels in LYN-005 relative to IR risperidone will be explored and detailed in the SAP.

9.4.5 Demographic and Baseline Characteristics

Descriptive statistics will be summarized for the Enrolled Set. Demographic and baseline characteristic data includes age, gender, ethnic group/race, height, weight, BMI at enrollment will be calculated.

9.5 Assessment of Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Protocol deviations may be defined as exclusionary from the analysis according to protocol objectives and endpoints. Prior to the final analysis of the study data, all protocol deviations will be reviewed by the Sponsor Medical representatives. Subjects with exclusionary protocol deviations will be identified, specified, and documented. Protocol deviations will be listed.

9.6 Safety Reviews

There is a planned safety review by the Investigator and Medical Monitor on interim blinded PK data after PK data through Day 14 are available from 12 subjects. Blinded safety data will also be reviewed at this interim look and will include adverse events, laboratory data, suicidality, and illness severity. Additionally, the PI or Sponsor may request an ad hoc review of safety information, e.g., serious adverse events, at any time during the study.

9.7 Data Entry and Management

In this study, all requested data will be entered onto eCRFs in a timely manner after each assessment by the Investigator and/or the Investigator's dedicated site staff. Data entered onto eCRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA, 1997) [48]. The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor or delegate prior to activation for data entry by sites. The Investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have exclusively "read only" access.

Additional data collection forms (e.g., Pregnancy and SAE Reporting Forms) will be provided to the site by the Sponsor or delegate, should a pregnancy or SAE occur. Instructions on how to complete and archive these forms will be provided to the Investigator by the Sponsor or delegate prior to the start of the study.

9.8 Data Clarification

As part of the conduct of the study, the Sponsor may have questions about the data entered by the site, referred to as queries. The Clinical Research Associates and Data Management are the

only parties that can generate a query, and they will generate queries on behalf of any other data reviewer with "read only" access to the EDC. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed eCRF, the Investigator must confirm and endorse the changes.

9.9 Data Protection

The Sponsor respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, Good Clinical Practices, the relevant ICH guidelines, the ethical principles that have their origins in the Declaration of Helsinki, and in accordance with the applicable regulatory requirements in the country where this study will be executed. As required by the Declaration of Helsinki; the study protocol, amendments, and, Informed Consent Form/Subject Information Sheet will be reviewed and approved by the study center's IRB.

10.2 Sponsor Medical Monitor

The Sponsor's Medical Monitor will be available to the Investigator for discussion of any safety events or findings. The Investigator and Lyndra Medical Monitor may review AE listings on a weekly basis to evaluate any trends until each subject reaches Day 35. Additionally, the Lyndra Medical Monitor may be engaged at an ad hoc basis at any time to review SAEs, any events that may trigger pausing or halting the study and will review the safety data for the final reporting of the study data.

10.3 Investigator and Institutional Review Board Responsibilities

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. Properly constituted IRB is defined in ICH Guideline for Good Clinical Practice [49]. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to the Sponsor or delegate before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor (or representative) monitors, auditors, other designated agents of the Sponsor, IRB, and regulatory authorities, as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

At the site level, the Investigator must ensure that any person(s) assisting with the study are adequately trained and informed about the protocol, the investigational product(s), and their study-related duties and functions, including study-related medical decisions and medical care of subjects experiencing any AE related to the study. Additional responsibilities include maintaining a list of appropriately qualified persons to whom s/he has delegated significant study-related duties, and ensuring that s/he has the capability, time and staffing to recruit the required number of suitable subjects within the recruitment period and properly conduct and complete the study within the agreed study period. When required, and if permission is given by the subject, the Investigator will ensure that the subject's primary healthcare provider is informed of the individual's participation in the study.

The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in staff, change of telephone number[s]). In addition, the Investigator or delegate Investigator, should document and explain any deviation from the approved protocol. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Sponsor for agreement, thereafter to the IRB for review and approval/favorable opinion, and if applicable, to the regulatory authority(ies).

10.4 Subject Information and Informed Consent

The informed consent and subject information sheets used for this study will meet requirements for subject information, as outlined ICH Guideline E6 and the Declaration of Helsinki.

Prior to the start of the study, the proposed ICF must be jointly agreed upon by the site and Sponsor or its delegate prior to submission to the IRB and a copy of the approved version must be provided to the Sponsor or delegate after IRB approval.

Eligible subjects may only be included in the study after providing written informed consent or assent. Before the start of the study, the Investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB. This review and approval will be documented and stored with other study documents. The Investigator or delegate must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject. The subject be allowed ample time to ask about the details of the study and to decide as to whether or not to participate in the study. The subject must sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted.

The informed consent process may be conducted up to 5 weeks prior to enrollment on Day -2.

Men and women of childbearing potential should be reminded of the requirement to use a highly effective method of contraception throughout the duration of the study, which should be recorded in the source documentation. Women of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that to participate in the study, they must adhere to the contraception requirements indicated in the protocol for the duration of the study. In case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study.

11 RECORDS MANAGEMENT

11.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The documents that will serve as source documents will be agreed between the Sponsor or its delegate and Investigator or delegate and specified in the source document agreement prior to subject enrollment.

In addition, source documentation must include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of AEs, documentation of prior/concomitant medication/drugs, study drug receipt/dispensing/return records, study drug administration information, any data collected by a telephone conversation with the subject and date of completion and reason.

The subject must also allow access to his or her own medical records. Each subject must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subjects must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an AE, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the AE eCRF.

11.2 Study Files and Record Retention

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “Essential Documents” are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12 AUDITING AND MONITORING

Study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated CRO standard operating procedures and applicable regulatory requirements (e.g., TGA and ICH guidelines).

Prior to enrollment of the first study healthy volunteer, the Sponsor or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. Electronic CRFs supplied by the Sponsor or delegate must be completed for each enrolled subject and limited data for all screened subjects who have swallowing questionnaire and imaging data available. Data and documents for all enrolled subjects will be checked by the Sponsor and/or monitor.

Prior to enrollment of the first study volunteer, the Sponsor or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how remote and/or on-site monitoring, including clinical specimen reconciliation, will be performed for the study. Study progress will be monitored by the Sponsor or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents, and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), Good Clinical Practice (GCP) and applicable regulatory requirements.

Contact details for the Sponsor or its designee involved in study monitoring will be provided to the Investigator in the Clinical Monitoring Plan. Study data recorded on eCRFs will be verified by checking the eCRF entries against source documents to ensure data completeness and accuracy as required by study protocol.

Data verification may also be performed through remote and/or centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the Investigator Site File, pharmacy records, and Informed Consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the Clinical Monitoring Plan, except in case of emergency.

The Investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification, and copying, as required by regulations, by officials of the regulatory health authorities and/or IRBs. The Investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

13 AMENDMENTS

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

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

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

14 STUDY REPORT, PUBLICATIONS, DATA POSTING

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

The Sponsor assures that the key design elements of this protocol will be posted in compliance with current regulations. The Sponsor also assures that key results of this clinical study will be posted within the required time frame from the end of study as defined in Section 5.4.

15 STUDY DISCONTINUATION

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

16 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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18 APPENDICES

18.1 Schedules of Events

18.1.1 Schedule of Events LYN-005-C-004: Screening and LYN-005 Doses 1 and 2

Visit Name		Screening Visit	Run-In (10 days)	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient
Subject Status		Outpatient		Inpatient Stay 1											
Study Day		- 21 to -14	-13 to -3	-2	-1	1[a]	2	3	4	5	6	7	8	9	10-13
Study Event	**Section**														
Study Treatment LYN-005 (N=24)															
Oral antipsychotic	4.1.1	X													
IR risperidone run-in[b]	4.1.2		X	X	X										
Randomization	4.1.4					X									
00EL placebo	6.3.3					X	X	X	X	X	X	X	X	X	X
LYN-005	6.3.3					X							X		
Study Treatment IR (00EL) risperidone (N=8)															
Oral antipsychotic	4.1.1	X													
IR risperidone run-in	4.1.2		X	X	X										
Randomization	4.1.4					X									
00EL placebo	6.3.3					X							X		
00EL risperidone	6.3.3					X	X	X	X	X	X	X	X	X	X
Screening and Safety Assessments															
Informed Consent[c]	8.1.1	X													
PILL-5 Questionnaire	8.1.2	X													
H. Pylori breath test	8.1.3	X													
Medical History	8.1.4	X													
MINI	8.1.5.1	X													
PANSS	8.1.5.2	X													

Visit Name		Screening Visit	Run-In (10 days)	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient
Subject Status		**Outpatient**		**Inpatient Stay 1**											
Study Day		**- 21 to -14**	**-13 to -3**	**-2**	**-1**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10-13**
CGI-S	8.1.5.3	X				X						X		X	
C-SSRS	8.1.5.4	X				X						X		X	
ESRS	8.1.5.5	X				X						X		X	
Fecal Occult Blood	8.1.6	X													
Physical Examination[d]	8.1.7	X		X	X	X							X		X
Vital Signs [e]	8.1.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram [f]	8.1.9	X	X	X	X	X			X				X		
CYP2D6 Genotype	8.1.10	X													
Serology Assessments [g]	8.1.11	X													
Safety Laboratory Assessments [h]	8.1.12	X	X	X	X				X				X		
Prolactin	8.1.13	X				X							X		
Pregnancy Test [i]	8.1.14	X				X							X		
Compliance Lab Assessments	8.1.15	X	X	X											
Inclusion/ Exclusion Criteria	5.1, 5.2	X		X											
Acid Reflux Symptom Severity Scale		X													
Solicitation of AEs	8.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	6.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GI Imaging (On Study)															
Abdominal X-ray	8.3											X			

Visit Name		Screening Visit	Run-In (10 days)	Admit to Unit	IR RSP Prep/ PK	LYN-005 Dose 1							LYN-005 Dose 2	DC From unit	Out Patient
Subject Status		**Outpatient**		**Inpatient Stay 1**											
Study Day		**- 21 to -14**	**-13 to -3**	**-2**	**-1**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10-13**
Pharmacokinetic Assessments (see Note)[j]															
Blood Sample/PK	8.4			S1[k]	S2[l]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S3[m]	S4[n]	S3[m]	S3[m]

AEs = Adverse Events; CGI-S = Clinical Global Impression – Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = Cytochrome P450; ESRS = Extrapyramidal Symptom Rating Scale; GI = Gastrointestinal; PK = Pharmacokinetics; RSP = Risperidone; PANSS = Positive and Negative Syndrome Scale.

General Notes:

a. Prior to dosing with LYN-005 Days 1, 8, 15, and 22, vital signs, ECG, PE, safety laboratory tests, AEs, CGI-S, ESRS will be collected. After dosing, safety assessments will be performed, including vital signs, directed physical examination, adverse event, and concomitant medication collection.

b. Subjects must receive at least 5 IR risperidone doses during the Run-in period, 3 in the outpatient setting and 2 in the inpatient setting.

c. Consent form is signed prior to performing any study related procedures.

d. General physical examinations will occur at Screening and Days -2; all other exams will be directed physical examinations.

e. Vital signs will be collected prior to (-60 min) and 12 hours (±45 min) after IR risperidone dosing on Days -2 to Day -1 and on Day 1 at prior to dosing and 4, 8, 12, 24 and 36 hours post dose. The timing and addition of further assessments will occur at the Investigator's discretion.

f. Electrocardiograms should be collected 4 hours (±15 mins) after IR dosing on Day -1, prior to and 4 hours (±15 mins) after dosing with LYN-005 and additionally where indicated.

g. Serological laboratory tests are for Hepatitis B, and C and HIV.

h. All safety laboratory assessments include serum chemistry, hematology, and coagulation. Measurement of HbA1C concentration only occurs at Screening.

i. Required in women of childbearing potential only.

j. Schedule for Pharmacokinetic (PK) collection:

   k. S1: Date and time of last dose is to be recorded, and PK samples to be collected upon arrival at unit, 12 pm and 6 pm (±30 min) on Day -2, prior to administration of half the regimen of daily IR risperidone in the evening (i.e. either 1 or 2 mg).

   l. S2: On the morning of Day -1, a dose of IR risperidone (2 or 4 mg based on dose allocation) will be administered to each subject after fasting with PK samples collected prior to and at 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 min), 16 h (±30 min), and 24 h (±30 min) after dosing. (The 24-hour post-dose sample is equivalent to the LYN-005 pre-dose sample.)

   m. S3: PK samples to be collected just prior to and following LYN-005 administration or 00EL placebo Day 1 at 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 min) post dose and every 12 hours (±30) thereafter through Day 7, and again on Day 9 through the morning of Day 10.

   n. S4: On Day 8, a PK sample will be taken prior to the administration of LYN-005 administration or 00EL placebo and at hours 4 and 8 (±15 min).

18.1.2 Schedule of Events LYN-005-C-004: LYN-005 Dose 3 through Study Completion

Visit Name		LYN-005 Dose 3						Resume Prior APD		EOS[a]
Subject Status		Inpatient Stay 2			Outpatient					
Study Day		14[b]	15	16	17	18	21	22	23	35
Window		-	-	-	-	+1	±1	±1	±1	±1
Study Event	**Section**									
Study Treatment: LYN-005 (N=24)										
Oral antipsychotic	4.1.1							X	X	X
IR risperidone run-in	4.1.2									
Randomization	4.1.4									
00EL placebo	6.3.3	X	X	X	X	X	X			
LYN-005	6.3.3		X							
Study Treatment: IR (00EL) risperidone (N=8)										
Oral antipsychotic	4.1.1							X	X	X
IR risperidone run-in	4.1.2									
Randomization	4.1.4									
00EL placebo	6.3.3		X							
00EL risperidone	6.3.3	X	X	X	X	X	X			
Safety Assessment										
Informed Consent	8.1.1									
Medical History	8.1.2									
PILL-5 Questionnaire	8.1.3									
H. Pylori breath test	8.1.4									
MINI	8.1.5.1									
PANSS	8.1.5.2									
CGI-S	8.1.5.3		X				X			X
C-SSRS	8.1.5.4		X				X			X
ESRS	8.1.5.5		X				X			X

Visit Name		**LYN-005 Dose 3**						**Resume Prior APD**		**EOS[a]**
Subject Status		**Inpatient Stay 2**			**Outpatient**					
Study Day		**14[b]**	**15**	**16**	**17**	**18**	**21**	**22**	**23**	**35**
Window		**-**	**-**	**-**	**-**	**+1**	**±1**	**±1**	**±1**	**±1**
Fecal Occult Blood	8.1.6									
Physical Examination[c]	8.1.7		X		X				X	X
Vital Signs	8.1.8		X	X	X	X	X	X	X	X
Electrocardiogram[d]	8.1.9		X		X			X		
CYP2D6 Genotype	8.1.10									
Serology Assessments	8.1.11									
Safety Laboratory Assessments [e]	8.1.12		X	X						X
Prolactin	8.1.13		X				X			X
Pregnancy Test [f]	8.1.14		X							
Compliance Laboratory Assessments	8.1.15				X					
Inclusion/ Exclusion Criteria	5.1, 5.2									
Solicitation of AEs	8.2.3	X	X	X	X	X	X	X	X	X
Concomitant Medications	6.5	X	X	X	X	X	X	X	X	X
GI Imaging (on study)										
Abdominal X-ray	8.3	X					X			X
Pharmacokinetics Assessments (see Note)[g]										
Blood Sample/PK	8.4	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]	S5[h]		

AEs = Adverse Events; CGI-S = Clinical Global Impression – Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = Cytochrome P450; ESRS = Extrapyramidal Symptom Rating Scale; GI = Gastrointestinal; PK = Pharmacokinetics; RSP = Risperidone; PANSS = Positive and Negative Syndrome Scale.

General Notes:

a. Final outpatient clinic visit will occur on Day 35 (EOS Visit).

b. Subjects will return to clinic on the evening of Day 14 to prepare for dosing on the morning of Day 15.

c. General physical examinations will occur on Day 35; all other examinations will be directed physical examinations.

d. 4 hours (±15 mins) after IR dosing on Day -1, prior to and 4 hours (±15 mins) after dosing with LYN-005 and additionally where indicated.

e. All safety laboratory assessments include serum chemistry, hematology, and coagulation.

f. Required in women of childbearing potential only.

g. Schedule for Pharmacokinetic (PK) collection:

h. S5: On Day 14, the subject will return to the clinic to prepare for an inpatient stay through Day 16. A PK sample will be collected upon arrival in the inpatient unit on Day 14. On Day 15, PK samples will be collected pre-dose and at 1 h (±5 min), 2 h (±15 min), 4 h (±15 min), 6 h (±15 min), 8 h (±15 min), 12 h (±30 mi), and 24 h (±30 min) (i.e., Day 16). Single samples also are to be collected on Days 17, 18, 21, and 22; on these study days, the sample is to be collected at the same time of day as the 24-hour post-dose sample on Day 16.

18.2 PILL-5 Questionnaire

The italicized text below is the questionnaire, which is to be administered to the individual during the Screening process.

The individual should complete this questionnaire independently and should answer all questions. If the subject has not experienced pill swallowing in the past week, they should answer for a previous week where they have taken oral medications. After the individual has provided his/her answers, the total score is achieved by adding together the numerical value from each question. Subjects with a PILL-5 questionnaire score of 5 or greater are to be excluded.

These are statements that many people have used to describe their problems swallowing pills. Please circle the response that indicates how frequently you had the same experience in the past week. If you do not have any problem swallowing pills, please circle zero (0) in response to these statements.

Please circle the response that indicates how frequently you experience these symptoms.

	Never	***Almost Never***	***Sometimes***	***Almost Always***	***Always***
1. Pills stick in my throat	0	1	2	3	4
2. Pills stick in my chest	0	1	2	3	4
3. I have a fear of swallowing pills	0	1	2	3	4
4. My problem swallowing pills interferes with my ability to take medication	0	1	2	3	4
5. I can't take my pills without crushing, coating, or using other forms of assistance	0	1	2	3	4

18.3 Mini International Neuropsychiatric Interview (MINI) version 7.0.2

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	F32.x	☐
		Past	☐	F32.x	☐
		Recurrent	☐	F33.x	☐
B	SUICIDALITY	Current (Past Month)	☐		☐
		Lifetime attempt	☐	☐ Low ☐ Moderate ☐ High	☐
	SUICIDE BEHAVIOR DISORDER	Current	☐	(In Past Year)	☐
		In early remission	☐	(1 - 2 Years Ago)	☐
C	MANIC EPISODE	Current	☐		
		Past	☐		
	HYPOMANIC EPISODE	Current	☐		
		Past	☐	☐ Not Explored	
	BIPOLAR I DISORDER	Current	☐	F31.0 - F31.76	☐
		Past	☐	F31.0 - F31.76	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/31.5/F31.64	☐
		Past	☐	F31.2/31.5/F31.64	☐
	BIPOLAR II DISORDER	Current	☐	F31.81	☐
		Past	☐	F31.81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31.89	☐
		Past	☐	F31.89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41.0	☐
		Lifetime	☐	F40.0	☐
E	AGORAPHOBIA	Current	☐	F40.00	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10 - F10.21	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10 - F19.21	☐

K	ANY PSYCHOTIC DISORDER	Current	☐	F20.81-F29	☐
		Lifetime	☐	F20.81-F29	☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F32.3/F33.3	☐
		Past	☐	F32.3/F33.3	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/F31.5/F31.64	☐
		Past	☐	F31.2/F31.5/F31.64	☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis or diagnoses is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:
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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	For the past two weeks, were you depressed or down, or did you feel sad, empty or hopeless, most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
		➡ IS **A1a** OR **A2a** CODED **YES**?	NO	YES

A3 IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **A1b** AND **A2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE.

Over that two-week period, when you felt depressed or uninterested: a	Past 2 Weeks		Past Episode	
a Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
d Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
IF **YES**, ASK FOR EXAMPLES. LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
f Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
g Did you repeatedly think about death **(FEAR OF DYING DOES NOT COUNT HERE),** or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? **IF YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4 Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED **YES** FOR THAT TIME FRAME?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO **YES**

MAJOR DEPRESSIVE EPISODE

CURRENT ☐
PAST ☐
RECURRENT ☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

C. MANIC AND HYPOMANIC EPISODES

(➡ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN MANIC AND HYPOMANIC DIAGNOSTIC BOXES, AND MOVE TO NEXT MODULE)

Do you have any family history of manic-depressive illness or bipolar disorder, or any family member who had mood swings treated with a medication like lithium, sodium valproate (Depakote) or lamotrigine (Lamictal)? NO YES

THIS QUESTION IS NOT A CRITERION FOR BIPOLAR DISORDER, BUT IS ASKED TO INCREASE THE CLINICIAN'S VIGILANCE ABOUT THE RISK FOR BIPOLAR DISORDER.

IF YES, PLEASE SPECIFY WHO:_____

C1 a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' and so active or full of energy or full of yourself that you got into trouble, - or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) NO YES

IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy or increased activity; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior; phoning or working excessively or spending more money.

IF NO, CODE **NO** TO **C1b**: **IF YES** ASK:

b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? NO YES

C2 a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? NO YES

IF NO, CODE **NO** TO **C2b**: **IF YES** ASK:

b Are you currently feeling persistently irritable? NO YES ➡

IS **C1a** OR **C2a** CODED **YES**? NO YES

C3 IF **C1b** OR **C2b** = **YES**: EXPLORE THE **CURRENT** EPISODE FIRST AND THEN THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **C1b** AND **C2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE

WHEN EXPLORING THE CURRENT EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over the past few days including today, when you felt high and full of energy or irritable, did you:

WHEN EXPLORING THE PAST EPISODE, PREFACE EACH QUESTION AS FOLLOWS:
Over a period of a few days in the past, when you felt most high and most full of energy or most irritable, did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? **IF YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes; Past Episode ☐ No ☐ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES

		Current Episode		Past Episode	
c	Talk too much without stopping, or felt a pressure to keep talking?	NO	YES	NO	YES
d	Notice your thoughts going very fast or running together or racing or moving very quickly from one subject to another?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Have a significant increase in your activity or drive, at work, at school, socially or sexually or did you become physically or mentally restless? This increase in activity may be with or without a purpose.	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

C3 **SUMMARY:** WHEN RATING CURRENT EPISODE: NO YES NO YES

IF **C1b** IS **NO,** ARE **4** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?
IF **C1b** IS **YES**, ARE **3** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

WHEN RATING PAST EPISODE:
IF **C1a** IS **NO**, ARE **4** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?
IF **C1a** IS **YES**, ARE **3** OR MORE **C3** ANSWERS **INCLUDING C3f** CODED **YES**?

CODE **YES** ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

RULE: ELATION/EXPANSIVENESS REQUIRES ONLY **3** OF THE **C3** SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **C3** SYMPTOMS.

C4 What is the longest time these symptoms lasted (most of the day nearly every day)?
ASSESS THIS DURATION FROM THE VERY START TO THE VERY END OF SYMPTOMS, NOT JUST THE PEAK.

a)	3 consecutive days or less	☐	☐
b)	4, 5 or 6 consecutive days or more	☐	☐
c)	7 consecutive days or more	☐	☐

C5 Were you hospitalized for these problems? NO YES NO YES

IF YES, CIRCLE **YES** IN MANIC EPISODE FOR THAT TIME FRAME AND GO TO **C7**.

C6 Did these symptoms cause significant problems at home, at work, socially, in your relationships, at school or in some other important way? NO YES NO YES

C7 Were these symptoms associated with a clear change in the way that you previously functioned and that was different from the way that you usually are? NO YES NO YES

ARE **C3 SUMMARY** AND **C7** AND (**C4c** OR **C5** OR **C6** OR ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K8**) CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

NO **YES**

MANIC EPISODE

CURRENT ☐
PAST ☐

IS **C3 SUMMARY** CODED **YES** AND ARE **C5** AND **C6** CODED **NO** AND **C7** CODED **YES**,
AND IS EITHER **C4b** OR **C4c** CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

AND

ARE **ALL** PSYCHOTIC FEATURES IN **K1** THROUGH **K8** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE, THEN CODE CURRENT HYPOMANIC EPISODE AS **NO**.

IF **YES** TO PAST MANIC EPISODE, THEN CODE PAST HYPOMANIC EPISODE AS **NOT EXPLORED**.

HYPOMANIC EPISODE

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

ARE **C3 SUMMARY** AND **C4a** CODED **YES** AND IS **C5** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **YES** TO CURRENT MANIC EPISODE OR HYPOMANIC EPISODE,
THEN CODE CURRENT HYPOMANIC SYMPTOMS AS **NO.**

IF **YES** TO PAST MANIC EPISODE OR **YES** TO PAST HYPOMANIC EPISODE,
THEN CODE PAST HYPOMANIC SYMPTOMS AS **NOT EXPLORED.**

HYPOMANIC SYMPTOMS

CURRENT ☐ **NO**
☐ **YES**

PAST ☐ **NO**
☐ **YES**
☐ **NOT EXPLORED**

C8 a) IF MANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (manic) episodes lasting 7 days or more (**C4c**) in your lifetime (including the current episode if present)? NO YES

b) IF MANIC OR HYPOMANIC EPISODE IS POSITIVE FOR EITHER CURRENT OR PAST ASK:
Did you have 2 or more of these (hypomanic) episodes lasting 4 days or more (**C4b**) in your lifetime (including the current episode)? NO YES

c) IF THE PAST "HYPOMANIC SYMPTOMS" CATEGORY IS CODED POSITIVE ASK:
Did you have these hypomanic symptoms lasting only 1 to 3 days (**C4a**) 2 or more times in your lifetime, (including the current episode if present)? NO YES

D. PANIC DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, very frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
D2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
D3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack - or did you make any significant change in your behavior because of the attacks (e.g., avoiding unfamiliar situations, or avoiding leaving your house or shopping alone, or doing things to avoid having a panic attack or visiting your doctor or the emergency room more frequently)?	NO	YES
D4		**During the worst attack that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing or a smothering sensation?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or feel faint?	NO	YES
	i	Did you have hot flushes or chills?	NO	YES
	j	Did you have tingling or numbness in parts of your body?	NO	YES
	k	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	l	Did you fear that you were losing control or going crazy?	NO	YES
	m	Did you fear that you were dying?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**?	➡ NO	YES ***PANIC DISORDER LIFETIME***
D6		In the past month did you have persistent concern about having another attack, or worry about the consequences of the attacks, or did you change your behavior in any way because of the attacks?	NO	YES ***PANIC DISORDER CURRENT***

IS EITHER **D5** OR **D6** CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR LIFETIME.

NO **YES**

PANIC DISORDER

LIFETIME ☐
CURRENT ☐

E. AGORAPHOBIA

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult if you had a panic attack or panic-like or embarrassing symptoms, like: being in a crowd, or standing in a line (queue), being in an open space or when crossing a bridge, being in an enclosed space, when you are alone away from home, or alone at home, or traveling in a bus, train or car or using public transportation?	➡ NO	YES
	ARE **2** OR MORE OF THE ABOVE SITUATIONS IN **E1** CODED **YES**?	➡ NO	YES
E2	Do these situations almost always bring on fear or anxiety?	➡ NO	YES
E3	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
E4	Is this fear or anxiety excessive or out of proportion to the real danger in the situation?	➡ NO	YES
E5	Did this avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
E6	Did these symptoms cause significant distress or problems at home, at work, socially, at school or in some other important way?	➡ NO	YES

IS **E6** CODED **YES**?

NO **YES**

AGORAPHOBIA CURRENT

F. SOCIAL ANXIETY DISORDER (Social Phobia)

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

F1	In the past month, did you have persistent fear and significant anxiety at being watched, being the focus of attention, or of being humiliated or embarrassed or rejected? This includes things like speaking in public, eating in public or with others, writing while someone watches, performing in front of others or being in social situations.	➡ NO	YES

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE

- INITIATING OR MAINTAINING A CONVERSATION,
- PARTICIPATING IN SMALL GROUPS,
- DATING,
- SPEAKING TO AUTHORITY FIGURES,
- ATTENDING PARTIES,
- PUBLIC SPEAKING,
- EATING IN FRONT OF OTHERS,
- PERFORMING IN FRONT OF OTHERS,
- URINATING IN A PUBLIC WASHROOM, ETC.

F2	Do these social situations almost always bring on fear or anxiety?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them, or suffer through them, or need a companion to face them?	➡ NO	YES
F4	Is this social fear or anxiety excessive or unreasonable in these social situations?	➡ NO	YES
F5	Did this social avoidance, fear or anxiety persist for at least 6 months?	➡ NO	YES
F6	Did these social fears cause significant distress or interfere with your ability to function at work, at school or socially or in your relationships or in some other important way?	➡ NO	YES

IS **F6** CODED **YES**?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NOTE TO CLINICIAN: PLEASE SPECIFY IF THE SUBJECT'S FEARS ARE RESTRICTED TO SPEAKING OR PERFORMING IN PUBLIC.

NO **YES**

SOCIAL ANXIETY DISORDER
(Social Phobia)
CURRENT

RESTRICTED TO PERFORMANCE SAD ONLY ☐

G. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1a	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? - (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though it disturbs or distresses you, or fear you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** religious obsessions.)	NO YES ↓ SKIP TO **G3**a
G1b	In the past month, did you try to suppress these thoughts, impulses, or images or to neutralize or to reduce them with some other thought or action? (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO HOARDING, HAIR PULLING, SKIN PICKING, BODY DYSMORPHIC DISORDER, EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **G3**a
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES **obsessions**
G3a	In the past month, did you feel driven to do something repeatedly in response to an obsession or in response to a rigid rule, like washing or cleaning excessively, counting or checking things over and over, or repeating or arranging things, or other superstitious rituals?	NO YES
G3b	Are these rituals done to prevent or reduce anxiety or distress or to prevent something bad from happening and are they excessive or unreasonable?	NO YES **compulsions**

➡

ARE (**G1a** AND **G1b** AND **G2**) OR (**G3a** AND **G3b**) CODED **YES**? NO YES

G4 In the past month, did these obsessive thoughts and/or compulsive behaviors cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way or did they take more than one hour a day?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?
(CHECK FOR ANY OBSESSIVE-COMPULSIVE SYMPTOMS STARTING WITHIN 3 WEEKS OF AN INFECTION)

SPECIFY THE LEVEL OF INSIGHT AND IF THE EPISODE IS TIC-RELATED.

NO **YES**

O.C.D. CURRENT

INSIGHT:

- GOOD OR FAIR ☐
- POOR ☐
- ABSENT ☐
- DELUSIONAL ☐

- TIC-RELATED ☐

H. POSTTRAUMATIC STRESS DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury or sexual violence to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, WAR, OR NATURAL DISASTER, WITNESSING THE VIOLENT OR SUDDEN DEATH OF SOMEONE CLOSE TO YOU, OR A LIFE-THREATENING ILLNESS.	NO ➡	YES
H2	Starting after the traumatic event, did you repeatedly re-experience the event in an unwanted mentally distressing way, (such as in recurrent dreams related to the event, intense recollections or memories, or flashbacks or as if the event was recurring) or did you have intense physical or psychological reactions when you were reminded about the event or exposed to a similar event?	NO ➡	YES

H3	**In the past month:**			
	a	Did you persistently try to avoid thinking about or remembering distressing details or feelings related to the event?	NO	YES
	b	Did you persistently try to avoid people, conversations, places, situations, activities or things that bring back distressing recollections of the event?	NO	YES
		ARE **1** OR MORE **H3** ANSWERS CODED **YES**?	NO ➡	YES
H4	**In the past month:**			
	a	Did you have trouble recalling some important part of the trauma? (but not because of or related to head trauma, alcohol or drugs).	NO	YES
	b	Were you constantly and unreasonably negative about yourself or others or the world?	NO	YES
	c	Did you constantly blame yourself or others in unreasonable ways for the trauma?	NO	YES
	d	Were your feelings always negative (such as fear, horror, anger, guilt or shame)?	NO	YES
	e	Have you become much less interested in participating in activities that were meaningful to you before?	NO	YES
	f	Did you feel detached or estranged from others?	NO	YES
	g	Were you unable to experience any good feelings (such as happiness, satisfaction or loving feelings)?	NO	YES
		ARE **2** OR MORE **H4** ANSWERS CODED **YES**?	NO ➡	YES

H5 **In the past month:**

a	Were you especially irritable or did you have outbursts of anger with little or no provocation?	NO	YES
b	Were you more reckless or more self-destructive?	NO	YES
c	Were you more nervous or constantly on your guard?	NO	YES
d	Were you more easily startled?	NO	YES
e	Did you have more difficulty concentrating?	NO	YES
f	Did you have more difficulty sleeping?	NO	YES
	ARE **2** OR MORE **H5** ANSWERS CODED **YES**? ➡	NO	YES
H6	Did all these problems start after the traumatic event and last for more than one month? ➡	NO	YES

H7 During the past month, did these problems cause significant distress, or interfere with your ability to function at home, at work, at school or socially or in your relationships or in some other important way?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY IF THE CONDITION IS ASSOCIATED WITH DEPERSONALIZATION, DEREALIZATION OR WITH DELAYED EXPRESSION.

NO **YES**

POSTTRAUMATIC STRESS DISORDER CURRENT

WITH

DEPERSONALIZATION ☐

DEREALIZATION ☐

DELAYED EXPRESSION ☐

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. THE PURPOSE OF THIS MODULE IS TO EXCLUDE PATIENTS WITH PSYCHOTIC DISORDERS. THIS MODULE NEEDS EXPERIENCE.

Now I am going to ask you about unusual experiences that some people have.

K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspapers, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES
	b	**IF YES:** do you currently believe these things?	NO	YES
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? CLINICIAN: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS **K1** TO **K4**. FOR EXAMPLE, RELIGIOUS, DEATH, DISEASE OR SOMATIC DELUSIONS, DELUSIONS OF GRANDIOSITY, JEALOUSY OR GUILT, OR OF FAILURE, INADEQUACY, RUIN, OR DESTITUTION, OR NIHILISTIC DELUSIONS.	NO	YES
	b	**IF YES:** do they currently consider your beliefs strange or unusual?	NO	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES
	b	**IF YES TO K6a:** have you heard sounds / voices in the past month?	NO	YES
		IF YES TO VOICE HALLUCINATION: Was the voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES

K7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

K8 a DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED, INCOHERENT OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED OR DERAILED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

K9 a DID THE PATIENT EVER IN THE PAST EXHIBIT DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

K10 a DID THE PATIENT EVER IN THE PAST HAVE NEGATIVE SYMPTOMS, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION)? NO YES

K10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT REDUCTION OF EMOTIONAL EXPRESSION OR AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

K11 a ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K7a**, CODED **YES**?

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT, RECURRENT OR PAST)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**?

AND

HOW LONG HAS THE MOOD EPISODE LASTED? _____
HOW LONG HAS THE PSYCHOTIC EPISODE LASTED? _____
IF SUCH A MOOD EPISODE IS PRESENT, CODE **YES** TO **K11a** ONLY IF THE MOOD DISTURBANCE IS PRESENT FOR THE MAJORITY OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PERIODS OF THE PSYCHOTIC SYMPTOMS. OTHERWISE CODE **NO**. NO YES
↳ **K13**

IF **NO** TO **K11a** AND THE TOTAL DURATION OF THE MOOD EPISODE IS **LESS THAN** THE TOTAL DURATION OF THE PSYCHOTIC EPISODE, THEN CIRCLE **NO** IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO **K13**.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **K1a** TO **K7a**) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST **2 WEEKS** OF HAVING THESE BELIEFS OR EXPERIENCE (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE **NO** TO THIS DISORDER.

IF THE ANSWER IS **NO** TO THIS DISORDER GROUPING, ALSO CIRCLE **NO** TO **K12** AND MOVE TO **K13**

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

LIFETIME

K12 a ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K7b** CODED **YES**?

AND IS EITHER:

MAJOR DEPRESSIVE EPISODE (CURRENT)

OR

MANIC OR HYPOMANIC EPISODE (CURRENT) CODED **YES**?

IF THE ANSWER IS **YES** TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE **NO** TO **K13** AND **K14** AND MOVE TO THE NEXT MODULE.

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

CURRENT

K13 ARE **1** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K8b**, CODED **YES**?

AND

ARE **2** OR MORE « **b** » QUESTIONS FROM **K1b** TO **K10b**, CODED **YES**?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

K14 IS **K13** CODED **YES**?

OR

(ARE **1** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K8a**, CODED **YES**?

AND

ARE **2** OR MORE « **a** » QUESTIONS FROM **K1a** TO **K10a,** CODED **YES**

AND

DID AT LEAST **2** OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1-MONTH PERIOD?)

AND

IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

N. GENERALIZED ANXIETY DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

N1	a	Were you excessively anxious or worried about several routine things, over the past 6 months? IN ENGLISH, IF THE PATIENT IS UNCLEAR ABOUT WHAT YOU MEAN, PROBE BY ASKING (Do others think that you are a worrier or a "worry wart"?) AND GET EXAMPLES.	➡ NO	YES
	b	Are these anxieties and worries present most days?	➡ NO	YES
		ARE THE PATIENT'S ANXIETY AND WORRIES RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
N2		Do you find it difficult to control the worries?	➡ NO	YES
N3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Have muscle tension?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
		ARE **3** OR MORE **N3** ANSWERS CODED **YES**?	➡ NO	YES
N4		Do these anxieties and worries significantly disrupt your ability to work, to function socially or in your relationships or in other important areas of your life or cause you significant distress? **AND** IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?	**NO**	**YES** ***GENERALIZED ANXIETY DISORDER*** **CURRENT**

O. RULE OUT MEDICAL, ORGANIC OR DRUG CAUSES FOR ALL DISORDERS

IF THE PATIENT CODES POSITIVE FOR ANY CURRENT DISORDER OR A MAJOR DEPRESSIVE EPISODE OR A MANIC OR A HYPOMANIC EPISODE ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines or in withdrawal from any of these?	☐ No	☐ Yes	☐ Uncertain
O1b	Did you have any medical illness?	☐ No	☐ Yes	☐ Uncertain
O2	IF **O1a** OR **O1b** IS CODED **YES**, IN THE CLINICIAN'S JUDGMENT, IS EITHER LIKELY TO BE A DIRECT CAUSE OF THE PATIENT'S DISORDER? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.	☐ No	☐ Yes	☐ Uncertain
O2 SUMMARY: HAS AN "ORGANIC" / MEDICAL / DRUG RELATED CAUSE BEEN RULED OUT?		☐ No	☐ Yes	☐ Uncertain

IF **O2** IS **YES**, THEN **O2** SUMMARY IS **NO**. IF **O2** IS **NO**, THEN **O2** SUMMARY IS **YES.** OTHERWISE IT IS UNCERTAIN.

MOOD DISORDERS: DIAGNOSTIC ALGORITHM

Consult Modules:
- A Major Depressive Episode
- C (Hypo)manic Episode
- K Psychotic Disorders

MODULE K:

1a	IS **K11b** CODED **YES**?	NO	YES
1b	IS **K12a** CODED **YES**?	NO	YES

MODULES A and C:		Current	Past
2	a CIRCLE **YES** IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e** OR IN ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7**	YES	YES
	b CIRCLE **YES** IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a** OR IN ANY PSYCHOTIC FEATURE IN **K1** THROUGH **K7**	YES	YES

c IS MAJOR DEPRESSIVE EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS HYPOMANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS "RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- IF THE DEPRESSIVE EPISODE IS **CURRENT** OR **PAST** OR BOTH
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1b** OR **2a** (CURRENT) = **YES**
  WITH PSYCHOTIC FEATURES, PAST: IF **1a** OR **2a** (PAST) = **YES**

MAJOR DEPRESSIVE DISORDER

	Current	Past
MDD	☐	☐

With Psychotic Features

Current	☐
Past	☐

d IS MANIC EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS **"**RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- IF THE BIPOLAR I DISORDER IS **CURRENT** OR **PAST** OR BOTH
- WITH SINGLE MANIC EPISODE: IF MANIC EPISODE (CURRENT OR PAST) = **YES** **AND** MAJOR DEPRESSIVE EPISODE (CURRENT AND PAST) = **NO**
- WITH PSYCHOTIC FEATURES, CURRENT: IF **1b** OR **2a** (CURRENT) OR **2b** (CURRENT) = **YES**
  WITH PSYCHOTIC FEATURES, PAST: IF **1a** OR **2a** (PAST) OR **2b** (PAST) = **YES**
- IF THE MOST RECENT EPISODE IS MANIC, DEPRESSED, OR HYPOMANIC (MUTUALLY EXCLUSIVE)
- IF THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES

  HYPO/MANIC WITH MIXED FEATURES = HYPO/MANIC + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**

  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR I DISORDER

	Current	Past
Bipolar I Disorder	☐	☐
Single Manic Episode	☐	☐

With Psychotic Features
Current ☐
Past ☐

Most Recent Episode
Manic ☐
Depressed ☐
Hypomanic ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

e IS MAJOR DEPRESSIVE EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS HYPOMANIC EPISODE CODED **YES** (CURRENT OR PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **"**RULE OUT ORGANIC CAUSE (**O2 SUMMARY**)" CODED **YES**?

SPECIFY:

- IF THE BIPOLAR DISORDER IS **CURRENT** OR **PAST** OR BOTH
- IF THE MOST RECENT MOOD EPISODE IS HYPOMANIC OR DEPRESSED (MUTUALLY EXCLUSIVE)
- IF THE MOST RECENT MOOD EPISODE IS WITH MIXED, ANXIOUS OR PSYCHOTIC FEATURES

  HYPOMANIC WITH MIXED FEATURES = HYPOMANIC + AT LEAST **3** SYMPTOMS FROM **A3**

  DEPRESSED WITH MIXED FEATURES = MAJOR DEPRESSIVE EPISODE + AT LEAST **3** SYMPTOMS FROM **C3**

  WITH ANXIOUS DISTRESS = WITH AT LEAST **3** SYMPTOMS FROM **N3**

BIPOLAR II DISORDER

	Current	Past
Bipolar II Disorder	☐	☐

Most Recent Episode
Hypomanic ☐
Depressed ☐

Most Recent Episode
With mixed features ☐
With anxious distress ☐

Most Recent Episode
Mild ☐
Moderate ☐
Severe ☐

f IS MAJOR DEPRESSIVE EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **C4b** CODED **YES** FOR THE APPROPRIATE TIME FRAME?
AND
IS **C8b** CODED **YES**?

OR

IS MANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS HYPOMANIC EPISODE CODED **NO** (CURRENT AND PAST)?
AND
IS **C4a** CODED **YES** FOR THE APPROPRIATE TIME FRAME?
AND
IS **C8c** CODED **YES**?

SPECIFY IF THE OTHER SPECIFIED BIPOLAR AND RELATED DISORDER IS **CURRENT** OR **PAST** OR BOTH.

OTHER SPECIFIED BIPOLAR AND RELATED DISORDER

	Current	Past
Other Specified Bipolar and Related Disorder	☐	☐

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18.4 Structured Clinical Interview – Positive and Negative Syndrome Scale (SCI-PANSS)

SCI-PANSS

SCI–PANSS

Structured Clinical Interview – Positive and Negative Syndrome Scale

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Stanley R. Kay, Ph.D.
J.P. Lindenmayer, M.D., &
Abraham Fiszbein, M.D.

MHS

Structured Clinical Interview for the Positive and Negative Syndrome Scale

SCI-PANSS

L. A. Opler, M.D., Ph.D. S. R. Kay, Ph.D. J. P. Lindenmayer, M.D. A. Fiszbein, M.D.

Patient Name or ID: _____

Interviewer: _____ Date: _____ / _____ / _____

Data on "Lack of Spontaneity and Flow of Conversation" (N6), "Poor Rapport" (N3), and "Conceptual Disorganization" (P2)

Hi, I'm ... We're going to be spending the next 30 to 40 minutes talking about you and your reasons for being here. Maybe you can start out by telling me something about yourself and your background?

(Instruction to interviewer: Allow at least 5 minutes for a non-directive phase serving to establish rapport in the context of an overview before proceeding to the specific questions listed below.)

Data on "Anxiety" (G2)

1. Have you been feeling worried or nervous in the past week? _____

   IF YES, skip to question 3. IF NO, continue.

2. Would you say that you're usually calm and relaxed? _____

   IF YES, skip to question 8. IF NO, continue.

3. What's been making you feel nervous (worried, not calm, not relaxed)? _____

4. Just how nervous (worried, etc.) have you been feeling? _____

5. Have you been shaking at times, or has your heart been racing? _____

6. Do you get into a state of panic? _____

7. Has your sleep, eating, or participation in activities been affected? _____

Data on "Delusions (General)" (P1) and "Unusual Thought Content" (G9)

8. Have things been going well for you? _____

9. Has anything been bothering you lately? _____

10. Can you tell me something about your thoughts on life and its purpose? _____

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11. Do you follow a particular philosophy (any special rules, teachings, or religious doctrine)? _____

12. Some people tell me they believe in the Devil; what do you think? _____

IF NO (i.e., he/she doesn't believe in the Devil), skip to question 14.
IF YES (i.e., he/she does believe), continue.

13. Can you tell me more about this? _____

14. Can you read other people's minds? _____

IF NO, skip to question 16. IF YES, continue.

15. How does that work? _____

16. Can others read your mind? _____

IF NO, skip to question 19. IF YES, continue.

17. How can they do that? _____

18. Is there any reason that someone would want to read your mind? _____

19. Who controls your thoughts? _____

Data on "Suspiciousness/Persecution" (P6) and "Poor Impulse Control" (GI4)

20. How do you spend your time these days? _____

21. Do you prefer to be alone? _____

22. Do you join in activities with others? _____

IF YES, skip to question 25. IF NO, continue.

23. Why not? ... Are you afraid of people, or do you dislike them? _____

IF NO, skip to question 26. IF YES, continue.

24. Can you explain? _____

Skip to question 26.

25. Tell me about it. _____

26. Do you have many friends? _____

IF YES, skip to question 30. IF NO, continue.

27. Just a few? _____

IF YES, skip to question 29. IF NO, continue.

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28. Any? .... Why? _____

Skip to question 32.

29. Why just a few friends? _____

30. Close friends? _____

IF YES, skip to question 32. IF NO, continue.

31. Why not? _____

32. Do you feel that you can trust most people? _____

IF YES, skip to question 34. IF NO, continue.

33. Why not? _____

34. Are there some people in particular who you don't trust? _____

IF NO to question 34 and YES to question 32, skip to question 41.

IF NO to question 34 and NO to question 32, skip to question 36.

IF YES to question 34, continue.

35. Can you tell me who they are? _____

36. Why don't you trust people (or name specific person)? _____

IF "DON'T KNOW" OR "DON'T WANT TO SAY," continue. Otherwise, skip to question 41.

37. Do you have a good reason not to trust ...?

_____

38. Is there something that .... did to you? _____

39. Perhaps something that ... might do to you now? _____

IF NO, skip to question 41. IF YES, continue.

40. Can you explain to me? _____

41. Do you get along well with others? _____

IF YES, skip to question 43. IF NO, continue.

42. What's the problem? _____

43. Do you have a quick temper? _____

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44. Do you get into fights? _____

IF NO, skip to question 48. IF YES, continue.

45. How do these fights start? _____

46. Tell me about these fights. _____

47. How often does this happen? _____

48. Do you sometimes lose control of yourself? _____

IF NO, skip to question 50. IF YES, continue.

49. What happens when you lose control of yourself? _____

50. Do you like most people? _____

IF YES, skip to question 52. IF NO, continue.

51. Why not? _____

52. Are there perhaps some people who don't like you? _____

IF NO, skip to question 54. IF YES, continue.

53. For what reason? _____

54. Do others talk about you behind your back? _____

IF NO, skip to question 57. IF YES, continue.

55. What do they say about you? _____

56. Why? _____

57. Does anyone ever spy on you or plot against you? _____

58. Do you sometimes feel in danger? _____

IF NO, skip to question 64. IF YES, continue.

59. Would you say that your life is in danger? _____

60. Is someone thinking of harming you or even perhaps thinking of killing you? _____

61. Have you gone to the police for help? _____

62. Do you sometimes take matters into your own hands or take action against those who might harm you?

_____

IF NO, skip to question 64. IF YES, continue.

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63. What have you done? _____

Data on "Hallucinatory Behavior" (P3) and associated delusions

64. Do you once in a while have strange or unusual experiences? _____

65. Sometimes people tell me that they can hear noises or voices inside their head that others can't hear. What about you? _____

IF YES, skip to question 68. IF NO, continue.

66. Do you sometimes receive personal communications from the radio or TV? _____

IF YES, skip to question 68. IF NO, continue.

67. From God or the Devil?: _____

IF NO, skip to question 83. IF YES, continue.

68. What do you hear? _____

69. Are these as clear and loud as my voice? _____

70. How often do you hear these voices, noises, messages, etc.? _____

71. Does this happen at a particular time of day or all the time? _____

IF HEARING NOISES ONLY, skip to question 80. IF HEARING VOICES, continue.

72. Can you recognize whose voices these are? _____

73. What do the voices say? _____

74. Are the voices good or bad? _____

75. Pleasant or unpleasant? _____

76. Do the voices interrupt your thinking or your activities? _____

77. Do they sometimes give you orders or instructions? _____

IF NO, skip to question 80. IF YES, continue.

78. For example? _____

79. Do you usually obey these orders (instructions)? _____

80. What do you make of these voices (or noises); where do they really come from? _____

81. Why do you have these experiences? _____

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82. Are these normal experiences? _____

83. Do ordinary things sometimes look strange or distorted to you? _____

84. Do you sometimes have "visions" or see things that others can't see? _____

IF NO, skip to question 88. IF YES, continue.

85. For example? _____

86. Do these visions seem very real or life-like? _____

87. How often do you have these experiences? _____

88. Do you sometimes smell things that are unusual or that others don't smell? _____

IF NO, skip to question 90. IF YES, continue.

89. Please explain. _____

90. Do you get any strange or unusual sensations from your body? _____

IF NO, skip to question 92. IF YES, continue.

91. Tell me about this. _____

Data on "Somatic Concern" (GI)

92. How have you been feeling in terms of your health? _____

IF OTHER THAN "GOOD," skip to question 94. IF "GOOD," continue.

93. Do you consider yourself to be in top health? _____

IF YES, skip to question 95. IF NO, continue.

94. What has been troubling you? _____

95. Do you have any medical illness or disease? _____

96. Has any part of your body been troubling you? _____

IF YES, skip to question 98. IF NO, continue.

97. How is your head? Your heart? Stomach? The rest of your body? _____

98. Could you explain? _____

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99. Has your head or body changed in shape or size? _____

IF NO, skip to question 102. IF YES, continue.

100. Please explain. _____

101. What is causing these changes? _____

Data on "Depression" (G6)

102. How has your mood been in the past week: mostly good, mostly bad? _____

IF "MOSTLY BAD," skip to question 104. IF "MOSTLY GOOD," continue.

103. Have there been times in the past week when you were feeling sad or unhappy? _____

IF NO, skip to question 114. IF YES, continue.

104. Is there something in particular that is making you sad? _____

105. How often do you feel sad? _____

106. Just how sad have you been feeling? _____

107. Have you been crying lately? _____

108. Has your mood in any way affected your sleep? _____

109. Has it affected your appetite? _____

110. Do you participate less in activities on account of your mood? _____

111. Have you had any thoughts of harming yourself? _____

IF NO, skip to question 114. IF YES, continue.

112. Any thoughts about ending your life? _____

IF NO, skip to question 114. IF YES, continue.

113. Have you attempted suicide? _____

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Data on "Guilt Feelings" (G3) and "Grandiosity" (P5)

114. If you were to compare yourself to the average person, how would you come out: a little better, maybe a little worse, or about the same? _____

IF "BETTER," skip to question 117.
IF "ABOUT THE SAME," skip to question 118.
IF "WORSE," continue.

115. Worse in what ways? _____

116. Just how do you feel about yourself? _____

Skip to question 120.

117. Better in what ways? _____

Skip to question 120.

118. Are you special in some ways? _____

IF NO, skip to question 120. IF YES, continue.

119. In what ways? _____

120. Would you consider yourself gifted? _____

121. Do you have talents or abilities that most people don't have? _____

IF NO, skip to question 123. IF YES, continue.

122. Please explain. _____

123. Do you have any special powers? _____

IF NO, skip to question 126. IF YES, continue.

124. What are these? _____

125. Where do these powers come from? _____

126. Do you have extrasensory perception (ESP), or can you read other people's minds? _____

127. Are you very wealthy? _____

IF NO, skip to question 129. IF YES, continue.

128. Explain please. _____

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129. Can you be considered to be very bright? _____

IF NO, skip to question 131. IF YES, continue.

130. Why would you say so? _____

131. Would you describe yourself as famous? _____

132. Would some people recognize you from TV, radio, or the newspaper? _____

IF NO, skip to question 134. IF YES, continue.

133. Can you tell me about it? _____

134. Are you a religious person? _____

IF NO, skip to question 140. IF YES, continue.

135. Are you close to God? _____

IF NO, skip to question 140. IF YES, continue.

136. Did God assign you some special role or purpose? _____

137. Can you be one of God's messengers or angels? _____

IF NO, skip to question 139. IF YES, continue.

138. What special powers do you have as God's messenger (angel)? _____

139. Do you perhaps consider yourself to be God? _____

140. Do you have some special mission in life? _____

IF NO, skip to question 143. IF YES, continue.

141. What is your mission? _____

142. Who assigned you to that mission? _____

143. Did you ever do something wrong — something you feel bad or guilty about? _____

IF NO, skip to question 149. IF YES, continue.

144. Just how much does that bother you now? _____

145. Do you feel that you deserve punishment for that? _____

IF NO, skip to question 149. IF YES, continue.

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146. What kind of punishment would you deserve? _____

147. Have you at times thought of punishing yourself? _____

IF NO, skip to question 149. IF YES, continue.

148. Have you ever acted on those thoughts of punishing yourself? _____

Data on "Disorientation" (GIO)

149. Can you tell me today's date (i.e., the day, month, and year)? _____

IF YES, skip to question 151. IF NO, continue.

150. Can you tell me what day of the week it is? _____

151. What is the name of the place that you are in now? _____

IF NOT HOSPITALIZED, skip to question 154. IF HOSPITALIZED, continue.

152. What ward are you on? _____

153. What is the address of where you're now staying? _____

IF ABLE TO TELL, skip to question 155. IF NOT ABLE TO TELL, continue.

154. Can you tell me your home address? _____

IF NOT HOSPITALIZED, skip to question 156. IF HOSPITALIZED, continue.

155. If someone had to reach you by phone, what number would that person call? _____

156. If someone had to reach you at home, what number would that person call? _____

157. What is the name of the doctor who is treating you? _____

IF NOT HOSPITALIZED, skip to question 159. IF HOSPITALIZED, continue.

158. Can you tell me who else is on the staff and what they do? _____

159. Do you know who is currently the president (prime minister, etc.)? _____

160. Who is our governor (premier, etc.)? _____

161. Who is the mayor (town supervisor, etc.) of this city (town, etc.)? _____

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Data on "Difficulty in Abstract Thinking" (N5)

I'm going to now say a pair of words, and I'd like you to tell me in what important way they're alike. Let's start, for example, with the words "apple" and "banana." How are they alike — what do they have in common? **IF THE RESPONSE IS THAT "THEY'RE BOTH FRUIT", THEN SAY:** Good. Now what about ...? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

IF AN ANSWER IS GIVEN THAT IS CONCRETE, TANGENTIAL, OR IDIOSYNCRATIC (E.G., "THEY BOTH HAVE SKINS," "YOU CAN EAT THEM," "THEY'RE SMALL," OR "MONKEYS LIKE THEM"), THEN SAY: OK, but they're both fruit. Now how about ... and ... : how are these alike? *(Select three other items from the Similarities list at varying levels of difficulty from Appendix A.)*

APPENDIX A
Items for Similarities in the evaluation of "Difficulty in Abstract Thinking"

Circle the Similarities Used

1. How are a ball and an orange alike?
2. Apple and banana ?
3. Pencil and pen?
4. Nickel and dime?

5. Table and chair?
6. Tiger and elephant?
7. Hat and shirt?
8. Bus and train?

9. Arm and leg?
10. Rose and tulip?
11. Uncle and cousin?
12. The sun and the moon?

13. Painting and poem?
14. Hilltop and valley?
15. Air and water?
16. Peace and prosperity?

Note on Appendix A: Similarities are generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Similarities responses:

You've probably heard the expression, "Carrying a chip on the shoulder." What does that really mean? There's a very old saying, "Don't judge a book by its cover." What is the deeper meaning of this proverb? *(Select two other proverbs from the list in Appendix B at varying levels of difficulty.)*

APPENDIX B
Items for assessing PROVERB INTERPRETATION in the evaluation of "Difficulty in Abstract Thinking"

Circle the Proverbs Used

What does the saying mean:
1. "Plain as the nose on your face"
2. "Carrying a chip on your shoulder"
3. "Two heads are better than one"
4. "Too many cooks spoil the broth"

5. "Don't judge a book by its cover"
6. One man's food is another man's poison"
7. "All that glitters is not gold"
8. "Don't cross the bridge until you come to it"

9. "What's good for the goose is good for the gander"
10. "The grass always looks greener on the other side"
11. "Don't keep all your eggs in one basket"
12. "One swallow does not make a summer"

13. "A stitch in time saves nine"
14. "A rolling stone gathers no moss"
15. "The acorn never falls far from the tree"
16. "People who live in glass houses should not throw stones at others"

Note on Appendix B: Proverb interpretation is generally assessed by sampling four items at different levels of difficulty (i.e., one item selected from each quarter of the full set). When using the PANSS longitudinally, items should be systematically altered with successive interviews so as to provide different selections from the various levels of difficulty and thus minimize repetition.

Notes on Proverb responses:

Data on "Lack of Judgment and Insight" (G12)

162. How long have you been in the hospital (clinic, etc.)? _____

163. Why did you come to the hospital (clinic, etc.)? _____

164. Did you need to be in a hospital (clinic, etc.)? _____

IF YES, skip to question 167. IF NO, continue.

165. Did you have a problem that needed treatment? _____

IF NO, skip to question 169. IF YES, continue.

166. Would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

167. Why?....would you say that you had a psychiatric or mental problem? _____

IF NO, skip to question 169. IF YES, continue.

168. Can you tell me about it and what it consisted of? _____

169. In your own opinion, do you need to be taking medicine? _____

IF YES, skip to question 171.
IF NO and <u>unmedicated</u>, skip to question 172.
IF NO and <u>medicated</u>, continue.

170. Why then are you taking medicines? _____

Skip to question 172.

171. Why?... Does the medicine help you in any way? _____

172. Do you at this time have any psychiatric or mental problems? _____

IF YES, skip to question 174. IF NO, continue.

173. For what reason are you at the hospital (clinic, etc.)? _____

Skip to question 175.

174. Please explain _____

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175. Just how serious are these problems? _____

IF UNHOSPITALIZED, skip to question 178.
IF HOSPITALIZED, continue.

176. Are you ready yet for discharge from the hospital? _____

177. Do you think you'll be taking medicine for your problems after discharge? _____

178. What are your future plans? _____

179. What about your longer-range goals? _____

Well, that's about all I have to ask of you now. Are there any questions that you might like to ask of me? Thank you for your cooperation.

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18.5 Clinical Global Impression – Severity Scale (CGI-S)

Clinical Global Impression (CGI)

Reference: **Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare**

Rating Clinician-rated

Administration time Varies with familiarity with patient

Main purpose To provide a global rating of illness severity, improvement and response to treatment

Population Adults

Commentary

Amongst the most widely used of extant brief assessment tools in psychiatry, the CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The Early Clinical Drug Evaluation Program (ECDEU) version of the CGI (reproduced here) is the most widely used format, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. Several alternative versions of the CGI have been developed, however, such as the FDA Clinicians' Interview-Based Impression of Change (CIBIC), which uses only information collected during the interview, not collateral. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer, provided that the clinician knows the patient well.

Scoring

The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) and 4 (unchanged or worse and side-effects outweigh the therapeutic effects). Each component of the CGI is rated separately; the instrument does not yield a global score.

Versions

CGI for bipolar disorder (CGI-BD), FDA Clinicians' Interview-Based Impression of Change (CIBIC), Clinicians' Interview-Based Impression of Change-Plus (CIBIC+), NYU CIBIC+, Parke-Davis Pharmaceuticals Clinical Interview-Based Impression (CIBI); the CGI has been translated into most languages.

Additional references

Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. J Clin Psychopharmacol 1993; 13(5):327–31.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997; 73(3):159–71.

Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med 2003; 33(4):611–22.

Address for correspondence

Not applicable – the CGI is in the public domain.

Clinical Global Impression - Severity (CGI-S)

CGI-S is to be collected at Screening and throughout the study where indicated in Schedule of Events

1. Severity of illness

Considering your total clinical experience with this particular population, 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

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

18.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Note that there are two specific scales, e.g., Baseline, Since Last Visit, and differentiated by footers.

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.

	Most Severe	Most Severe
Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)		
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	____	____

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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* _____

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

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

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18.7 Acid Reflux Severity Scale

The ARSS scale is as follows:

None = 0 no symptoms

Mild = 1 awareness of symptom, but easily tolerated

Moderate = 2 discomfort sufficient to cause interference with normal activities

Severe = 3 incapacitating, with inability to perform normal activities.

18.8 Extrapyramidal Symptom Rating Scale (ESRS)

Administration instructions below are excerpted from the article by Chouinard et al. 2005 with edits from the Erratum, 2006

Instruction 1: Patient is asked to remove his/her shoes, to remove anything from his/her mouth (except dentures) and to sit facing the examiner on a chair with no armrests.

The removal of shoes can be omitted if an assessment of lower extremity dyskinetic movements is not required. In clinical trials it is completed unless clinically inappropriate for the patient (often patients do not feel comfortable removing their shoes) or it can be delayed until the testing of postural stability. Removing food and gum from the mouth is necessary in order to assess bucco–labial, lingual and jaw movements. The armless chair is essential for detection of tremors, decreased spontaneous movements, dyskinesia and akathisia.

Instruction 2: Complete the questionnaire.

The questionnaire rates subjective DIMD, i.e., Parkinsonism, akathisia, dystonia, and dyskinesia, as reported by the patient and which are experienced at periods other than the time of examination during the last week. For demented patients or autistic children, a nurse or key relative may also provide information in relation to the questionnaire. The questionnaire permits the evaluator to spend time with the patient to observe spontaneous DIMD.

Instruction 3: Observe facial expressiveness, speech, akathisia, dystonia and dyskinesia while completing the questionnaire and while completing items 4, 5, and 6.

Items in the objective examination are assessed during the course of standard tests of neurological examination (there is no new procedure to be learned by the physician when the physician is the examiner).

Instruction 4: Patient is asked to extend both arms forward, with palms down and eyes closed.

This test of posture tremors along with observing the patient's tremors at rest and the copying of a spiral with each hand (Instruction 6) is part of an overall assessment of tremors, which includes rest, posture and action tremors. Eyes are kept closed so that the patient is unable to correct if there is a lateralized neurological lesion.

Instruction 5: The patient is asked to carry out pronation and supination of both hands as fast as possible and to perform rapid alternate movements of both wrists simultaneously. Repeat as necessary.

Both tests are useful in the evaluation of tardive dyskinesia, as well as in the rating of slowness and difficulty in initiating movement. For bradykinesia, these two tests were selected because the initiation of several repetitive movements can be observed and for one test simultaneous movements of both wrists permit the detection of impaired ability to perform simultaneous tests. The inability to stop a movement should also be observed. For TD, the

Table 1
Summary of the ESRS examination procedure

1. Patient is asked to remove their shoes (omitted if judged clinically inappropriate or when patient hesitates, or delayed after patient has walked (after # 7). The patient is asked to remove anything from their mouth (except dentures). The patient is asked to sit facing the examiner on a chair with no armrests.
2. Complete the questionnaire.
3. Observe facial expressiveness, speech and dyskinesia while completing the questionnaire and while completing items 4, 5, and 6 below.
4. Patient is asked to extend both arms forward, with palms down and eyes closed.
5. The patient is asked to carry out pronation and supination of both hands as fast as possible, and to perform rapid alternate movements of both wrists. Repeat as necessary.
6. While the patient sits facing the examiner on a chair with no armrests about 1 foot (approx. 30 cm) from a table with his upper body turned, the patient is asked to copy a spiral with each hand and to write the name of his town, province/state and country.
7. Patient is asked to walk a distance of 12–15 feet (4–5 m) away from, and then back towards the examiner. Repeat as necessary.
8. Patient is asked to stand erect with eyes open with feet slightly apart (1–2 cm). The examiner pushes the patient on each shoulder, the back and pushes the chest or pulls from the back while asking the patient to keep his balance.
9. Carry out the examination of the muscular tonus of the four limbs.

oral–facial region is observed while the patient is performing pronation–supination and alternate movement tests; these voluntary movements help to uncover buccal–labial–masticatory and lower extremity dyskinesias.

Instruction 6: While the patient sits facing the examiner on a chair with no armrests about 1 foot (approx. 30 cm) from a table with his/her upper body turned, the patient is asked to copy a spiral with each hand and to write the name of his town, province/state and country.

This test permits the assessment of action tremors through graphic oscillation, and dyskinetic movements may be unmasked or augmented when the patient completes Instruction 6, for the test is performed under some emotional tension and uses other voluntary muscle groups. In this regard, it is important to encourage the patient to concentrate on the task requested.

Instruction 7: Patient is asked to walk a distance of 12–15 feet (4–5 m) away from, and then back towards, the examiner. Repeat as necessary.

This permits the evaluator to rate gait and posture. Absence of or a decrease in unilateral or bilateral pendular moments is observed. Abnormalities of posture are also looked for: flexed head, stiff posture, stooped posture. TD and/or chronic dystonia of upper limbs and trunk are looked for while the patient is walking.

Instruction 8: Patient is asked to stand erect with eyes open and feet together or slightly apart (1–2 cm). The examiner pushes the patient gently but firmly (strongly if necessary) on each shoulder (for lateropulsion), the back (for anteropulsion), and pushes the chest or pulls from the back (for retropulsion) while asking the patient to keep his balance and resist. Preferably, the patient removes his/her shoes before the test.

This test evaluates postural stability. The examiner should be ready to catch the patient from falling especially if the patient has an obvious impairment of balance at rest before testing. For patients who are already unstable, the test is completed gently.

Instruction 9: Carry out the examination of the muscular tonus of the four limbs.

Both limbs are examined as a pair in order to observe differences between the left and right side. Patient is asked to relax. Both arms are simultaneously rotated to permit examination of shoulders and, subsequently, elbows and wrists. Left and right knees are then successively moved and a comparison between the two sides made. Examination of hips and ankles does not provide more sensitivity and can be disturbing to psychotic patients. As with IPD, proximal joints are the most affected and rigidity may be more present in one part and/or one side of the body.

4. Scoring instructions

4.1. Questionnaire for Parkinsonism, akathisia, dystonia and dyskinesia

For the subjective examination (subscale I of the ESRS) scoring is on a 4-point scale (0=Absent; 1=Mild, 2=Moderate, 3=Severe). The evaluator takes into account the verbal report of the patient on: 1) the frequency and duration of the symptom during the day; 2) the number of days the symptom was present during the last week; and, 3) the subjective evaluation of the intensity of the symptom by the patient. When rating subjective EPS, severity is assessed over the last 7 days. One inquires about how persistent symptoms have been on the most typical day in the past 7 days.

4.2. Examination: Parkinsonism and akathisia

Both tremors and rigidity (items 1 and 4) are scored on a 7-point item scale (0=none–6=severe) for each part of the body, which are scored as separate items. The ESRS and the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) rate each part of the body separately for tremors and rigidity, since, in both drug-induced Parkinsonism and IPD, the symptoms can be seen initially in one limb and when it progresses it may involve several limbs, thus increasing the number of items in each scale, but permitting the rating of severity in each part of the body involved.

Ratings for tremors are made taking into account two axes: the amplitude of the movement and the number of times with which it is observed during the

interview. Assessment of tremors includes rest, posture and action tremors. Ratings of the other items of Parkinsonism and akathisia are recorded on a 7-point item scale (0=absent–6=most severe) with anchor points.

One difficulty in the rating of abnormal movements was to include both the amplitude of the abnormal movement (the higher the amplitude, the more severe the disorder) and the frequency that an abnormal movement is observed (the more frequent, the greater the severity). Thus, it appeared necessary to rate hyperkinetic disorders, tremors and dyskinesia, on a two-axis dimension to take into account that a small amplitude tremor seen frequently is as pathological as a larger amplitude tremor seen less frequently.

4.3. Examination: dystonia

Both acute and chronic dystonic movements are scored on a 7-point item scale (0=absent–6=most severe). Each body part is rated separately including right upper limb, left upper limb, right lower limb, left lower limb, head, jaw, tongue, lips, face, trunk and other (any other area).

4.4. Examination: dyskinesia

Dyskinetic movements at each site (tongue, jaw, bucco–labial, trunk, upper and lower extremities, and others {any other area including face}) are evaluated as individual items. They are rated similarly to tremors. Involuntary dyskinetic movements are repetitive, although not rhythmic and not oscillating along an axis, and their amplitude is usually greater with a low frequency cycle/s. Consequently we applied the same logic of a two-axis scale of amplitude and frequency as in the rating of tremors.

5. ESRS total and subtotal scores

5.1. ESRS Parkinsonism and akathisia scores in the era of classical antipsychotics

The score for Parkinsonism (including akathisia), ranges from 0 to 102 (17 items), and is based on all items of the Parkinsonism examination (subscale II): tremor (0–48), gait and posture (0–6), postural stability (0–6), rigidity (0–24), expressive automatic movements (0–6), bradykinesia (0–6), akathisia (0–6). In clinical trials, when establishing presence of Parkinsonism to initiate an antiParkinsonian medication, a score of 3 or greater is required on at least one of the above listed items including the 8 items of tremor or the 4 items of rigidity. When establishing the presence versus absence of Parkinsonism, a score of 2 on 2 items or a score of 3 or greater on one item is required to establish the presence.

Subscores: Two subscores were formed using the objective examination of Parkinsonism: a hypokinesia factor, ranging from 0 to 42, calculated as the sum of items: gait and posture (0–6), rigidity (0–24), expressive automatic movements (0–6), and bradykinesia (0–6); and a hyperkinesia factor, ranging from 0 to 54, calculated as the sum of items: tremor (0–48) and akathisia (0–6).

5.2. ESRS Parkinsonism and akathisia scores in the era of atypical antipsychotics

The Parkinsonism score, ranging from 0 to 96 (16 items), and the 2 factors (hypokinesia (0–42) and hyperkinesia (0–49) used now are similar to the previous ones (described in Section 5.1) minus one item: akathisia (0–6). The score for akathisia is separated from the Parkinsonism score and is based on the combined score of subjective akathisia (item 6 of the questionnaire) and objective akathisia (item 7 of the Parkinsonism/Akathisia objective examination). When establishing presence versus absence of akathisia, a total score of 3 or greater on the 2 items is required for presence.

5.3. Dystonia scores

The score for dystonia ranges from 0 to 60 (10 items), and is formed by including both acute and chronic dystonia, based on the dystonia examination (Subscale III). When establishing presence versus absence of dystonia, a score of 3 or greater on at least one item, or a score of 2 on 2 items is required to indicate presence of dystonia.

5.4. Dyskinesia and subtotal scores

Score for TD, ranging from 0 to 42, is based on the sum of all seven items in the TD objective examination. When scoring presence versus absence of TD, a score of 3 or greater on at least one item or a score of 2 on 2 items is required to indicate presence of TD. For tardive dyskinesia, scores for each item can be analyzed separately. A buccal–lingual–masticatory (BLM) subtotal, ranging from 0 to 18, is obtained from the sum of items 1, 2 and 3, and an extremities subtotal, ranging from 0 to 12, by adding the score for items 5 and 6.

5.5. ESRS total and subtotal scores for clinical trials and inter-rater reliability certification

For clinical trials, a total score for DIMD or EPS is formed based on all 41 items of the ESRS. It includes the 7 items of Subscale I (questionnaire), 17 items of Subscale II (Parkinsonism/Akathisia), 10 items of Part III (dystonia), and 7 items of Part IV (dyskinesia). For inter-rater reliability certification, the ESRS 41 item total score also includes the 4 CGI-S's and thus becomes ESRS 45 item total.

5.6. Clinical global impression of severity (CGI-S)

The clinical global impression of severity (CGI-S) of Parkinsonism, akathisia, dystonia, and tardive dyskinesia are rated according to results of the subjective questionnaire, examination subscales, and the evaluator's clinical experience by applying an 8 point rating (0: absent; 1: borderline; 2: very mild; 3: mild; 4: moderate; 5: moderately severe; 6: marked; 7: severe; 8: extremely severe). The 4 CGI-S's are analyzed as separate items.

Appendix A. ESRS Manual and scoring sheet

Extrapyramidal symptom rating scale (ESRS) (Chouinard) © 1979

In case of doubt score the lesser severity.

I. QUESTIONNAIRE : Parkinsonism, Akathisia, Dystonia and Dyskinesia. *In this questionnaire, take into account the verbal report of the patient on the following: 1) the duration of the symptom during the day; 2) the number of days where the symptom was present during the last week; and, 3) the evaluation of the intensity of the symptom by the patient.*

Enquire into the status of each symptom and rate accordingly

	Absent	Mild	Moderate	Severe	
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	0	1	2	3	⌊__⌋
2. Difficulty walking or with balance					
3. Stiffness, stiff posture	0	1	2	3	⌊__⌋
4. Restless, nervous, unable to keep still	0	1	2	3	⌊__⌋
	0	1	2	3	⌊__⌋
5. Tremors, shaking					
6. Oculogyric crisis, abnormal sustained posture	0	1	2	3	⌊__⌋
7. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips, face, extremities or trunk	0	1	2	3	⌊__⌋
	0	1	2	3	⌊__⌋

II. EXAMINATION: PARKINSONISM AND AKATHISIA

Items based on physical examinations for Parkinsonism.

	Occasional	Frequent	Constant or almost so				
1. Tremor							
None:	0			Right upper limb			⌊__⌋
Borderline:	1			Left upper limb			⌊__⌋
Small amplitude:	2	3	4	Right lower limb			⌊__⌋
Moderate amplitude:	3	4	5	Left lower limb			⌊__⌋
Large amplitude:	4	5	6	Head	⌊__⌋	Jaw/Chin	⌊__⌋
				Tongue	⌊__⌋	Lips	⌊__⌋
2. Bradykinesia	0:	normal					
	1:	global impression of slowness in movements					
	2:	definite slowness in movements					
	3:	very mild difficulty in initiating movements					⌊__⌋
	4:	mild to moderate difficulty in initiating movements					
	5:	difficulty in starting or stopping any movement, or freezing on initiating voluntary act					
	6:	rare voluntary movement, almost completely immobile					
3. Gait & posture	0:	normal					
	1:	mild decrease of pendular arm movement					
	2:	moderate decrease of pendular arm movement, normal steps					
	3:	no pendular arm movement, head flexed, steps more or less normal					⌊__⌋

	4:	stiff posture (neck, back) small step (shuffling gait)		
	5:	more marked, festination or freezing on turning		
	6:	triple flexion, barely able to walk		
4. Postural stability	0:	normal		
	1:	hesitation when pushed but no retropulsion		
	2:	retropulsion but recovers unaided		
	3:	exaggerated retropulsion without falling		⌊⌋
	4:	absence of postural response would fall if not caught by examiner		
	5:	unstable while standing, even without pushing		
	6:	unable to stand without assistance		⌊⌋
5. Rigidity	0:	normal muscle tone	Right upper limb	⌊⌋
	1:	very mild, barely perceptible	Left upper limb	⌊⌋
	2:	mild (some resistance to passive movements)	Right lower limb	⌊⌋
	3:	moderate (definite difficulty to move the limb)	Left lower limb	⌊⌋
	4:	moderately severe (moderate resistance but still easy to move limb)		
	5:	severe (marked resistance with definite difficulty to move the limb)		
	6:	extremely severe (limb nearly frozen)		

Items based on overall observation during examination for Parkinsonism.

6 . Expressive automatic movements (Facial mask / speech)	0:	normal	
	1:	very mild decrease in facial expressiveness	
	2:	mild decrease in facial expressiveness	
	3:	rare spontaneous smile, decrease blinking, voice slightly monotonous	⌊⌋
	4:	no spontaneous smile, staring gaze, low monotonous speech, mumbling	
	5:	marked facial mask, unable to frown, slurred speech	
	6:	extremely severe facial mask with unintelligible speech	
7 . Akathisia	0:	absent	
	1:	looks restless, nervous, impatient, uncomfortable	
	2:	needs to move at least one extremity	
	3:	often needs to move one extremity or to change position	⌊⌋

4:	moves one extremity almost constantly if sitting, or stamps feet while standing
5:	unable to sit down for more than a short period of time
6:	moves or walks constantly

III. EXAMINATION: DYSTONIA

Based on examination and observation

Acute torsion, and non acute or chronic or tardive dystonia

0:	absent	Right upper limb			⌊⌋
1:	very mild	Left upper limb			⌊⌋
2:	mild	Right lower limb			⌊⌋
3:	moderate	Left lower limb			⌊⌋
4:	moderately severe	Head	⌊⌋	Jaw/Chin	⌊⌋
5:	severe	Tongue	⌊⌋	Lips	⌊⌋
6:	extremely severe	Eyes	⌊⌋	Trunk	⌊⌋

IV. EXAMINATION: DYSKINETIC MOVEMENT

Based on examination and observation

		Occasional*	Frequent**	Constant or almost so	
1. Lingual movements (slow lateral or torsion movement of tongue)					
none:	0				
borderline:	1				
clearly present, within oral cavity:		2	3	4	
with occasional partial protrusion:		3	4	5	
with complete protusion:		4	5	6	⌊⌋
2. Jaw movements (lateral movement, chewing, biting clenching)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude: but without mouth opening:		3	4	5	
large amplitude: with mouth opening:		4	5	6	⌊⌋
3. Bucco-labial movements (puckering, pouting, smacking, etc.)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude, forward movement of lips:		3	4	5	
large amplitude; marked, noisy smacking of lips:		4	5	6	⌊⌋

4. Truncal movements (involuntary rocking, twisting, pelvic gyrations)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude:		3	4	5	
greater amplitude:		4			⌊⌋
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)			5	6	
none:	0				
borderline:	1				
clearly present, small amplitude, movement of one limb:		2	3	4	
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs:		3	4	5	
greater amplitude, movement involving two limbs:		4	5	6	⌊⌋
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)					
none:	0				
borderline:	1				
clearly present, small amplitude, movement of one limb:		2	3	4	
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs:		3	4	5	
greater amplitude, movement involving two limbs:		4	5	6	⌊⌋
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude:		3	4	5	
greater amplitude:		4	5	6	⌊⌋

Specify……..…….

* when activated or rarely spontaneous;
** frequently spontaneous and present when activated

V. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA

Considering your clinical experience, how severe is the dyskinesia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VI. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM

Considering your clinical experience, how severe is the parkinsonism at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSTONIA

Considering your clinical experience, how severe is the dystonia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VIII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF AKATHISIA

Considering your clinical experience, how severe is the akathisia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe