Clinical Study Protocol

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia

Date of Protocol: 20 January 2016

NCT Number: NCT02876900

Clinical Study Protocol

Protocol Title:	**A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia**
Protocol Number:	**HP-3070-GL-04**
Date of Protocol:	**20 January 2016**
Protocol Version:	**Version 2.0 Amendment 1**
Product:	**Asenapine Transdermal Patch**
Pre-IND No.:	**125707**
EudraCT No.:	**2015-005134-21**
Study Phase:	**3**
Sponsor:	**Noven Pharmaceuticals, Inc. Empire State Building, 350 Fifth Avenue, 37th Floor, New York, NY 10118**
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Signatures

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia

PROTOCOL NO: HP-3070-GL-04

Dana Annunziato — Signature — 20 Jan 2016

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SYNOPSIS

Name of Sponsor/Company:	Noven Pharmaceuticals, Inc.
Name of Finished Product:	HP-3070
Name of Active Ingredient:	Asenapine
Title of Study:	A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia
Protocol No:	HP-3070-GL-04
Investigators:	TBD
Study center(s):	Approximately 70 centers
Study duration: Screening/Run-in, Washout Period: Maximum 14 days Double-blind Treatment Period: 6 weeks Follow-up Visit/Telephone call: 30 days after the last patch is removed	**Phase: 3**

Objectives:

Primary Objective:

The primary objective of the study is to evaluate efficacy of HP-3070 compared with placebo for the treatment of schizophrenia as evaluated by Positive and Negative Syndrome Scale (PANSS) total score.

Secondary Efficacy Objectives:

- Key Secondary Efficacy Objective:
  - Clinical Global Impression – Severity of Illness Scale (CGI-S)
- Other Secondary Efficacy Objectives: To evaluate the efficacy of HP-3070 using the following measures:
  - PANSS total score at each time point
  - Clinical Global Impression – Severity of Illness Scale (CGI-S) at each time point
  - Clinical Global Impression – Improvement Scale (CGI-I) at each time point
  - Proportion of CGI-I responders at each time point including Week6; CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved)
  - Positive, negative, and general pathology subscores of PANSS
  - Proportion of PANSS responders; PANSS responders are defined as subjects who have a ≥30% reduction in PANSS total score between Baseline and at each time point including Week 6
  - Calgary Depression Scale for Schizophrenia (CDSS)
  - Medication Satisfaction Questionnaire (MSQ) score

Safety Objectives:

- Adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs leading to discontinuation from the study drug, serious adverse events (SAEs), and deaths
- Change from Baseline in clinical laboratory results (including prolactin, fasting glucose, and lipids), ECG results, body weight, and vital signs
- Results of C-SSRS, BARS, AIMS, and SAS
- Dermal safety

Exploratory Objective:

- To assess the impact of covariates on asenapine exposure using a model-based approach and to explore the exposure-response relationship with relevant endpoints.

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled, in-patient, safety, and efficacy study to evaluate HP-3070 for the treatment of schizophrenia.

This study will consist of a Screening/placebo Run-in Period of 3 to 14 days, a 6-week double-blind Treatment Period and a 30 day Follow-up Period.

This study will enroll subjects who are in an acute exacerbation (i.e., have had an acute episode no longer than 8 weeks prior to the Screening Visit), have a PANSS total score ≥80 with scores of 4 or higher on at least 2 out of the 4 pre-defined PANSS positive subscale items, and have a CGI-S ≥4. Subjects will be hospitalized at the Screening Visit and will remain hospitalized during the study. The subject may leave the hospital for necessary personal business. During this time, the subject must be supervised by study staff or a responsible caretaker. Any subject who leaves the site must have an alcohol breathalyzer and urine drug and pregnancy tests when they return to the site. Investigator should contact Medical Advisor to discuss specifics of subject off-site overnight travel to confirm appropriateness.

The study will evaluate 9.0 mg (HP-3070-9.0) and 18.0 mg (HP-3070-18.0) of HP-3070 transdermal patches versus placebo transdermal patches. To maintain double-blind each subject will wear two patches. Patches will be applied by site personnel at approximately the same time daily and site personnel will remove the patches at approximately 24 hours after patch application. Each patch will be worn for 24 hours. Every day, approximately 24 hours after patch application, site personnel will remove previous day's patches and apply new patches. Patch adhesion will be assessed at specified time points and prior to patch removal.

In this study, efficacy will be evaluated using widely accepted, standard questionnaires. These include the PANSS, CDSS, CGI-S, CGI-I, and MSQ.

In addition to standard safety measures (AEs, clinical laboratory assessments, vital signs, weight, ECG results), this study will also include assessments of EPS symptoms using the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS). Suicidality will be monitored using the Columbia-Suicide Severity Rating Scale (C-SSRS). Dermal safety will be assessed by a review of any dermal reactions (such as irritation and discomfort due to the patch) reported as AEs.

Screening/Run-In Period: At the Screening Visit, subjects will be asked to sign the informed consent form (ICF). No screening procedures may begin prior to obtaining informed consent. Each subject will be assigned a unique subject number after signing the ICF.

After obtaining informed consent, the subject will be enrolled and hospitalized for the duration of the study. The subject will stay in the unit throughout the study, except for supervised leave for personal business. While undergoing screening procedures and waiting for results of laboratory tests, electrocardiograms (ECGs), and other assessments, the subject will be enrolled in the Run-in Period and start treatment with the single-blind placebo patch. Subjects will be blinded to the treatment during the Run-in Period. The subject must have the single-blind placebo patch applied for a minimum of 3 days prior to entering the double-blind Treatment Period. In addition, current antipsychotic and other prohibited medications will be washed out during this period and wash-out must be completed prior to randomization and entering the double-blind Treatment Period. Subjects who do not meet the eligibility criteria at the Screening/Run-In Visit and the Baseline Visit will be discontinued from the study. Subjects who are not compliant with wearing the run-in patches will also be discontinued from the study.

Double-blind Treatment Period: Subjects eligible for enrollment in the double-blind Treatment Period will be randomly assigned to HP-3070-9.0 or HP-3070-18.0, or placebo in a 1:1:1 ratio stratified by country. All trial personnel and subjects will be blinded to the treatment for the duration of the trial. Subjects will receive treatment with study medication daily for 6 weeks. Patches will be applied by site personnel at approximately the same time every day and each patch will be worn for 24 hours. Every day, approximately 24 hours after patch application, site personnel will remove previous day's patches and apply new patches.

In the event that the patches are detached completely, new patches should be applied immediately, provided that there are at least 6 hours of time remaining before the next dose.

Blood samples will be collected at 2, 14, and 22 hours with ± 2 hour- window on Day 21 and 42 and analyzed

for asenapine and desmethyl asenapine concentrations. Actual blood sampling time will be recorded. A model-based approach will be used to assess the impact of covariates on asenapine exposure and to explore the exposure-response relationship of relevant endpoints. Details on the methodology will be included in a standalone pharmacokinetic (PK) report. At discharge (Week 6 or early termination), the subject will be prescribed an approved antipsychotic treatment and returned to the care of their physician. **Follow-up Period:** All subjects will have a follow-up contact (site visit or telephone call, at the discretion of the Investigator) 30 days after the last patch is removed. This contact will be used to collect information about any AEs or SAEs that may have occurred since discharge and to follow-up on any AE that was on-going at discharge.	
Planned number of subjects:	Sufficient number of subjects will be screened to randomize approximately 612 subjects (approximately 204 in each of the 3 treatment arms).
Diagnosis and main criteria for inclusion:	The assessment and documentation of the subject's eligibility is the responsibility of the Investigator. The Sponsor/designee reserves the right to provide final approval of subject eligibility. Inclusion Criteria: Subjects must meet **all** of the following criteria to be considered eligible to participate in the study: 1. Adult male or female subjects, ≥18 years of age 2. Subject is able to undergo informed consent process and signs ICF. 3. Subject has current diagnosis of schizophrenia as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5 Criteria, Mini International Neuropsychiatric Interview (MINI), and as confirmed by Investigator assessment. 4. Subject has PANSS total score ≥80, AND score of 4 or more in at least 2 of the following PANSS items at Screening and at Baseline: a. Conceptual disorganization b. Delusions c. Hallucinatory behavior d. Unusual thought content 5. Subject has CGI-S scale score of ≥4 (moderately ill) at Screening and Baseline. 6. Subject has history of relapse and/or exacerbation of symptoms when they are not receiving antipsychotic treatment, excluding the current episode. 7. Subject is confirmed by the Investigator to be experiencing an acute exacerbation of schizophrenia, as evidenced by ALL of the following: a. The duration of the current episode is no more than 8 weeks. b. The subject's current symptoms represent a marked and substantial exacerbation of schizophrenia compared with the subject's symptomatic state prior to the emergence of the current episode. c. A corresponding functional deterioration to the symptomatic exacerbation is evident.

	8. Subject has not been hospitalized for more than 21 days for the current episode by the day of the Screening Visit, not including social hospitalization (e.g., homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition). 9. Subject agrees not to begin formal, structured psychotherapy targeting the symptoms of schizophrenia from the time of the Screening Visit until the last dose of study drug. 10. Subject would benefit from hospitalization or continued hospitalization for the treatment of schizophrenia (as determined by the Investigator). 11. Subjects must not be treatment naïve or treatment resistant. Treatment resistance is defined as having little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the drug's package insert). 12. Subject has had previous positive response to an antipsychotic medication other than clozapine in a prior episode. 13. Subject has a stable living situation and caretaker support when not hospitalized. 14. Subject is male, or a female who is not of childbearing potential (i.e., surgically sterile, postmenopausal for at least 1 year) or who is non-pregnant, non-lactating, and is using a medically accepted method of contraception. Acceptable methods of contraception include condoms (male or female) with a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device, and hormonal contraceptives. A female of child-bearing potential who is not currently sexually active must agree to use a medically accepted method of contraception should she become sexually active while participating in the study. Each sexually active female of child-bearing potential must also agree to use a medically accepted method of contraception for 1 month after the final dose of study medication. 15. Subjects must agree that they will not donate sperm or eggs from the time of the Screening Visit until 3 months following administration of the last treatment or dose of study medication. 16. Agrees not to use any other transdermal patch products (e.g., nicotine replacement patch, hormonal replacement patch, etc.) for the duration of the study. 17. Subjects must be able to wear a transdermal patch for 24 hours. <u>Exclusion Criteria</u> The subject will be excluded from the study if **any** of the following exclusion criteria are met: 1. Subject is presenting with a first episode of schizophrenia based on the clinical judgment of the Investigator. 2. Subject has been diagnosed with schizophrenia less than 6 months prior to Screening Visit. 3. Subject has received electroconvulsive therapy, transcranial magnetic stimulation, vagal nerve stimulation, or other brain stimulation treatments within 90 days of Screening Visit. 4. Subject has a current DSM-5 diagnosis other than schizophrenia

	including (but not limited to) schizoaffective disorder, major depressive disorder, bipolar disorder, post-traumatic stress disorder, anxiety disorders, delirium, dementia, amnestic, or other cognitive disorders 5. Subject has a diagnosis of mental retardation, history of traumatic brain injury causing ongoing cognitive difficulties, Alzheimer's Disease or another form of dementia (or suspicion thereof), or any chronic organic disease of the central nervous system that would interfere with the efficacy or safety endpoints of the study. 6. Subject has experienced acute depressive symptoms within 30 days prior to Screening Visit that requires treatment with an antidepressant, as determined by the Investigator. 7. Subject is a known non-responder to previous asenapine treatment, as per Investigator judgment. 8. Subject is currently taking clozapine for the treatment of schizophrenia. Subjects taking low doses of clozapine (up to 100 mg/day) for sedative properties and not treatment resistance or suicidality may be acceptable as per Investigator judgment and as approved by the Sponsor/designee. 9. Subject with schizophrenia who is considered resistant/refractory to antipsychotic treatment by history or who has a history of failure to respond to clozapine or response to clozapine treatment only. Treatment resistance is defined as having little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the drug's package insert). 10. Subject who is unwilling to discontinue or, in the opinion of the Investigator, unable to discontinue any prohibited medication prior to the Baseline Visit without significant medical or psychiatric destabilization, or increased suicidality, as per the washout requirements. Prohibited medications include: a. Antipsychotics, including depot or long-acting injectables b. Antidepressants c. Mood stabilizers d. Stimulants e. Nonpsychopharmacologic medications with psychotropic properties, per Investigator and approved by Sponsor/designee f. Herbal drugs/dietary supplements unless approved by Sponsor/designee 11. Subjects taking drugs (current antipsychotic or other prohibited medication) that require >14 days for washout 12. Subject who is involuntarily committed, incarcerated, or under legal compulsion to seek psychiatric treatment. 13. Subject currently has clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, human

	immunodeficiency virus seropositive status/acquired immunodeficiency syndrome. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the study. Subjects with chronic Hepatitis B or C may be included provided that their condition is stable and values for liver function tests and other laboratory test results meet the criteria specified in the protocol for entry into the study. The Sponsor/designee should be contacted in any instance where the Investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on study participation. 14. Subject has any other medical condition or laboratory result that, in the opinion of the Investigator, may make the subject unsuitable for the study. 15. Subjects with the following laboratory test and ECG results are excluded: a. Platelets ≤75,000/mm^3 b. Hemoglobin ≤9 g/dL c. Neutrophils, absolute ≤1000/mm^3 d. Aspartate transaminase >2×upper limit of normal (ULN) e. Alanine transaminase >2×ULN f. Creatine phosphokinase >3×ULN, unless discussed with and approved by the Medical Advisor g. Creatinine ≥2 mg/dL or ≥176.8 µmol/L h. Hemoglobin A1c (HbA1c) ≥6.5% unless the subject has a diagnosis of stable diabetes i. QT interval corrected using Fridericia's formula (QTcF) ≥450 msec (males), QTcF ≥470 msec (females) j. Prolactin. The enrollment of subjects with prolactin levels equal or higher than 5 X ULN should be discussed with the Medical Advisor 16. Subject with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days); subjects with abnormal free T4 and thyroid stimulating hormone (TSH) levels. 17. Subject is currently treated with insulin for diabetes. Subjects being treated for diabetes with medications other than insulin are eligible for the study if their condition is stable as determined by satisfying ALL of the following criteria: a. HbA1c <7.0%, AND b. Screening glucose ≤125 mg/dL or ≤6.94 mmol/L (fasting) or <200 mg/dL or <11.1 mmol/L (nonfasting). Note: If the nonfasting screening glucose is ≥200 mg/dL or ≥11.1 mmol/L, subjects must be retested in a fasted state and the retest value must be ≤125 mg/dL or ≤6.94 mmol/L, AND c. Subject has been maintained on a stable regimen of

	oral anti-diabetic medication(s) for at least 28 days prior to Screening or diabetes has been well-controlled by diet for at least 28 days prior to Screening, AND d. Subject has not had any hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, AND e. Subject's diabetes is not newly diagnosed during Screening. 18. Subject has epilepsy or history of seizures, with the exception of a single seizure episode (e.g., childhood febrile, post traumatic). 19. Subject has uncontrolled hypertension (diastolic blood pressure >95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥30 mmHg in systolic blood pressure and/or a decrease of ≥20 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, OR development of symptoms. Note: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above. 20. Subject has a history of neuroleptic malignant syndrome. 21. Subject has a score of >2 (mild) on any item of the AIMS at Screening. 22. Subject has a score of 5 (severe akathisia) on the Barnes Akathisia Rating Scale (BARS) global clinical assessment of akathisia at Screening. 23. Subject has a history of pituitary adenoma or cancer <5 years prior to Screening. Subjects currently being treated for cancer may not be enrolled in the study. 24. Female subject who is breastfeeding. 25. Female subject with a positive urine pregnancy test that is confirmed positive by serum pregnancy test at Screening or Baseline. 26. Subject who currently (within the past 6 months) meets the DSM-5 criteria for substance use disorders (excluding nicotine and caffeine). 27. Subject has positive urine drug/alcohol screen at the Screening Visit. Positive results that are due to short-term prescription medications that can be safely discontinued (e.g., opioids for acute pain that has resolved) may continue at the discretion of the Investigator with the agreement of the Sponsor/designee. Subjects with positive cannabis results may be included, provided the Investigator does not feel the subject is a compliance risk, the subject does not fulfill the criteria for substance abuse or dependence as stated in Exclusion Criterion 26, the subject agrees to abstain for the duration of the study, and with concurrence with the Sponsor/designee. 28. Subject is at imminent risk of self-harm or harm to others in the Investigator's opinion based on clinical interview and responses provided on the Columbia Suicide Severity Rating Scale (C-SSRS). Note that subjects will be excluded if they report

	suicidal ideation meeting the description of C-SSRS Type 4 or 5 (i.e., suicidal ideation with intent, with or without a plan) in the past 6 months or suicidal behavior (as described by the C-SSRS) in the past 12 months at Screening. Subjects will also be excluded at Baseline if they report suicidal ideation of Type 4 or 5 or suicidal behavior, as measured by the C-SSRS between Screening and Baseline. 29. Subject has a known allergy or hypersensitivity to asenapine. 30. Subject has current or history of allergy or hypersensitivity to adhesive dressings. 31. Subject has history of allergy to more than 2 distinct chemical classes of drug (e.g., sulfas and penicillins). 32. Subject has any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo. 33. Subject has participated in a previous HP-3070 study. 34. Subject has participated in any other investigational trial or used investigational drugs within 30 days prior to the Screening Visit or has participated in more than 2 studies in the past 12 months. 35. Any subject who, in the opinion of the Investigator or Medical Advisor, should not participate in the study. 36. Subject is a Study Investigator, sub-Investigator, study coordinator, employees of a participating Investigator, or immediate family member of the aforementioned.
Test product, dose and mode of administration:	HP-3070 (Asenapine maleate, transdermal patch) : During the double-blind Treatment Period, subjects randomly assigned to the HP-3070 treatment arms will have the following 2 patches applied: • HP-3070 9.0 mg treatment arm: one (1) 9.0 mg 20 cm^2 patch and one (1) placebo patch, once daily or • HP-3070 18.0 mg treatment arm: two (2) 9.0 mg 20 cm^2 patches, once daily
Reference therapy, dose, and mode of administration:	Matching placebo patch: During the double-blind Treatment Period, subjects randomly assigned to the placebo treatment arm will have 2 placebo patches applied (0 mg, 20 cm^2), once daily.
Patch application and removal	During the double-blind treatment period, each subject will have 2 patches applied once daily. Patches will be removed after approximately 24 hours and new patches will be applied daily. Patches will be applied and removed by site personnel. Both patches will be applied to one of the following application sites daily: abdomen, hip, upper arm, upper back, and upper chest each day. Application sites will be rotated daily. In the event that a patch should detach completely, the time and activity at the time of patch detachment must be documented. If both patches are detached completely then 2 new patches from the subject's kit should be applied immediately, provided that there are at least 6 hours of time remaining before the next dose.

	If only one patch detaches completely, then the other patch should also be removed and two new patches from the subject's kit should be applied immediately, provided that there are at least 6 hours of time remaining before the next dose. Regardless of what time the new patches are applied, patch removal time of the new patches will be approximately 24-hours after the application of the original patches. In other words, removal time of the new patches may not exceed 24 hours from the time the first patches were applied. Under no circumstances should the detached patch/patches be reapplied to the subject. Under no circumstances should the patches be reinforced or taped.

Criteria for evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint is the change in Positive and Negative Syndrome Scale (PANSS) total score between Baseline and Week 6.

Secondary Efficacy Endpoints:

The key secondary endpoint is:

- To evaluate the efficacy of HP-3070 compared with placebo for the treatment of schizophrenia as evaluated by change in Clinical Global Impression – Severity of Illness Scale (CGI-S) scores between Baseline and Week 6

Other secondary efficacy endpoints include:

- Change from Baseline in PANSS total score at each time point in addition to Week 6
- Change from Baseline in CGI-S at each time point in addition to Week 6
- CGI-I score at each time point
- The proportion of CGI-I responders at each time point including Week 6; CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved)
- Change from Baseline in positive, negative, and general pathology subscores of PANSS at each time point
- Proportion of PANSS responders; PANSS responders are defined as subjects who have a $\geq$30% reduction in PANSS total score between Baseline and at each time point including Week 6
- Change from Baseline in CDSS score at each time point
- MSQ score at each time point

Safety Endpoints:

- AEs, including TEAEs, AEs leading to discontinuation from the study drug, SAEs, and deaths
- Change from Baseline in clinical laboratory results (including prolactin, fasting glucose, and lipids), ECG results, body weight and vital signs
- Results of C-SSRS, BARS, AIMS, and SAS
- Dermal safety

Exploratory Endpoints

- A model-based approach will be used to assess the impact of covariates on asenapine exposure and to explore the exposure-response relationship with relevant endpoints.

Statistical methods:

Analysis Sets: Four analysis sets will be used in analyzing the data obtained from this protocol:

- Intent-to-Treat (ITT): includes all consented and randomized subjects. Regardless of any protocol deviations, analyses performed on the ITT set will be based on the randomized treatment assignment and all available data.
- Full Analysis Set (FAS): includes all randomized subjects who have had at least 1 patch of double-blind study medication applied and who have a Baseline PANSS total score and at least 1 post-Baseline assessment of the primary efficacy measure (PANSS total score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.
- Safety Analysis Set (SAF): includes all subjects who have had at least 1 patch of double-blind study medication applied and who have at least 1 post-dose safety measurement during the double-blind treatment period. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the SAF will be based on treatment actually received. The SAF will be used for the analysis of dermal evaluations and safety endpoints.
- Pharmacokinetic Analysis Set (PAS): includes all subjects who have received at least 1 dose of study medication during the double blind treatment period and have at least 1 blood sample for PK assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model based approach. Excluded cases will be documented together with the reason for exclusion.

Statistical Analyses:

- Primary Efficacy Analysis: The primary efficacy endpoint of this trial is the change from Baseline to Week 6 in the PANSS total score by dose; the primary analysis set is the FAS. The comparisons of interest are:
  - HP-3070 9.0 mg versus placebo
  - HP-3070 18.0 mg versus placebo

  The p-values for the comparisons are adjusted for multiple comparisons using Hochberg procedure. The primary efficacy variable, change from Baseline to Week 6 in the PANSS total score for each of the 3 treatment arms, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in PANSS total score as the repeated dependent variable, with country, treatment (HP-3070-9.0 [9.0 mg], HP-3070-18.0 [18.0 mg], and placebo), visit, treatment by visit interaction, and the Baseline PANSS total score as covariates. An unstructured covariance matrix will be assumed. The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If normality assumption is violated, ANCOVA analysis on rank-transformed data will be used as a supportive analysis.
- Key Secondary Analysis: The key secondary endpoint is CGI-S.. If either or both doses are positive in the primary efficacy analysis, analysis for the key secondary efficacy endpoint will be carried out using Hochberg-based gatekeeping procedure to limit the overall Type I error rate to <0.05.
  In summary, the Hochberg-based tree-gatekeeping procedure will be applied to p-values from the mixed models for repeated measurements (MMRM) analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints.
- Additional Analyses of Primary and Key Secondary Endpoints: Other sensitivity analyses may be performed on the primary and key secondary endpoints to assess the robustness of the results based

on the model used for primary analysis. Details will be provided in the Statistical Analysis Plan. The analyses will be performed according to the National Academy of Sciences (2010) guidelines.

- Analysis of Other Secondary Efficacy Endpoints: Other secondary efficacy endpoints will be summarized but will not be adjusted as part of the tree-gatekeeping procedure.
- Analysis of Safety: All safety summaries will be descriptive; no statistical significance tests will be performed on safety data.
- Analysis of PK: model based assessment including the population PK following HP-3070 administration will be evaluated using asenapine concentrations in plasma and relevant endpoints. The methodology and results will be described in a standalone PK report.

Sample Size Calculation:

Assuming an effect size of 0.35 on the change in PANSS total score from baseline to Week 6 for the 2 pairwise comparisons between each active HP-3070 treatment arm and placebo, the power for detecting a statistically significant HP-3070 advantage will be approximately 0.90 having 204 evaluable subjects per each treatment arm using a 2-side alpha level of 0.025 for each comparison. A 2-sided overall Type I error is equal to 0.05. Having 3 treatment arms, the total number of subjects randomized in the trial and included in the primary analysis set will be approximately 612. A sufficient number of subjects will be screened to randomize the proposed sample size.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AR(1)	Autoregressive (1)
ARH(1)	Heterogeneous autoregressive (1)
AST	Aspartate transaminase
AUC	Area under the concentration time curve
BARS	Barnes Akathisia Rating Scale
BID	Twice daily
BUN	Blood urea nitrogen
CDSS	Calgary Depression Scale for Schizophrenia
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity of Illness scale
CI	Confidence interval
CPK	Creatine phosphokinase
C_{max}	Maximum plasma concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Compound symmetry
CSH	Heterogeneous compound symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form

ECT	Electroconvulsive therapy
EDC	Electronic data capture
EPS	Extrapyramidal symptoms
ET	Early termination
EU	European Union
FA0	No Diagonal Factor Analytic
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transaminase
HbA1c	Hemoglobin A1c
HBAg	Hepatitis B antigen
HCV	Hepatitis C
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-To-treat
IUD	Intrauterine device
IVRS	Interactive Voice-Activated Response System
IWRS	Interactive Web-based Response System
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
MAR	Missing at random
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at random

MSQ	Medication Satisfaction Questionnaire
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic
prn	as needed
QTcF	QT interval corrected by Friderica's formula
RBC	Red blood cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SD	Standard deviation
SL	Sublingual
SOC	Standard of care
SOP	Standard Operating Procedures
SSR	Sample size recalculation
SUSARs	Serious Unexpected Adverse Event Reactions
$t_{1/2}$	Elimination half life
TEAE	Treatment-Emergent Adverse Event
TMS	Transcranial magnetic stimulation
TOEPH	Heterogeneous Toeplitz structure
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
VNS	Vagal nerve stimulation
WBC	White blood cell

2.0 INTRODUCTION

2.1 Background Information

Schizophrenia is a serious and chronic disabling disorder that affects approximately 1% of the world's population.[1] It is characterized by positive symptoms (e.g., delusions, hallucinations, and disorganized speech), negative symptoms (e.g., affective flattening, alogia, avolition, and anhedonia social withdrawal), cognitive deficits, including attention, memory, and learning dysfunction. Further, anxiety and depression are prominent features of schizophrenia. These symptoms result in marked personal, familial, social, and occupational dysfunction. These subjects are also at an increased risk of suicide, require extensive healthcare resource utilization, and have a poor prognosis. The onset of the disorder occurs relatively early in life (adolescence to early adulthood). Most schizophrenia patients have recurrent exacerbations of the positive symptoms and persistent negative and cognitive symptoms. Schizophrenia patients require lifetime disease management and treatment.

Asenapine is a second-generation antipsychotic agent, and the sublingual dosage form is marketed under the trade name of SAPHRIS® in the United States (US) and Sycrest® in the European Union (EU). Asenapine is a potent multireceptor antagonist with a high affinity for several serotonin, dopamine, noradrenaline, and histamine receptors. In the United States, asenapine is indicated for the treatment of schizophrenia as well as for the acute treatment (as monotherapy or adjunctive therapy) of manic or mixed episodes associated with bipolar disorder. In the EU it is approved for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

Sublingual (SL) asenapine has to be administered twice daily. The SL tablet should be placed under the tongue and left to dissolve completely and patients are advised to avoid eating or drinking for 10 minutes after administration.

Asenapine can cause dysgeusia (distorted, altered, or unpleasant taste) or oral hypoesthesia (numbness) due to its local anesthetic effect and the oral hypoesthesia usually resolves within 1 hour after dosing. Across the 6-week schizophrenia trials and the 52-week schizophrenia trial with sublingual asenapine 5 or 10 mg administered twice daily, the rate of discontinuation due to oral hypoesthesia was 0.27%. However, in a study that examined the effect of absorption site on the pharmacokinetics (PK) of asenapine in healthy male subjects, reported rates of oral paresthesias were 75.8%, 55.9%, and 45.7% for the SL, supralingual, and buccal absorption sites, respectively.

Application site reactions, primarily in the SL area, have been reported during post-approval use of sublingual asenapine. These application site reactions included oral ulcers, blisters, peeling/sloughing, and inflammation. In many cases, the occurrence of these application site reactions led to discontinuation of therapy.

Noven has developed HP-3070 (asenapine maleate transdermal drug delivery system), a transdermal patch which will be dosed once daily. The transdermal route of application will

provide the patients with another treatment option that may have certain advantages over the sublingual (SL) formulation of asenapine, such as:

- HP-3070 patch will mitigate oral hypoesthesia and/or dysgeusia that is commonly observed with SL asenapine;
- HP-3070 patch may have less variability in asenapine absorption and a more gradual increase in plasma concentration compared to the SL route of administration;
- HP3070 patch may potentially have improved tolerability over the current SL route of administration for SAPHRIS®; because it has better PK characteristics;
- HP-3070 patch may provide a means for physicians and caregivers to visually check a patient's treatment compliance ;
- HP-3070 patch has no restrictions related to eating and drinking

In pre-clinical studies, HP-3070 transdermal patch has shown transdermal absorbability and dermal tolerability.

To date, Noven has conducted a total of 4 Phase 1 clinical studies; 3 PK studies (HP-3070-US-01, HP-3070-US-02 and HP-3070-US-03) in healthy volunteers and 1 PK study (HP-3070-US-02b) in patients diagnosed with schizophrenia. From these PK studies, it can be concluded that HP-3070 transdermal patch delivers steady plasma levels throughout the 24-hour application period with low variability and has reproducible PK metrics across all studies.

HP-3070 was first administered to healthy volunteers in HP-3070-US-01, the first-in-human patch application study designed to evaluate the single-dose PK, safety, and tolerability of the transdermal patch system HP-3070 compared with SL asenapine. Eighteen healthy adults completed the study.

After a single SL administration of Sycrest®, asenapine concentrations rose rapidly and exhibited single peak profiles, whereas following transdermal patch application, asenapine concentrations rose gradually and remained relatively constant over the dosing interval. A plateau in the plasma concentration was reached from 12 hours after patch application until removal of the patch 24 hours after patch application.

The mean maximum plasma concentration (C_{max}) following SL administration of 5 mg of Sycrest® was considerably higher than that attained with 3.6-mg and 4.8-mg patches and was attained much sooner. The lower and more gradual progression to C_{max} observed with the transdermal patches has the potential to reduce the incidence of adverse events (AEs) in the immediate post dosing period. Mean asenapine exposure area under the concentration curve (AUC_{0-t}) following use of the 4.8-mg transdermal patch was slightly higher than after the administration of the 5-mg SL tablet. When the patch was removed, the plasma concentration of asenapine and its metabolite, desmethyl-asenapine, decreased at a rate similar to that seen after SL dosing (elimination half-life [$t_{1/2}$] of ~23 hours).

HP-3070-US-02 was designed to evaluate the PK profile, dose proportionality, safety, and tolerability of HP-3070. Part 1 evaluated single doses of 9.0 mg, 13.5 mg, and 18.0 mg in 24 healthy volunteers. The patch doses (sizes) were chosen based on the results obtained in

HP-3070-US-01. In Part 2, healthy volunteers received 9-mg patches applied for 24-hours daily for 7 days.

Single application of a 13.5-mg patch and multiple applications of a 9.0-mg patch resulted in a total of 115 AEs. As a result, the 18.0-mg dose was not administered due to the unfavorable tolerability profile of 13.5 mg in healthy volunteers. Further, only 3 subjects among the 11 subjects who started multiple applications of the 9-mg patch completed the 7-day multiple applications. No deaths or other serious adverse events (SAEs) occurred during this study. As healthy volunteers were not able to tolerate higher doses and multiple doses of HP-3070, this study in healthy volunteers (HP-3070-US-02) was stopped early and a multiple dose PK study (HP-3070-US-02b) was conducted in patients diagnosed with schizophrenia.

The statistical analysis of relative exposure for both asenapine and desmethyl-asenapine were within the 80% to 125% limits for both dose-normalized C_{max} and AUC, confirming the dose-proportionality between the 9.0-mg and the 13.5-mg HP-3070 patches. These similar desmethyl-asenapine/asenapine ratios and the percentage of the drug released between 9.0 mg and 13.5 mg HP-3070 patches corresponded well to the dose-proportionality results for C_{max} and AUC.

HP-3070-US-02b was an open-label, non-randomized, multiple-ascending dose study designed to evaluate the PK of asenapine and dopamine D2 receptor occupancy relative to steady state plasma levels in subjects with schizophrenia treated with HP-3070 patches (4.5 mg, 9.0 mg, 13.5 mg, and 18.0 mg) for 7 days.

Plasma asenapine concentrations following multiple ascending doses 4.5 mg, 9.0 mg, 13.5 mg, and 18.0 mg of HP-3070 patches increased with increasing dose. The estimated slopes for the steady state C_{max}, C_{min}, and AUC_{0-24} following multiple ascending doses of HP-3070 patches fell within the pre-defined criteria, confirming the dose-proportionality between 4.5 mg and 18.0 mg of HP-3070 patches. These similar desmethyl-asenapine/asenapine ratios and percentage of drug released among all 4 dosages corresponded well to the dose-proportionality results. Plasma asenapine concentration reached the steady state at around 72 hours after the first patch and showed sustained plasma concentrations at steady state.

The D_2/D_3 receptor occupancy in the caudate and putamen regions were increased between the doses of 4.5 and 9.0 mg followed by an observed plateau between the 9.0-mg and 18.0-mg doses, with maximum occupancy of around 60% when ^{11}C-PHNO was used as a radiolabeled ligand. Receptor occupancy observed in this study is comparable to that obtained with other antipsychotics such as risperidone and olanzapine (at clinical dose) as measured with ^{11}C-PHNO.[2]

Treatment with multiple doses of the HP-3070 patch for a total of 28 days was safe and well tolerated in patients with schizophrenia. A total of 33 treatment-emergent adverse events (TEAEs) were observed in this study. The most frequently reported TEAEs were somnolence (6 events), dizziness (4 events), and headache (3 events). There were no deaths

or SAEs reported during the study. No subjects were discontinued during the study due to AEs.

HP-3070-US-03 was designed to examine the PK, safety, tolerability, adhesion and irritation potential of the 9.0-mg HP-3070 transdermal patch at 5 different application sites (upper arm, upper chest, upper back, abdomen, and hip area) in healthy Japanese (n = 20) and Caucasian (n = 20) subjects.

All PK parameters assessed were similar among the 5 different application sites and asenapine exposure, measured as C_{max} and AUC, from all tested application sites (upper chest, upper back, abdomen, and hip area) was bioequivalent to that of the upper arm (reference application site) with the exception of C_{max} for the abdomen compared with the upper arm for which the lower boundary was slightly out of criteria. The results of this study suggest that the 5 application sites evaluated in this study (abdomen, hip area, upper arm, upper back, and upper chest) can be used as application sites for the HP-3070 transdermal patch.

Following 24-hour HP-3070 patch applications, no marked ethnic differences between Caucasian and Japanese subjects were found for all PK parameters assessed for both asenapine and desmethyl-asenapine.

Treatment with the 9-mg patch applied for 24 hours was safe and well tolerated in healthy male and female Caucasian and Japanese subjects. There were no deaths or SAEs reported during the study. No subjects were discontinued during the study due to AEs. The most frequently reported TEAEs were somnolence (25 events), insomnia (10 events), nausea (8 events), fatigue (7 events), headache (6 events), influenza-like illness (6 events), irregular menstruation (5 events), and dizziness (4 events). No difference in patch adhesion was seen between Caucasian and Japanese subjects and between the application sites of upper back, abdomen, upper chest, hip area, and upper arm.

In all of the PK studies completed to date, adhesion of HP-3070 transdermal patch was good and treatment with HP-3070 transdermal patches was safe and well tolerated. There were no difficulties associated with patch application and skin irritation and discomfort scores suggest good dermal tolerability of the transdermal patches.

2.2 Rationale

This study is designed to evaluate efficacy and safety of HP-3070 compared with placebo transdermal patch in subjects diagnosed with schizophrenia, who are in an acute exacerbation and to assess the impacts of covariates on asenapine exposure as delivered in a patch formulation, using a population-based approach.

2.3 Hypothesis

The null hypothesis of the primary endpoint is that there is no difference between treatment arms in the change from Baseline in Positive and Negative Syndrome Scale (PANSS) total

score at Week 6. The alternative hypothesis is that the treatment arms differ in the change from Baseline in PANSS total score at Week 6.

2.4 Risk Assessment

Potential risks associated with participation in this study have been identified through the review of information available from marketed formulations containing asenapine (SAPHRIS® and Sycrest®). These products have been marketed since 2009 and the safety profile of asenapine is well-established.

The most common AE associated with SAPHRIS® and Sycrest® have been anxiety and somnolence. Less common AEs include nervous system disorders (as dystonia, akathisia, sedation, dizziness, and dyskinesia), oral hypoesthesia, muscle rigidity, and fatigue. Increases in liver transaminases have been reported, as well as increased appetite and weight increase. The SAEs known to be associated with antipsychotics include tardive dyskinesia, suicidality, and neuroleptic malignant syndrome. Other risks associated with this drug class include orthostatic hypotension, syncope, weight gain, metabolic imbalance, neutropenia, and allergic reactions. More details are presented in the Investigator Brochure.

The risks specific to the HP-3070 patch (as opposed to the molecule [asenapine] itself) are limited to potential dermal reactions to the patch. A potential risk of the study is treatment failure (particularly in the placebo control group), which may result in worsening symptoms. Hospitalization of the subjects for the entire duration of the study will enable close observation of the subjects whereby the risk of treatment failure as well as potential dermal reactions can be addressed in real-time. The subjects will be under observation and they will be monitored for changes in extrapyramidal symptoms (EPS) scores, electrocardiograms (ECGs), laboratory values, vital signs, and physical examination. Psychotropic medications which can be used concomitantly to manage the patient's symptoms are discussed in Section 5.10.

2.5 Study Compliance

This study will be performed in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate efficacy of HP-3070 compared with placebo for the treatment of schizophrenia as evaluated by PANSS total score.

3.2 Secondary Objectives

- Key Secondary Efficacy Objective:
  - Clinical Global Impression – Severity of Illness Scale (CGI-S)
- Other Secondary Efficacy Objectives: To evaluate the efficacy of HP-3070 using the following measures:
  - PANSS total score at each time point
  - Clinical Global Impression – Severity of Illness Scale (CGI-S) at each time point
  - Clinical Global Impression – Improvement Scale (CGI-I) at each time point
  - Proportion of CGI-I responders at each time point including Week6; CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved).
  - Positive, negative, and general pathology subscores of PANSS
  - Proportion of PANSS responders; PANSS responders are defined as subjects who have a $\geq$30% reduction in PANSS total score between Baseline and at each time point including Week 6
  - Calgary Depression Scale for Schizophrenia (CDSS)
  - Medication Satisfaction Questionnaire (MSQ) score

3.3 Safety Objectives

- AEs, including TEAEs, AEs leading to discontinuation from the study drug, SAEs, and deaths
- Change from Baseline in clinical laboratory results (including prolactin, fasting glucose, and lipids), ECG results, body weight and vital signs
- Results of C-SSRS, BARS, AIMS, and SAS
- Dermal Safety

3.4 Exploratory Objective

To assess the impact of covariates on asenapine exposure using a model-based approach and to explore the exposure-response relationship with relevant endpoints.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, in-patient, safety, and efficacy study to evaluate HP-3070 for the treatment of schizophrenia.

This study will enroll subjects who are in an acute exacerbation (i.e., have had an acute episode no longer than 8 weeks prior to the Screening Visit), have a PANSS total score ≥80 with scores of 4 or higher on at least 2 out of the 4 pre-defined PANSS positive subscale items, and have a CGI-S ≥4. Subjects will be hospitalized at the Screening Visit and will remain hospitalized during the study. The subject may leave the hospital for necessary personal business. During this time, the subject must be supervised by study staff or a responsible caretaker. Any subject who leaves the site must have an alcohol breathalyzer and urine drug and pregnancy tests when they return to the site. Investigator should contact Medical Advisor to discuss specifics of subject off-site overnight travel to confirm appropriateness.

This study will consist of a Screening/placebo Run-in Period of 3 to 14 days (described in Section 4.1.1), a 6-week double-blind Treatment Period (described in Section 4.1.2) and a 30 day Follow-up Period (described in Section 4.1.3).

The study will evaluate 9.0 mg (HP-3070-9.0) and 18.0 mg (HP-3070-18.0) of HP-3070 transdermal patches versus placebo transdermal patches. Patches will be applied by site personnel at approximately the same time daily and each patch will be worn for 24 hours. Every day, approximately 24 hours after patch application, site personnel will remove previous day's patches and apply new patches. Patch adhesion will be assessed at specified time points.

In this study, efficacy will be evaluated using widely accepted, standard questionnaires. These include the PANSS, CDSS, CGI-S, CGI-I, and MSQ. Efficacy measures are described in Section 6.1. The methods used for the analysis of efficacy data are presented in Section 8.3.

In addition to standard safety measures (AEs, clinical laboratory assessments, vital signs, weight, ECG results), this study will also include assessments of EPS symptoms using the, Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS). Suicidality will be monitored using the Columbia-Suicide Severity Rating Scale (C-SSRS). Dermal safety will be assessed by daily evaluation of irritation at the site of patch application and by a review of any dermal reactions reported as AEs. Safety measures are described in Section 6.2.

The schedule of study procedures and assessments is presented in Table 1.

4.1.1 Screening/Run-in Period

Subjects will be asked to sign the informed consent form (ICF). No screening procedures may begin prior to obtaining informed consent.

After obtaining informed consent, each subject will be assigned a unique subject number. Eligible subjects will be hospitalized for the duration of the study. While undergoing screening procedures, including the MINI, and waiting for results of laboratory tests, ECGs, and other assessments, the subject will start treatment with the single-blind placebo patch. Subjects will be blinded to the treatment during the Run-in Period. The subject must have the single-blind placebo patch applied for a minimum of 3 days prior to being randomized into the double-blind Treatment Period. In addition, current antipsychotic and other prohibited medications will be washed out during the run-in period and must be completed prior to randomization into the double-blind treatment period. Subjects who have a decrease in PANSS total score ≥20% from Screening to Baseline or a PANSS total score <80 at Screening or Baseline will be discontinued from the study and will not enter the double-blind Treatment Period. Subjects who are not compliant with wearing the run-in patches will also be discontinued from the study. Subjects who are screened but discontinued before randomization will be considered screen failures.

Rescreening of subjects will be considered on a case-by-case basis and must be approved by the medical monitor.

4.1.2 Double-blind Treatment Period

Eligible subjects will be randomized at Baseline (Day 0) and randomly assigned to HP-3070 (9.0 mg or 18.0 mg) or placebo in a 1:1:1 ratio. Subjects will receive treatment with study medication daily starting on Day 1 and up to Day 42 for a total of 6 weeks.

Efficacy and safety data will be collected in accordance with the Schedule of Events.

Blood samples will be collected at pre-determined time points and analyzed for asenapine and desmethyl asenapine concentrations.

At discharge (Week 6 or early termination [ET]), the subject will be prescribed an approved antipsychotic treatment and returned to the care of their physician.

4.1.3 Follow-up Period

All subjects will have a follow-up contact (site visit or telephone call, at the discretion of the Investigator) 30 days after the last patch is removed. This contact will be used to collect information about any AEs or SAEs that may have occurred since discharge and to follow-up on any AE that was on-going at discharge.

The Schedule of Events is presented in Table 1.

Table 1 Schedule of Events

Study Period	Screening/ Single-blind Placebo Run-In Period [a]	Double-Blind Treatment Period							Safety Follow-up Visit or Telephone Call [b]
Week/Day	3 to 14 days	Baseline Day 0 [c]	Day 7/ Wk 1	Day 14/ Wk 2	Day 21/ Wk 3	Day 28/ Wk 4	Day 35/ Wk 5	Day 42/ Wk 6 or ET	30 days after removal of last patch
Visits	1	2	3	4	5	6	7	8	8
Informed consent	X								
Pre-randomization form	X								
Assign subject number from IWRS	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Physical examination including skin examination	X							X	
Medical history including psychiatric history	X								
MINI [d]	X								
PANSS [d]	X	X	X	X	X	X	X	X	
CDSS [d]	X	X	X	X	X	X	X	X	
C-SSRS [d]	X	X	X	X	X	X	X	X	
CGI-S [d]	X	X	X	X	X	X	X	X	
CGI-I [d]			X	X	X	X	X	X	
AIMS [d]	X	X	X	X	X	X	X	X	
SAS and BARS [d]	X	X	X	X	X	X	X	X	
MSQ [d]	X			X		X		X	
Vital signs [e]	X	X	X	X	X	X	X	X	
Weight and height [f]	X	X	X	X	X	X	X	X	
Standard 12-lead ECG [g]	X	X	X	X	X	X	X	X	
Clinical laboratory testing (fasting)	X	X			X			X	
Urine drug screen/blood alcohol [h]	X								
Serum/urine pregnancy test [i]	X	X	X	X	X	X	X	X	
Serology (HIV, HBsAg, anti-HCV) [j]	X								
Concomitant therapies	X	X	X	X	X	X	X	X	X

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Study Period	Screening/ Single-blind Placebo Run-In Period [a]	Double-Blind Treatment Period							Safety Follow-up Visit or Telephone Call [b]
Week/Day	3 to 14 days	Baseline Day 0 [c]	Day 7/ Wk 1	Day 14/ Wk 2	Day 21/ Wk 3	Day 28/ Wk 4	Day 35/ Wk 5	Day 42/ Wk 6 or ET	30 days after removal of last patch
Visits	1	2	3	4	5	6	7	8	8
Adverse events	X	X	X	X	X	X	X	X	X
PK blood samples [k]					X			X	
Blood sample for prolactin level [l]		X			X			X	
Dispense run-in kit	X								
Randomization/ assign double-blind kit		X							
Provide subject identification card	X								
Dosing with single-blind patch (patch application and removal of previous patch, if applicable)	X								
Dosing with double-blind patch (patch application and removal of previous patch, if applicable)		X	X	X	X	X	X	X	
Skin Irritation Assessment [m]	X	X	X	X	X	X	X	X	
Patch Adhesion Assessment [m]	X	X	X	X	X	X	X	X	
Patch Discomfort Assessment [m]	X	X	X	X	X	X	X	X	
Adhesive Residue Assessment [m]	X	X	X	X	X	X	X	X	
Drug accountability	X	X	X	X	X	X	X	X	

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression - Improvement scale; CGI-S = Clinical Global Impression - Severity of Illness scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = end of treatment; HBsAg = hepatitis B antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = Interactive Web-Based Response System; MINI = Mini International Neuropsychiatric Interview; MSQ = Medication Satisfaction Questionnaire; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetics; SAS = Simpson Angus Scale; Wk = week

a. The subject must use the single-blind placebo patch for a minimum of 3 days prior to entering the double-blind Treatment Period. Washout of the subject's current antipsychotic and other prohibited medications must be completed by the end of the Screening/Run-in Period. Subjects who have a decrease in PANSS total score ≥20% from Screening to Baseline or a PANSS total score <80 at Screening or Baseline will be discontinued from the study.

b. Subjects will have a follow-up contact (site visit or telephone call, at the discretion of the Investigator) 30 days after the last patch is removed.

c. All baseline assessments and laboratory samples will be performed prior to randomization.

d. It is suggested that assessment scales should be performed in the order they appear in the Schedule of Events

e. Blood pressures (sitting) and pulse rates should be measured after subject has rested (sitting quietly) for 5 minutes. In addition, assessments for orthostatic hypotension will be performed at each visit. Blood pressure readings and pulse rate will be obtained after the subject has been supine for 5 minutes. These will be repeated after the subject has been standing up for approximately1 to 3 minutes.

f. Height will be obtained at Screening, only.

g. ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes.

h. Urine drug screen and alcohol breathalyzer test should be completed if the subject leaves the study site.

i. All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at screening must not be enrolled. Subjects with positive urine and serum pregnancy test results during the trial must discontinue treatment. Urine pregnancy test to be repeated if subject leaves the study site.

j. Subjects with chronic Hepatitis B or C may be included provided that their condition is stable and that values for liver function tests and other laboratory tests results meet the criteria specified for entry into the study.

k. At least 3 blood samples will be collected at 2, 14, and 22 hours after application of the patch with ± 2 hour- window on Day 21 and 42. Actual blood sampling time will be recorded.

l. The central laboratory will not report prolactin levels to the sites nor the Sponsor, because this could potentially result in unblinding the treatment. The central laboratory will report prolactin levels as "masked" on the laboratory report (see Section 6.2.2.2.3 for more details).

m. Patch adhesion will be evaluated throughout the day including at the time points during which the site staff collects routine vital signs as per hospital policy/SOP; and immediately prior to removal of previous day's patch. In addition, subjects will be asked to check patch adhesion throughout the day and report immediately to site personnel if the patch detaches completely or detaches partially (i.e., some edges of the patch are lifting off the skin). Irritation at the site of patch application will be assessed each day between 30 and 60 minutes after patch removal. Subjects will be asked to report to the site staff any discomfort or skin irritation due to the patch. Discomfort and skin irritation reported by the subjects will be recorded as AEs. Patch application site will be assessed weekly for adhesive residue.

4.2 Discussion of Study Design

This is a Phase 3, multi-center, placebo-controlled, randomized, double-blind, in-patient study designed to demonstrate the efficacy and safety of HP-3070 transdermal patches when used in subjects diagnosed with schizophrenia.

A parallel-group design was selected because it is free of the assumptions underlying competing designs (for example, crossover). A parallel group approach is considered the optimal study design to evaluate efficacy.

The use of a randomized double-blind design will minimize bias by randomly assigning the subjects to treatment arms, and ensuring that the subjects, the Investigators and site personnel, and the Sponsor/designee are blinded to the treatment allocations.

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. The comparison with placebo is justified as this is an in-patient study and subjects will be closely monitored and study treatment will be discontinued and the subject will be returned to standard of care (SOC) treatment if their mental status deteriorates.

The study population will include male and female subjects, ≥18 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia who are in an acute exacerbation. These subjects represent an appropriate population in which to evaluate the efficacy of the HP-3070 patch.

The rationale for dose selection is described in Section 5.6.

The 6-week duration is considered to be sufficient for achieving a steady state condition of HP-3070. This time period is also sufficient to evaluate changes in the primary and secondary outcome measures.

Subjects will be hospitalized throughout the study to ensure proper medical care, and to allow for the close monitoring of mental status and any potential negative effects of treatment.

Severity of illness and psychopathology will be measured using the PANSS and CDSS. The CGI-S and the CGI-I will be used to confirm clinical relevance of changes in the efficacy assessment scales. The efficacy measurements chosen for this study are standard validated instruments and these are commonly used to evaluate efficacy endpoints in subjects with schizophrenia who are in an acute exacerbation.

The primary efficacy endpoint is change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score. The PANSS scale is a standard validated instrument that is a gold standard in acute schizophrenia studies and is an appropriate instrument to evaluate efficacy in patients diagnosed with schizophrenia who are in acute exacerbation. This instrument is the primary efficacy endpoint that has been used for pivotal trials for several products such as SAPHRIS®, Latuda®, and Vraylar®.

The key secondary endpoint is change from baseline to week 6 in the CGI-S score.

The Clinical Global Impression – Severity (CGI-S) scale is an accepted, standard efficacy rating scale in acute schizophrenia trials. CGI-S is an acceptable key secondary variable: (i) based on precedence (SAPHRIS® and other approved antipsychotics); (ii) CGI-S assesses a domain of the illness other than that assessed by the primary efficacy variable, therefore, there is no redundancy with the primary efficacy variable (PANSS total score).

While the PANSS is the cornerstone for evaluation of efficacy of antipsychotic drugs in patients with schizophrenia who are in an acute exacerbation and is a useful clinical research tool, clinical implications of PANSS scores are not very well defined and the PANSS scores are not intuitively understood by clinicians; whereas, scores from the Clinical Global Impression (CGI) scale are better understood by clinicians and are better translated into clinical practice as they inform the clinician of the subject's overall clinical status.

The CGI-S is a valid and reliable clinician administered scale and has widespread use in psychiatry clinical trials. The CGI-S scale measures the clinician's global impression of the severity of illness at each time point taking into account the reported and observed symptoms in the past 7 days. In the HP-3070-GL-04 study, the CGI-S will be analyzed as change from baseline to Week 6. Inclusion of the CGI-S as key secondary endpoint in the HP-3070-GL-04 will facilitate replication of SAPHRIS® data.

The safety measures used in this study are standard safety measures which include AEs, concomitant therapy, clinical laboratory results, medical history, physical examination, vital signs, weight gain and ECGs. In addition, the AIMS, BARS, and SAS will be used to assess EPS. The C-SSRS will be used to assess suicidality. The C-SSRS facilitates prospective, systematic monitoring for emergence of suicidality within clinical trials and it is a low-burden, clinician-administered tool that covers the wide spectrum of suicidality from ideation to behavior. Skin irritation and discomfort reported by the subjects will be recorded as AEs. Skin irritation and discomfort at the patch application site is an important assessment because the condition of the skin may influence the absorption of the drug from the transdermal patch.

This study also includes assessment of patch adhesion and evaluation of amount of adhesive residue at the patch application site. Adhesion of transdermal patch to the skin is a critical factor and one of the most important functional properties directly related to drug delivery and therapeutic effect. Patch adhesion must be satisfactory in order for requirement for any clinical conclusions to be valid.

4.3 Selection of Study Population

The assessment and documentation of the subject's eligibility is the responsibility of the Investigator. The Sponsor/designee reserves the right to provide final approval of subject eligibility.

4.3.1 Inclusion Criteria

Subjects must meet **all** of the following criteria to be considered eligible to participate in the study:

1. Adult male or female subjects, ≥18 years of age
2. Subject is able to undergo informed consent process and signs ICF.

3. Subject has current diagnosis of schizophrenia as per DSM-5 Criteria, Mini International Neuropsychiatric Interview (MINI), and as confirmed by Investigator assessment.
4. Subject has PANSS total score ≥80, AND score of 4 or more in at least 2 of the following PANSS items at Screening and at Baseline:
    a. Conceptual disorganization
    b. Delusions
    c. Hallucinatory behavior
    d. Unusual thought content
5. Subject has CGI-S scale score of ≥4 (moderately ill) at Screening and Baseline.
6. Subject has history of relapse and/or exacerbation of symptoms when they are not receiving antipsychotic treatment, excluding the current episode.
7. Subject is confirmed by the Investigator to be experiencing an acute exacerbation of schizophrenia, as evidenced by ALL of the following:
    a. The duration of the current episode is no more than 8 weeks.
    b. The subject's current symptoms represent a marked and substantial exacerbation of schizophrenia compared with the subject's symptomatic state prior to the emergence of the current episode.
    c. A corresponding functional deterioration to the symptomatic exacerbation is evident.
8. Subject has not been hospitalized for more than 21 days for the current episode by the day of the Screening Visit, not including social hospitalization (e.g., homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition).
9. Subject agrees not to begin formal, structured psychotherapy targeting the symptoms of schizophrenia from the time of the Screening Visit until the last dose of study drug.
10. Subject would benefit from hospitalization or continued hospitalization for the treatment of schizophrenia (as determined by the Investigator).
11. Subjects must not be treatment naïve or treatment resistant. Treatment resistance is defined as having little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the drug's package insert).
12. Subject has had previous positive response to an antipsychotic medication other than clozapine in a prior episode.
13. Subject has a stable living situation and caretaker support when not hospitalized.
14. Subject is male, or a female who is not of childbearing potential (i.e., surgically sterile, postmenopausal for at least 1 year) or who is non-pregnant, non-lactating, and is using a medically accepted method of contraception. Acceptable methods of contraception include condoms (male or female) with a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), and hormonal contraceptives. A female of child-bearing potential who is not currently sexually active must agree to use a medically accepted method of contraception should she become sexually active while participating in the study. Each sexually active female of child-bearing potential must also agree to use a medically accepted method of contraception for 1 month after the final dose of study medication.

15. Subjects must agree that they will not donate sperm or eggs from the time of the Screening Visit until 3 months following administration of the last treatment or dose of study medication.
16. Agrees not to use any other transdermal patch products (e.g., nicotine replacement patch, hormonal replacement patch, etc.) for the duration of the study.
17. Subject must be able to wear a transdermal patch for 24 hours.

4.3.2 Exclusion Criteria

The subject will be excluded from the study if **any** of the following exclusion criteria are met:

1. Subject is presenting with a first episode of schizophrenia based on the clinical judgment of the Investigator.
2. Subject has been diagnosed with schizophrenia less than 6 months prior to Screening Visit.
3. Subject has received electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS), or other brain stimulation treatments within 90 days of Screening Visit.
4. Subject has a current DSM-5 diagnosis other than schizophrenia including (but not limited to) schizoaffective disorder, major depressive disorder, bipolar disorder, post-traumatic stress disorder, anxiety disorders, delirium, dementia, amnestic, or other cognitive disorders.
5. Subject has a diagnosis of mental retardation, history of traumatic brain injury causing ongoing cognitive difficulties, Alzheimer's Disease or another form of dementia (or suspicion thereof), or any chronic organic disease of the central nervous system that would interfere with the efficacy or safety endpoints of the study.
6. Subject has experienced acute depressive symptoms within 30 days prior to Screening Visit that requires treatment with an antidepressant, as determined by the Investigator.
7. Subject is a known non-responder to previous asenapine treatment, as per Investigator judgment.
8. Subject is currently taking clozapine for the treatment of schizophrenia. Subjects taking low doses of clozapine (up to 100 mg/day) for sedative properties and not treatment resistance or suicidality may be acceptable as per Investigator judgment and as approved by the Sponsor/designee.
9. Subject with schizophrenia who is considered resistant/refractory to antipsychotic treatment by history or who has a history of failure to respond to clozapine or response to clozapine treatment only. Treatment resistance is defined as having little or no symptomatic response to at least 2 courses of antipsychotic treatment of an adequate duration (at least 6 weeks) and at a therapeutic dose (according to the drug's package insert).
10. Subject who is unwilling to discontinue or, in the opinion of the Investigator, unable to discontinue any prohibited medication prior to the Baseline Visit without significant medical or psychiatric destabilization, or increased suicidality, as per the washout requirements. Prohibited medications include:
    a. Antipsychotics, including depot or long-acting injectables

b. Antidepressants
c. Mood stabilizers
d. Stimulants
e. Non-psychopharmacologic medications with psychotropic properties, per Investigator and approved by Sponsor/designee
f. Herbal drugs/dietary supplements unless approved by Sponsor/designee

11. Subjects taking drugs (current antipsychotic or other prohibited medication) that require >14 days for washout
12. Subject who is involuntarily committed, incarcerated, or under legal compulsion to seek psychiatric treatment.
13. Subject currently has clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome (AIDS). Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the study. Subjects with chronic Hepatitis B or C may be included provided that their condition is stable and values for liver function tests and other laboratory test results meet the criteria specified in the protocol for entry into the study. The Sponsor/designee should be contacted in any instance where the Investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on study participation.
14. Subject has any other medical condition or laboratory result that, in the opinion of the Investigator, may make the subject unsuitable for the study.
15. Subjects with the following laboratory test and ECG results are excluded:
    a. Platelets $\leq 75{,}000/mm^3$
    b. Hemoglobin ≤ 9 g/dL
    c. Neutrophils, absolute $\leq 1000/mm^3$
    d. Aspartate transaminase (AST) >2×upper limit of normal (ULN)
    e. Alanine transaminase (ALT) >2×ULN
    f. Creatine phosphokinase (CPK) >3×ULN, unless discussed with and approved by the Medical Advisor
    g. Creatinine ≥ 2 mg/dL or ≥ 176.8 µmol/L
    h. Hemoglobin A1c (HbA1c) $\geq 6.5\%$ unless the subject has a diagnosis of stable diabetes
    i. QT interval corrected using Fridericia's formula (QTcF) ≥ 450 msec (males), QTcF ≥ 470 msec (females)
    j. Prolactin. The enrollment of subjects with prolactin levels equal or higher than 5 X ULN should be discussed with the Medical Advisor
16. Subject with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days); subjects with abnormal free T4 and thyroid stimulating hormone (TSH) levels.

17. Subject is currently treated with insulin for diabetes. Subjects being treated for diabetes with medications other than insulin are eligible for the study if their condition is stable as determined by satisfying ALL of the following criteria:
    a. HbA1c <7.0%, AND
    b. Screening glucose ≤125 mg/dL or ≤6.94 mmol/L (fasting) or <200 mg/dL or <11.1 mmol/L (nonfasting). Note: If the nonfasting screening glucose is ≥200 mg/dL or ≥11.1 mmol/L, subjects must be retested in a fasted state and the retest value must be ≤125 mg/dL or ≤6.94 mmol/L, AND
    c. Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to Screening or diabetes has been well-controlled by diet for at least 28 days prior to Screening, AND
    d. Subject has not had any hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, AND
    e. Subject's diabetes is not newly diagnosed during Screening
18. Subject has epilepsy or history of seizures, with the exception of a single seizure episode (e.g., childhood febrile, post traumatic).
19. Subject has uncontrolled hypertension (diastolic blood pressure [DBP] >95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥30 mmHg in systolic blood pressure (SBP) and/or a decrease of ≥20 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, OR development of symptoms. Note: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above.
20. Subject has a history of neuroleptic malignant syndrome.
21. Subject has a score of >2 (mild) on any item of the AIMS at Screening.
22. Subject has a score of 5 (severe akathisia) on BARS global clinical assessment of akathisia at Screening.
23. Subject has a history of pituitary adenoma or cancer <5 years prior to Screening. Subjects currently being treated for cancer may not be enrolled in the study.
24. Female subject who is breastfeeding.
25. Female subject with a positive urine pregnancy test that is confirmed positive by serum pregnancy test at Screening or Baseline.
26. Subject who currently (within the past 6 months) meets the DSM-5 criteria for substance use disorders (excluding nicotine and caffeine).
27. Subject has positive urine drug/alcohol screen at the Screening Visit. Positive results that are due to short-term prescription medications that can be safely discontinued (e.g., opioids for acute pain that has resolved) may continue at the discretion of the Investigator with the agreement of the Sponsor/designee. Subjects with positive cannabis results may be included, provided the Investigator does not feel the subject is a compliance risk and the subject does not fulfill the criteria for substance abuse or dependence as stated in Exclusion Criterion 26 above, the subject agrees to abstain for the duration of the study, and with the concurrence with the Sponsor/designee.
28. Subject is at imminent risk of self-harm or harm to others, in the Investigator's opinion based on clinical interview and responses provided on the C-SSRS. Note that

subjects will be excluded if they report suicidal ideation meeting the description of C-SSRS Type 4 or 5 (i.e., suicidal ideation with intent, with or without a plan) in the past 6 months or suicidal behavior (as described by the C-SSRS) in the past 12 months at Screening. Subjects will also be excluded at Baseline if they report suicidal ideation of Type 4 or 5 or suicidal behavior, as measured by the C-SSRS between Screening and Baseline.

29. Subject has a known allergy or hypersensitivity to asenapine.
30. Subject has current or history of allergy or hypersensitivity to adhesive dressings.
31. Subject has history of allergy to more than 2 distinct chemical classes of drug (e.g., sulfas and penicillins).
32. Subject has any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo.
33. Subject has participated in a previous HP-3070 study.
34. Subject has participated in any other investigational trial or used investigational drugs within 30 days prior to the Screening Visit or has participated in more than 2 studies in the past 12 months.
35. Any subject who, in the opinion of the Investigator or Medical Advisor, should not participate in the study.
36. Subject is a Study Investigator, sub-Investigator, study coordinator, employees of a participating Investigator, or immediate family member of the aforementioned.

4.3.3 Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor or Quintiles must be contacted. An exception may be granted in rare circumstances where there is a compelling reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor/designee to allow the subject to continue in the study.

In addition, subjects will be withdrawn from study drug and from the study in the following circumstances:

- The Investigator decides that the subject should be withdrawn. Subjects may be withdrawn if continuing in the study is not in the subject's best interest, their condition worsens during the study or for safety reasons, as determined by the Investigator.
    - If this decision is made because of an AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor/designee is to be notified immediately.
- The subject is unwilling to continue in the study.

- Subject requires treatment with a prohibited concomitant medication
- The subject becomes pregnant. All pregnancies must be followed to conclusion to determine their outcome.
- The subject has one of the following elevated liver enzyme conditions, confirmed by repeat testing:
    - ALT or AST >3×ULN and total bilirubin >2×ULN
    - ALT or AST >8×ULN
    - ALT or AST >5×ULN for more than 2 weeks
    - ALT or AST >3×ULN with the appearance of jaundice, worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- The subject has an absolute neutrophil count of <1000 per mm^3, and after repeat testing in the subsequent 48 hours, the values fail to normalize.
- Lack of compliance with protocol.
- The Investigator or the Sponsor, for any reason, stops the study.

Subjects who discontinue the study early will have ET procedures performed as shown in the Schedule of Events (see Table 1). Randomized subjects who discontinue the study early will be considered dropouts. Subjects who withdraw from the study may remain hospitalized as needed for safety while they transition to SOC treatment and into the care of their personal physician.

A follow-up phone call will be made to the subject 30 days (±2 days) after the ET visit. Subjects who are withdrawn from the study will not be replaced.

In all cases, the reason for withdrawal must be recorded. If the reason for subject withdrawal is not known, considerable efforts must be made to establish whether the reason for withdrawal was an AE. Subjects, for whom the study drug is discontinued, will be encouraged to continue to complete all the scheduled procedures.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Subjects will receive treatment with HP-3070 (asenapine maleate, transdermal patch) 9.0 mg or 18.0 mg or placebo. Information concerning the application and removal of the patches is available in Section 5.7.

5.2 Identity of Investigational Product

HP-3070 contains asenapine maleate (trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7] oxepino[4,5-c]pyrrolidine maleate) as a white crystalline powder. It is supplied as a dermal patch consisting of a plastic film, adhesive matrix and backing film.

The investigational product and placebo comparator used in this study are described in Table 2.

Table 2 Investigational Products

Investigational Product	Dosage Form and Strength	Dosage Form	Shape/Size
HP-3070-9.0	One patch contains 9.0 mg asenapine maleate (0.45 mg of asenapine maleate per 1.0 cm^2)	Transdermal patch	square with an area of 20 cm^2
HP-3070-9.0 Placebo	One patch contains 0 mg asenapine maleate	Transdermal patch	square with an area of 20 cm^2

5.3 Packaging, Labelling and Storage

Each patch is packed in an aluminum foil sachet with light shading capacity. The sachet is air tight, and sealed by a heat sealer. The appropriate number and sizes of sachets are provided in a box.

The study drug will be labeled in accordance with all regulatory requirements. The Investigator/designee will complete the blank spaces on the label for the subject number, site number, and date dispensed.

The Sponsor will be responsible for ensuring that the quality of the study drug is adequate for the duration of the trial. Study drug is to be stored at room temperature in a secure area according to local regulations. The study drug must be dispensed only from official study sites by authorized personnel according to local regulations.

All study drug supplies that will be used in the study must be maintained securely under the direct responsibility of the Investigator or delegated by the Investigator to the hospital pharmacist, or other personnel licensed to store and dispense drugs. All drugs shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of drugs issued and returned is maintained. Under no circumstances will the Investigator allow the study drug to be used other than as directed by the protocol. Storage conditions should be monitored by the site personnel for adherence to label specifications.

5.4 Study Drug Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using a drug accountability form. These forms must be available for inspection at any time.

Used, partially used, the aluminum foil sachet of used and partially used patches, and unused study drug products should be retained until the Clinical Research Associate (CRA) has been able to complete drug accountability and reconciliation.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All used, partially used, and unused study medication supplies and packaging materials are to be inventoried and returned to Sponsor/designee by the Investigator. The Investigator is not permitted to return or destroy used, partially used, or unused clinical drug supplies or packaging materials unless authorized by the Sponsor/designee.

5.5 Method of Assigning Subjects to Treatment

Subjects will be randomly assigned to treatment using a 1:1:1 ratio to 1 of 3 treatment arms (HP-3070-9.0, HP-3070-18.0, or placebo) stratified by country.

Once the subject meets all the eligibility criteria for randomization in the double-blind Treatment Period, the study center will request the study medication assignment using the Interactive Voice Activated Response System (IVRS) or Interactive Web-based Response System (IWRS). All randomized subjects will be managed by IVRS/IWRS. Detailed information will be provided in the Study Manual.

5.6 Selection of Doses in the Study

The results of placebo-controlled clinical trials of SL asenapine have demonstrated a similar efficacy of the 5.0 mg and 10.0 mg twice daily (BID) doses in reducing the total PANSS score. The exposure response relationship of the effect of asenapine on the time course of PANSS total score using data from the Phase 2 and Phase 3 studies of SL asenapine has been characterized and published.[4] Based on this analysis, asenapine effect was best described by an inhibitory E_{max} model and the area under the concentration time curve (AUC) was a better predictor of response than dose.

The rationale supporting the selection of the 2 doses (9.0 mg and 18.0 mg) to be studied in Study HP-3070-GL-04 is based on (a) the comparison of exposure (AUC_{0-24}) between approved doses of SAPHRIS® and selected doses for HP-3070 in the target population and (b) safety assessment for HP-3070.

In Study HP-3070-US-02b, the steady-state PK of HP-3070 transdermal patch at the doses of 4.5 mg, 9.0 mg, 13.5 mg and 18.0 mg were evaluated in a multiple ascending-dose study in patients diagnosed with schizophrenia. As shown in Table 3, the doses selected to be investigated in this study are expected to provide an exposure which is within the range of exposure provided by the approved doses of SAPHRIS®. The mean AUC_{0-24} following the 9.0 mg of once daily HP-3070 patch is similar to the mean AUC_{0-24} obtained by the administration of SAPHRIS® 5.0 mg BID while mean exposure following 18.0 mg of once daily HP-3070 patch is similar to that following the administration of SAPHRIS® 10.0 mg BID.

Table 3 Steady-State Pharmacokinetics of HP-3070 Transdermal Patch

Formulation	Dose	Population	Mean Body Weight (kg)	Mean C_{max} ng/mL (%CV)	Mean AUC_{0-24} ng.h/mL (%CV)	Data source
HP-3070	4.5 mg (n=22)	Schizophrenia patient (Mostly Caucasian)	86.6	1.14 (30%)	22.3 (28%)	HP-3070-US-02b
	9.0 mg (n=21)	Schizophrenia patient (Mostly Caucasian)	87.0	2.26 (24%)	45.8 (25%)	
	13.5 mg (n=20)	Schizophrenia patient (Mostly Caucasian)	87.0	3.40 (19%)	69.3 (20%)	
	18.0 mg (n=20)	Schizophrenia patient (Mostly Caucasian)	87.0	4.68 (17%)	96.2 (19%)	
SAPHRIS®	5.0 mg BID (n=28)	Schizophrenia patient (Caucasian, Black, Other)	82.1	4.23 (45%)	53.0 (38%)	NDA 22-117 (Study A7501001)[5]
	10.0 mg BID (n=25)	Schizophrenia patient (Caucasian, Black, Other)	82.1	6.56 (51%)	86.8 (53%)	

AUC = area under the plasma concentration time curve; BID = twice daily; C_{max} = maximum plasma concentration.
Note: AUC_{0-24} is indicated as arithmetic mean (%CV).
For SAPHRIS®, mean AUC_{0-24} was calculated as double of mean AUC_{0-12}

Study HP-3070-US-02b also demonstrated that daily application of HP-3070 transdermal patches for 7 days at doses of 4.5 to 18.0 mg was safe and well tolerated. After dosing with HP-3070, there were no clinically significant findings with respect to vital signs, 24-hour cardiac Holter, 12-lead ECG, clinical laboratory, or C-SSRS assessments.

Based on safety assessments and comparison of exposure between approved doses of SAPHRIS® and 9.0 mg and 18.0 mg of HP-3070, patches are considered to be appropriate doses to be studied in this trial.

5.7 Dosing of Subjects

During the single-blind Run-in Period, site personnel will apply 2 placebo patches to subjects once daily. The subject must use the single-blind placebo patch for a minimum of 3 days prior to being randomized into the double-blind Treatment Period. Subjects will be blinded regarding the placebo status of the patches.

During the double-blind Treatment Period (Day 1 through Day 42) site personnel will apply 2 patches to subjects per the randomization code. The treatment received by each subject will be:

- HP-3070 9.0-mg treatment arm: one (1) 9.0-mg 20 cm^2 patch and one (1) placebo patch (0-mg, 20 cm^2), once daily;
- HP-3070 18.0-mg treatment arm: two (2) 9.0-mg 20 cm^2 patches, once daily; and
- Placebo treatment arm: two (2) placebo patches (0 mg, 20 cm^2) once daily.

Patch Application and Removal

There are no special requirements related to food and beverage or other medications in regard to the timing of patch application.

The application area should be clean, dry, non-oily, non-hairy, and not irritated. Patches will be applied by site personnel at approximately the same time every day and each patch will be worn for 24 hours. Every day, approximately 24 hours after patch application, site personnel will remove previous day's patches and apply 2 new patches.

Both patches will be applied in close proximity without overlapping to 1 of the following application sites: abdomen, hip, upper arm, upper back, and upper chest. Patch application site will be rotated daily.

In the event that a patch should detach completely, the time, activity and reason at the time of patch detachment must be documented. Under no circumstances should the detached patch/patches be reapplied to the subject. Under no circumstances should the detached patch be reinforced with tape.

If both patches are detached completely then 2 new patches from the subject's kit should be applied immediately, provided that there are at least 6 hours of time remaining before the next dose. If only one patch detaches completely, then the other patch should also be

removed and 2 new patches from the subject's kit should be applied immediately, provided that there are at least 6 hours of time remaining before the next dose.

Regardless of the time when the new patches are applied, patch removal time of the new patches will be approximately 24 hours after the application of the original patches. In other words, removal time of the new patches may not exceed 24 hours from the time the first patches were applied.

The time of patch application, removal, and detachment will be recorded. If a patch is removed prior to the scheduled removal time, the time and reason for early patch removal will be recorded.

Detailed information regarding patch application and removal will be provided in the Study Manual.

5.8 Treatment Interruptions or Modifications

Dose modifications are not permitted. If the patient misses a dose or receives an extra dose for any reason, this should be recorded and discussed with the Medical Advisor.

5.9 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. The HP-3070 patches and placebo patches will be identical in physical appearance; subjects treated with active drug and placebo will receive the same number of patches.

The treatment each subject will receive will not be disclosed to the Investigator, study center staff, subject, or Sponsor/designee. The treatment codes will be held by the IVRS/IWRS vendor.

The process for breaking the blind will be handled through the IVRS/IWRS.

Investigators are strongly discouraged from requesting that the blind be broken for an individual subject, unless there is an emergency and the Investigator determines that unblinding and identification of the study drug is necessary for the purpose of providing urgent patient care and knowledge of the subject's treatment assignment will alter subsequent care. The reason for unblinding should be discussed with the Medical Advisor prior to unblinding, if possible. If the subject's condition requires unblinding prior to contact with the Medical Advisor or if the subject and/or Investigator are inadvertently unblinded during the course of the study, then the Medical Advisor should be contacted within 24 hours after the unblinding.

Pertinent information regarding the circumstances of unblinding a subject's treatment code must be documented.

5.10 Prior and Concomitant Treatments

Medications taken from 6 months prior to the Screening visit through the End of Study (including the 30 day Follow-up Period) must be recorded. The Investigator should instruct

the subject to notify the site about any new medication he or she takes after the start of the study.

5.10.1 Medications Prohibited during the Study

Prohibited/restricted medications and washout periods for specific drugs are presented in Table 4.

Table 4 Prohibited/Restricted Medications and Washout Prior to Baseline

Prohibited/Restricted Medication	Washout/Other Conditions
Antipsychotics, oral or immediate release IM Antipsychotics, depot or long acting injectable	Washout: 3 days, 7 days for aripiprazole One full cycle plus ½ cycle as per prescribing label[a]
Antidepressants Fluoxetine Monoamine oxidase inhibitors All other antidepressants	Washout: 28 Days 14 days 7 days Prohibited during the study
Mood stabilizers Lithium Anticonvulsants	Washout: 3 days 3 days Prohibited during the study
Varenicline	Washout: 5 days Prohibited during the study
Benzodiazepines other than the ones used as per protocol specifications	Washout: 3 days Prohibited during the study
Ramelteon or Tasimelteon	Prohibited during the study starting at Screening Visit
Antihistamines	Diphenhydramine and hydroxyzine prohibited during the study. Only non-sedating antihistamines are allowed for the treatment of allergy during the study
Narcotic Analgesics	Subject must have a negative urine drug screen prior to Baseline. Prohibited during the study starting at Screening Visit. Exception: during study, these drugs may be allowed for acute pain conditions (e.g., tooth extraction) for a maximum of 3 days.
Vitamins, non-prescription herbal preparations, other supplements[b]	Washout: 7 days, (14 days for St. John's Wort) Prohibited during the study
Antiemetic drugs containing dopamine antagonists	Prohibited during the study starting at Screening Visit
Stimulants	Prohibited during the study starting at Screening Visit
Other medications with psychotropic properties	Prohibited during the study, starting at the Screening Visit

Note: Subjects taking drugs that require a washout-out period >14 days are not eligible for the study.
Note: The Investigator should contact the Medical Advisor with any concerns about the acceptability of any medication.

a. Concerns about label interpretation should be discussed with Medical Advisor.
b. Supplements for general health and other non-psychiatric purposes, such as daily vitamins may be allowed with the approval of the Medical Advisor. Supplements for established medical conditions, such as iron for iron deficiency anemia, are not exclusionary.

5.10.2 Permitted Medications

Medications used for chronic non-psychiatric medical conditions (e.g., antihypertensives, oral hypoglycemic, etc.) are allowed if the condition and treatment regimen are stable before

Screening. Initiation or adjustments of therapies for non-psychiatric concurrent conditions will be left to the Investigator's discretion. If necessary, the Medical Advisor may be contacted.

Psychotropic medication, other than the study medication, may be initiated during the study. Conditions for the use of psychotropic concomitant medications are presented in Table 5.

Table 5 Medications Permitted for Specific Conditions

Medication	Use
Lorazepam	Oral medication allowed as needed (prn use only) for the treatment of insomnia, agitation, and or anxiety only. Maximum 6 mg/day during Screening and for the first 2 weeks of treatment, 4 mg/day during weeks 3 to 4 of treatment, and 2 mg/day for the remainder of the study. If lorazepam is not available in certain regions, another locally available benzodiazepine at equivalent doses may be approved by the Medical Advisor.[a,b,c]
Benztropine	Allowed for the use of treatment-emergent EPS, up to 4 mg/day or equivalent anticholinergic dose if benztropine is not available in certain countries.[b] The EPS scales are to be administered before medication is given (except in case of dystonia), to ensure documentation of the decision to administer the treatment. Not permitted within 12 hours of EPS scale administration.
Zolpidem	Allowed on an as needed basis (prn use only) for the treatment of insomnia as per prescribing label. If zolpidem is not available in specific regions, another hypnotic may be approved by the Medical Advisor.[b,c] Not permitted within 12 hours of EPS scale administration.
Propranolol	Not permitted within 12 hours of EPS scale administration. Allowed up to 60 mg/day in 20-mg doses for the treatment of akathisia.[b]

a. If a subject requires greater than then maximum allowances, then the Investigator must discuss the suitability of the subject to continue with the Medical Advisor
b. Not to be given within 12 hours prior to efficacy or safety assessments
c. Recommend reduced dosages for subjects older than 65 years of age

5.10.3 Concomitant Medication Cautions

Investigator's clinical judgment will be used in the following situations (the Medical Advisor for the study may be contacted if necessary):

- Caution should be used with co-administration with agents/conditions that induce CYP1A2 (e.g., smoking, rifampin) or inhibit CYP1A2 (e.g., fluvoxamine, ciprofloxacin, ketoconazole);
- Paroxetine (CYP2D6 substrate and inhibitor) dose should be reduced by half when used in combination with HP-3070;
- Potential additive effect on QT-interval prolongation; avoid concomitant use of other drugs known to prolong QTc intervals including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin); and

- May enhance hypotensive effects of certain antihypertensive agents and other drugs that can cause hypotension or bradycardia. Use concomitantly with caution; consider monitoring orthostatic vital signs in such subjects.

5.10.4 Other Restrictions

Other restrictions are summarized in Table 6.

Table 6 Other Restrictions

Restriction	Timeframe
ECT, TMS, VNS, or other brain stimulation treatment	90 days prior to Screening and for the duration of study participation
Formal, structured psychotherapy targeting the symptoms of schizophrenia	For duration of study participation
Transdermal medical patches other than study drug	For the duration of study participation.

ECT = electroconvulsive therapy; TMS = transcranial magnetic stimulation; VNS = vagal nerve stimulation

Note: If a subject is a smoker and the hospital does not allow smoking, they may use nicotine replacement options, but the use of a nicotine transdermal patch is not permitted.

5.11 Medical Care of Subjects after End of Study

After the end of the study, subjects may remain hospitalized as needed for safety while they transition to standard of care (SOC) treatment and into the care of their personal physician.

5.12 Treatment Compliance

To ensure treatment compliance, patches will be applied and removed by designated qualified staff. The exact times of patch application and removal will be recorded. In addition, patch adhesion will be assessed throughout the day (during routine check of vital signs as per hospital policy/SOP and before removal of previous day's patch).

Noncompliance is defined as using less than 80% or more than 120% of study medication during any evaluation period (visit to visit). If the subject is noncompliant, the Medical Advisor should be contacted to discuss the subject's eligibility to continue in the study.

6.0 EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

6.1 Efficacy

The raters administering the efficacy assessments must be qualified and experienced. All assessment scales should be performed in the order they appear in the Schedule of Events (Table 1). Raters will be trained to administer these scales. Raters must be certified to administer the PANSS. Qualified personnel, who are approved by the Sponsor/designee to administer the efficacy assessments, will be participating in initial and ongoing training sessions. Details of the training will be provided in the Rater Qualification Methodology. The number of raters within each study site should be kept to a minimum. All efforts will be

made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings.

6.1.1 M.I.N.I. International Neuropsychiatric Interview (MINI)

The MINI. International Neuropsychiatric Interview (MINI 6.0) for Schizophrenia and Psychotic Disorders is a short, structured, diagnostic interview developed by psychiatrists and clinicians in the United States and Europe for DSM-IV and ICD-10 diagnoses of schizophrenia and other psychotic disorders.[6] The MINI is the most widely used psychiatric structured diagnostic interview instrument in the world, employed by mental health professionals and health organizations in more than 100 countries. The questions on the MINI are designed to be answered generally with just "Yes" or "No." The MINI has been shown to be valid, reliable, and more time-efficient than other, lengthier diagnostic interviews.

6.1.2 Positive and Negative Syndrome Scale (PANSS)

The PANSS[7] consists of 3 subscales containing a total of 30 items. For each item, severity is rated on an anchored 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. The items for each subscale are as follows:

1) Positive Subscale (7 positive items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility),

2) Negative Subscale (7 negative items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking), and

3) General Psychopathology Subscale (16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

A copy of the PANSS is provided in Appendix 2 (Section 12.0).

6.1.3 Secondary Efficacy

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

The severity of illness for each subject will be rated using the CGI-S.[8] To perform this assessment, the rater or Investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include: 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; and

7 = among the most extremely ill subjects. A sample of the CGI-S is provided in Appendix 3 (Section 13.0).

6.1.3.2 Clinical Global Impression - Improvement Scale (CGI-I)

The efficacy of trial medication will be rated for each subject using the CGI-I.[7] The rater or Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared with the subject's condition at Baseline prior to the first dose of double-blind study drug. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. A sample of the CGI-I is provided in Appendix 4 (Section 14.0).

6.1.3.3 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a nine-item scale designed for assessment of the level of depression in patients with schizophrenia.[9] Each of the 9 items is rated on a 4-point scale, scored from 0 to 3. The first 8 items are rated on the basis of responses during a semi-structured interview conducted by a qualified clinician. The ninth item (Observed Depression) is rated by evaluating signs and symptoms over the course of the interview. The total score is derived by adding each of the 9 items together. Totals scores of 6 or more identifies the presence of treatment-emergent depression predictive of major depressive episodes. A sample is included in Appendix 5 (Section 15.0).

6.1.3.4 Medication Satisfaction Questionnaire (MSQ)

The Medication Satisfaction Questionnaire (MSQ) includes one simple question to ask patients about their satisfaction with their medication. Vernon et al. evaluated the psychometric properties in psychotic populations of the MSQ and found that responses to this one question were able to separate patients receiving active drug from those receiving placebo and was a good proxy for efficacy.[10] As such, it was determined that a 1-point change on the MSQ may be considered clinically meaningful. A sample is provided in Appendix 6 (Section 16.0).

6.2 Safety

Safety variables included in this study are: AEs, physical examinations, vital signs, body weight, clinical laboratory tests (including prolactin levels, fasting glucose, and lipids), ECGs, C-SSRS, evaluations of EPS (BARS, AIMS, and SAS), and dermal adverse events.

6.2.1 Adverse Events and Serious Adverse Events

6.2.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject given study drug. The event does not necessarily have to have a causal relationship with this treatment. The recording of AEs will begin when the subject signs the ICF and will continue up to the 30 day follow-up period. AEs that are ongoing at discharge will be followed until resolution or for 30 days after the last dose of study drug, whichever comes first.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of laboratory values or other clinical tests (e.g., ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline.

For the purpose of this study, in addition to the AE definitions described above the following definitions will also be used.

- Treatment-emergent depression defined a priori as a CDSS score ≥6.
- Abnormalities in physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with a clinical event that has already been reported.
- Worsening in the subject's symptoms of schizophrenia or new symptoms will be considered AEs.
- Symptoms of other psychiatric disorders will be considered AEs if they are new (not part of the subject's medical history) or if their severity and/or frequency are greater than those noted in the subject's medical history.
- Overdose: An overdose is defined as the ingestion of study drug beyond the dosing regimen defined in the study protocol and/or an overdose of any other product. An overdose, and any symptoms resulting from the overdose, are considered AEs and should be recorded. An overdose will be considered an SAE if it meets the definition of an SAE described in Section 6.2.1.2.
- Spontaneous complaints of dermal reactions (skin irritation, discomfort) will be recorded as AEs (see Section 6.2.6 for details). Spontaneous reports might include but are not limited to the following: initial dermal response and exacerbation of an existing response.

6.2.1.2 Serious Adverse Events

Definition of SAE: An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994). It should be noted that hospitalization for a pre-planned procedure or diagnostic tests is not considered an AE or SAE.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Potential Hy's Law cases should be reported via the SAE process. This is defined as:

- ALT or AST >3×ULN AND
- ALP <2×ULN AND
- Increase in bilirubin ≥2×ULN

The process for reporting SAEs is described in Section 6.2.1.5.

6.2.1.3 Categorization of Adverse Events

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

6.2.1.3.1 Severity

The severity of the AE will be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.

- Severe events interrupt the subject's usual daily activity.

6.2.1.3.2 Relationship

All efforts should be made to categorize an AE by its relationship to drug. The Investigator will determine the relationship of the AE to the study drug by using the following definitions.

Probable (must meet first 3 criteria): This category applies to those AEs which are considered, with a high degree of certainty, to be related to the test drug. An AE may be considered probable, if:

- It follows a reasonable temporal sequence from administration of the drug;
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias);
- It follows a known pattern of response to the suspected drug; and
- It reappears upon rechallenge.

Possible (must meet the first 2 criteria): This category applies to those AEs in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when:

- It follows a reasonable temporal sequence from administration of the drug;
- It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; and
- It follows a known pattern of response to the suspected drug.

Unlikely (must meet the first two criteria): In general, this category is applicable to an adverse event which meets the following criteria:

- It does not follow a reasonable temporal sequence from administration of the drug;
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- It does not follow a known pattern of response to the suspected drug; and
- It does not reappear or worsen when the drug is readministered.

Unrelated: This category is applicable to those AEs which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under unlikely, possible or probable.

6.2.1.4 Reporting of Adverse Events

All AEs, regardless of severity and when they occurred (any time after the ICF is signed and through the Follow-up Period), are to be recorded. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, relationship to study drug. Each event should be recorded separately.

6.2.1.5 Reporting of Serious Adverse Events

All SAEs will be recorded using the electronic data capture (EDC) system. The Investigator will be instructed to contact the Sponsor/designee for any questions on SAE reporting. Contact details will be provided per country, and per region (please refer to Study Manual for the appropriate information).

Urgent safety queries issued in EDC must be followed up and addressed within 1 business day. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up. In the event that the EDC system is unavailable, SAEs are to be reported by faxing/emailing the paper SAE Form to Quintiles using the appropriate fax number provided for each country or project safety mailbox.

6.2.1.5.1 Notification of Regulatory Authorities, Investigators, and Institutional Review Board/Independent Ethics Committee

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the site's knowledge of the event). Additional information will be available in the Study Manual.

The report will contain as much available information concerning the SAE to enable the Sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs during the 30 day follow-up period will be collected and reported as previously described.

6.2.1.5.2 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

Investigators will be notified by the Sponsor or Quintiles of all Serious Unexpected Adverse Event Reactions (SUSARs) that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or Quintiles.
The Sponsor or Quintiles will ensure that all SUSARs are reported to the appropriate regulatory authorities.

6.2.1.6 Follow-up of Adverse Events

All AEs will be followed up to resolution. However, AEs and SAEs that are ongoing at the subject's last study visit (i.e., discharge from the clinic at the end of the double-blind treatment period or early termination) will be followed until resolution or for 30 days after last dose of study drug, whichever comes first. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs and SAEs that occur during the 30 day follow-up period should be reported to the Sponsor or Quintiles.

6.2.1.7 Pregnancy and Contraception

It is important that female subjects and the partners of male subjects do not become pregnant during the study.

Instructions for Male Subjects

All male subjects should avoid fathering a child by the use of an effective means of contraception (see below), unless their partner is not of childbearing potential, i.e. postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

Male subjects (including men who have had vasectomies) whose partners are currently pregnant should use a condom for the duration of the study and for 1 month after the last patch is removed. This is to ensure that the fetus is not exposed to the drug product via the ejaculate.

Male subjects must not donate sperm for 3 months following the removal of the last patch. Males should continue using contraception for 1 month after the last patch is removed.

Instructions for Female Subjects

Female subjects must use contraception unless they are not of childbearing potential, i.e. postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy). Sexually active females of child-bearing potential must agree to use a medically accepted method of contraception during the study and for 1 month after the final dose of study medication. Female subjects must not donate eggs for 3 months after the last patch is removed.

Acceptable forms of contraception

- Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
- Established use of oral, injected or implanted hormonal methods of contraception;
- Established use of medically prescribed topically-applied transdermal contraceptive patch;
- Documented placement of an IUD or intra-uterine system (by female partner); and

- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

The Sponsor/designee must be notified within 24 hours of the site's knowledge of any subject who becomes pregnant while participating in a clinical study. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject which occurs during the study by using the Pregnancy form.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs.

6.2.2 Clinical Laboratory Evaluations

6.2.2.1 Clinical Laboratory Assessments

A central laboratory designated by the Sponsor will be used for all laboratory assessments during the trial. If an immediate result is required, a sample should be sent to both the local and central laboratory.

Urine samples and fasting blood samples will be collected from each subject as presented in Table 1 (Schedule of Events). The clinical laboratory parameters evaluated in this study are presented in Table 7.

Table 7 Clinical Laboratory Tests

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis: pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (performed only if any part of the urinalysis is not negative) Urine Drug Screens: [a] Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Opiates Phencyclidine Propoxyphene Additional Tests (screening only): HIV HbsAg [d] Anti-HCV [d] Blood alcohol [e]	Serum Chemistry: ALP ALT AST BUN CPK [f] Creatinine LDH Total bilirubin Triglycerides Cholesterol (total, LDL, and HDL) Calcium Chloride Glucose Insulin Magnesium Bicarbonate Inorganic phosphorus Sodium Potassium Total protein Uric acid GGT Prolactin [b] Albumin Additional Tests: Urine pregnancy (women of child-bearing capacity) [c] TSH (free T_4, if TSH is abnormal) HbA1c Alcohol breathalyzer test [g]

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = Hepatitis B antigen; HCV = Hepatitis C Virus; HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDH = lactic dehydrogenase; LDL = low density lipoprotein; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell count.

a. Urine drug screens may be done at the Investigator's discretion. If the subject is allowed to leave the unit, a urine drug screen must be done when the subject returns.

b. The central laboratory will not report prolactin levels to the sites nor the Sponsor, because this could potentially result in unblinding the treatment. The central laboratory will report prolactin levels as "masked" on the laboratory report. See Section 6.2.2.2.3 for additional information.

c. All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at Screening must not be enrolled. Subjects with positive urine and serum pregnancy test results during the trial must discontinue treatment and be withdrawn from the trial. If the subject is allowed to leave the unit, a urine pregnancy test must be done when the subject returns.

d. Subjects with chronic Hepatitis B or C may be included in the study provided that their condition is stable and that values for liver function tests and other laboratory tests results meet the criteria specified for entry into the study.

e. A serum blood sample will be collected to test blood alcohol level at the screening visit.

f. Reflex testing for urine myoglobin will be done in cases where CPK > 1000 U/L.

g. If the subject is allowed to leave the unit, an alcohol breathalyzer test must be done when the subject returns.

Clinical laboratory tests will be reviewed for results of potential clinical significance at each time point during the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

6.2.2.2 Monitoring of Selected Laboratory Values

6.2.2.2.1 Liver Enzymes

Subjects should be closely observed if they meet the definition of Hy's Law cases, defined as:

- ALT or AST >3×ULN AND
- Alkaline phosphatase (ALP) <2×ULN AND
- increase in bilirubin ≥2×ULN

If the subject's laboratory results meet these criteria, the subject should be evaluated and repeat or additional testing should be performed. Elevations in liver enzymes that require discontinuation of the subject are presented in Section 4.3.3. Potential Hy's Law cases should be reported as SAEs.

6.2.2.2.2 Neutrophil Counts

Subjects with an absolute neutrophil count of <1000 per mm^3 should have an additional test within 24 hours. If the values are not within normal limits or increasing, the subject will be discontinued from the study.

6.2.2.2.3 Prolactin

The central laboratory will not report the prolactin levels after baseline to the sites or Sponsor/designee, as this value could unblind the subject's treatment. The central laboratory will report prolactin levels as "masked" on the laboratory report. If an Investigator suspects hyperprolactinemia (due to symptoms or signs that could be attributed to a high prolactin level), a blood sample should be taken and sent to the central laboratory. Blood samples for prolactin levels should not be sent to the local laboratory.

If a subject's serum prolactin level is >10×ULN, the site will be notified by the central laboratory and the Investigator will do a repeat blood draw within 3 days. If the subject's prolactin level is still >10×ULN, the Investigator should consider other possible causes of hyperprolactinemia (e.g., primary hypothyroidism, chronic renal failure, cirrhosis, use of drugs [opiates, estrogens, cimetidine, etc.], pregnancy for female subjects).

If the laboratory requests a prolactin re-test, a "dummy" request will be sent for another subject at the same clinical site and the subject will be selected randomly in order to preserve the blind. Such cases will be discussed with the study Medical Advisor.

The Medical Advisor and site will remain blinded to the subject's treatment allocation.

6.2.3 Vital Signs, Physical Findings and Other Safety Assessments

Height will be recorded at Screening, only. Weight will be recorded at each visit. A complete physical examination including examination of the head, neck, ears and throat, thorax, abdomen, urogenital, extremities, neurological, and skin and mucosae will be performed at Screening and at end of study. Abnormal physical examination findings at the Screening will be recorded as medical history and abnormal physical examinations findings at subsequent visits will be recorded as AEs.

Vital sign measurements will include temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Blood pressures (sitting) and pulse rates should be measured after subject has rested (sitting quietly) for 5 minutes.

In addition, assessments for orthostatic hypotension will be performed. Blood pressure readings and pulse rate will be obtained after the subject has been supine for 5 minutes. These will be repeated after the subject has been standing up for approximately 1 to 3 minutes.

Subjects with a decrease of ≥30 mmHg in SBP and/or a decrease of ≥20 mmHg in DBP after ≥3 minutes standing compared with the previous supine blood pressure, OR development of symptoms are considered to have orthostatic hypotension.

Twelve-lead ECGs will be recorded at Screening and at the visits specified in Table 1. An ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the Investigator's discretion and should always be obtained if the subject discontinues the study. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. The Investigator or designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered by the Investigator to be clinically significant.

6.2.4 Evaluation of Extrapyramidal Symptoms (EPS)

The rater who administers the EPS scales must be trained and experienced. Raters will be trained to administer these scales. The number of raters should be kept to a minimum and all efforts should be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings.

6.2.4.1 Simpson Angus Scale (SAS)

The SAS[11] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms, and a score of 4 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Table 5). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the

SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration. A copy of the scale is included in Appendix 7 (Section 17.0).

6.2.4.2 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[8] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (e.g., in the waiting room), and the Investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Table 5). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration. The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (i.e., items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements). A copy of the scale is presented in Appendix 8 (Section 18.0).

6.2.4.3 Barnes Akathisia Rating Scale (BARS)

The BARS[12] consists of 4 items related to akathisia. These include objective observation of akathisia by the Investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (e.g., while engaged in neutral conversation or engaged in activity on the ward) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Table 5). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration. The BARS Global Score is defined as the global clinical assessment of akathisia. A copy of the scale is presented in Appendix 9 (Section 19.0).

6.2.5 Suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the trial using the C-SSRS.[13] The C-SSRS facilitates prospective, systematic monitoring for emergence of suicidality within clinical trials and it is a low-burden, clinician-administered tool that covers the wide spectrum of suicidality from ideation to behavior. A training tool will be supplied to the site by the Sponsor for use by staff members that have not had C-SSRS training within the past 2 years. The site will document training of selected staff members and file the training certificates in the trial master file.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at the Screening and Baseline visits to determine eligibility (prior to the first dose). Any subject with suicidal ideation within the last 6 months or suicidal behavior within the past 12 months or who in the clinical judgment of the Investigator presents a serious risk of suicide should be excluded from the study. Subjects will also be excluded if they report suicidal ideation or suicidal behavior at Baseline. The "Since Last Visit" C-SSRS form will be completed at all post-Screening visits. A copy of the scale is presented in Appendix 10 (Section 20.0).

6.2.6 Evaluations of Patch and Dermal Assessments

Each subject will wear 2 patches simultaneously; both patches will be applied in close proximity without overlapping to 1 application site. Dermal assessments for both patches will be assessed but only the worse of the 2 scores will be recorded. Dermal assessments will be conducted as follows:

- Patch adhesion will be evaluated throughout the day including at the time points during which the site staff collects routine vital signs as per hospital policy/SOP; and immediately prior to removal of previous day's patch. In addition, subjects will be asked to check patch adhesion throughout the day and report immediately to site personnel if the patch detaches completely or detaches partially (i.e., some edges of the patch are lifting off the skin).
- Irritation at the site of patch application will be assessed each day between 30 and 60 minutes after patch removal.
- Subjects will be asked to report to the site staff any discomfort or skin irritation due to patch. Discomfort and skin irritation reported by the subjects will be recorded as AEs.
- Once a week, after removal of the patch, site personnel will assess patch application sites for adhesive residue.

Spontaneous complaints of dermal reactions will be recorded as AEs. Spontaneous reports might include but are not limited to the following: initial dermal response and exacerbation of an existing response.

The actual time of all scheduled and unscheduled evaluations will be recorded.

Skin irritation at patch application site

Thirty to 60 minutes after patch removal site personnel will conduct a visual inspection of the skin at the patch application site and will record any irritation observed using the descriptors provided in the Berger and Bowman scale[14] presented in Table 8. The investigator will assess any irritation observed at the patch application site as clinically significant or not clinically significant.

In addition, spontaneous reports of skin irritation by the subject will be recorded as an AE. If a subject reports skin irritation, then site personnel will conduct visual inspection of the skin at the application site and will record the description of the observed skin irritation using the descriptors provided in the Berger and Bowman scale[14] presented in Table 8.

Table 8 Skin Irritation Descriptors

Observation
No evidence of irritation
Minimal erythema (barely perceptible)
Definite erythema, readily visible; minimal edema, or minimal papular response
Erythema and papules
Definite edema
Erythema, edema, and papules
Vesicular eruption
Strong reaction spreading beyond test (application) site
Slightly glazed appearance
Marked glazed appearance
Glazing with peeling and cracking
Glazing with fissures
Film of dried serous exudates covering all or part of the patch site
Small petechial erosions and/or scabs

Discomfort at patch application site

Report of discomfort at the patch application site will be recorded as an AE. If a subject reports discomfort at the patch application site, the site personnel will ask the subject to rate the discomfort as mild, moderate, or severe, and will ask the subject to describe the discomfort. The description of discomfort as reported by the subject should be recorded verbatim.

Patch adhesion

Patch adhesion will be assessed by site personnel at the time points defined in the Schedule of Events (Table 1). Adhesion will be evaluated according to Yes/No questions as follows:

1. Is the patch fully attached to the skin? Yes/No
2. If 'No', did the patch detach completely? Yes/No

- If "Yes" and the patch/patches are completely detached, the time and activity at the time of patch detachment will be documented.
  - If both patches are detached completely, then two new patches from the subject's kit should be applied immediately, provided that there is at least 6 hours of time remaining before the next dose;
  - If only one patch detaches completely, then the other patch should also be removed and two new patches from the subject's kit should be applied immediately, provided that there is at least 6 hours of time remaining before the next dose;
  - Under no circumstances should the detached patches be reapplied to the subject; and
  - Regardless of what time the new patches are applied, patch removal time of the new patches will be approximately 24 hours after the application of the original patches. In other words, removal time of the new patches may not exceed 24 hours from the time the first patches were applied.
- If "No" and partial patch detachment (i.e., some edges of the patch are lifting off the skin) is observed then the site personnel/subject should smooth the patch down such that the complete patch is in contact with the skin again.

In addition to patch adhesion assessments by site personnel at specified time points, subjects should be instructed to should check adhesion of the patch throughout the day and report to site personnel immediately if patch detaches completely or if partial patch detachment is observed.

Adhesive Residue

Once a week, immediately after the removal of a patch, the amount of adhesive residue remaining at the application site will be examined by site personnel and graded as described in Table 9.

Table 9 Adhesive Residue Scale

Adhesive Residue	
Score	**Definition**
0	None
1	Light
2	Medium
3	Heavy
4	Patch not present

6.3 Pharmacokinetics

6.3.1 Pharmacokinetic Blood Sampling

At least 3 blood samples will be collected at 2, 14, and 22 hours after application of the patch with ± 2 hour window on Day 21 and 42. Actual blood sampling time will be recorded.

Blood will be obtained for the determination of asenapine and selected metabolites in human plasma as per the instructions provided by the laboratory.

The samples obtained for PK analysis may be used for analysis of other metabolites in the future. The potential future analysis will be limited to the analysis of study drug metabolites.

A model-based approach including population PK analysis will be used to assess the impact of covariates on asenapine exposure and to explore the exposure-response relationship of relevant endpoints. The detailed methodologies and results will be presented in a separate PK analysis report.

6.3.2 Drug Concentration Measurements

The bioanalysis of asenapine and desmethyl-asenapine in plasma samples will be performed using a liquid chromatography tandem mass spectrometry method. The bioanalytical methodology and procedures will be documented in a Bioanalytical Study Plan. The Bioanalytical Report will be included in a separate PK analysis report.

Other asenapine metabolites might be assessed using remaining plasma samples in a separate analysis study if deemed necessary.

6.4 Appropriateness of Measurements

The efficacy assessments used in this study are standard and validated instruments in this population. The safety assessments include standard measures (hematology, clinical chemistry [including prolactin levels], and urinalysis), vital signs, ECGs and physical examination findings and dermal adverse events.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the Sponsor/designee is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs). This study will be conducted following Quintiles SOPs.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s);
- Central laboratories for clinical laboratory parameters and ECGs;
- Center Initiation visit;
- Early center visits post-enrollment;
- Routine center monitoring;

- Ongoing center communication and training;
- Data management quality control checks;
- Continuous data acquisition and cleaning;
- Internal review of data; and
- Quality control check of the final clinical study report.

In addition, Sponsor and/or Quintiles Clinical Quality Assurance Department may conduct periodic audits of the study processes, including, but not limited to study center, center visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be granted for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

The Sponsor has engaged the services of a contract research organization (CRO), Quintiles, to perform all monitoring functions within this clinical study. Noven representatives, or their designees, will conduct visits to the clinical sites to monitor the various aspects of the study. The Investigator agrees to allow these monitors and other authorized Noven personnel, including quality assurance monitors, access to the clinical supplies, dispensing and storage area, and clinical files of the study subjects, and agrees to assist the Noven personnel in their activities, if requested. Study sites are also subject to inspection by Food and Drug Administration (FDA) representatives or other regulatory authorities. The Investigator agrees to assist such inspectors in their duties.

Prior to each monitoring visit, the Investigator or designee should record all data generated since the last visit on the electronic case report forms (eCRFs). The Investigator and site staff will be expected to cooperate with the monitor, and to be available during at least a portion of the monitoring visit to sign eCRFs, answer questions, and to provide any missing information.

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of Quintiles.

Subjects will be enrolled in the study and randomized to a study treatment using the IVRS/IWRS. The IVRS/IWRS and eCRF are validated real-time systems and are compliant with *Guidance for Industry, Part 11, electronic records; Electronic Signatures – Scope and Application; Computerized Systems Used in Clinical Investigations; General Principles of Software Validation; Final Guidance for Industry and FDA Staff*.

Electronic Data Capture will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and

security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects. Data management will be conducted under Quintiles SOPs.

All data must be entered in English. The eCRFs should always reflect the latest observations.

The eCRF is considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Any data captured electronically will be pre-specified in the data management plan. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the Study Monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events, medical history, and concomitant diseases will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Concomitant medications will be coded using the World Health Organization drug dictionary.

7.3 Quality Assurance Audit

Study centers, the study database, and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or Quintiles. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICAL METHODS

8.1 Determination of Sample Size

Assuming an effect size of 0.35 on the change in PANSS total score from baseline to Week 6 for the 2 pairwise comparisons between each active HP-3070 treatment arm and placebo, the power for detecting a statistically significant HP-3070 advantage will be approximately 0.90 having 204 evaluable subjects per each treatment arm using a 2-side alpha level of 0.025 for each comparison. A 2-sided overall Type I error is equal to 0.05. Having 3 treatment arms, the total number of subjects randomized in the trial and included in primary analysis set will be approximately 612. A sufficient number of subjects will be screened to randomize the proposed sample size.

The effect size of 0.35 was chosen based on the lowest effect size observed in results from the studies conducted with SL asenapine and approved by FDA (Sycrest®/SAPHRIS® [Study 041004, and Study 041023]).

8.2 Sample Size Recalculation

Sample size recalculation (SSR) will be conducted on the blinded data after approximately 50% of the desired number of patients have been randomized and completed up to 6 weeks of study treatment. This SSR will be directed and conducted by an independent statistician from Quintiles, who is not involved in the trial conduct other than this SSR.

The purpose of this SSR is to assess the assumption made regarding the sample size calculation for the primary endpoint. No other information will be generated.

This SSR will NOT be conducted with an intention of decreasing the original sample size or stopping the trial early. There will be no Type I error adjustment due to this SSR.

8.2.1 Procedures for Sample Size Recalculation

The expected common (pooled) standard deviation is 20, which corresponds to a difference in means of 7 for our assumed effect size of 0.35. Using the transferred blinded data, the independent statistician will calculate the following metrics for the primary endpoint (PANSS Total Score):

- The common (pooled) SD

Using these metrics and the original assumptions of mean difference in reduction of PANSS scores from Baseline to Week 6, between treatment arms Type I error rate (0.025) and 90% power of the new sample size will be recalculated. More details, including decision rules and maximum increase in sample size, are available in the Statistical Analysis Plan (SAP). The independent statistician will provide a report which will include the following:

- Re-estimation of sample size
- The common SD for the primary endpoint

Based on the documented SSR and the observed dropout rate, the independent statistician may recommend a new sample size to be sent to the Sponsor for final decision.

8.3 Study Endpoints

8.3.1 Primary Analyses Endpoint

The primary efficacy endpoint is the change in PANSS total score between Baseline and Week 6.

8.3.2 Key Secondary Analysis Endpoint

The key secondary endpoints is:

- To evaluate the efficacy of HP-3070 compared with placebo for the treatment of schizophrenia as evaluated by change in Clinical Global Impression – Severity of Illness Scale (CGI-S) scores between Baseline and Week 6

8.3.3 Other Secondary Analyses Endpoints

The other secondary endpoints include:

- Change from Baseline in PANSS total score at each time point in addition to Week 6;
- Change from Baseline in CGI-S at each time point in addition to Week 6;
- CGI-I score at each time point;
- The proportion of CGI-I responders at each time point including Week 6; CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved);
- Change from Baseline in positive, negative, and general pathology subscores of PANSS at each time point;
- Proportion of PANSS responders; PANSS responders are defined as subjects who have a ≥30% reduction in PANSS total score between Baseline and at each time point including Week 6;
- Change from Baseline in CDSS score at each time point; and
- MSQ score at each time point.

8.3.4 Exploratory Endpoint

A model-based approach will be used to assess the impact of covariates on asenapine exposure and to explore the exposure-response relationship with relevant endpoints.

8.4 Statistical Methods

All analyses, summaries, and listings will be performed using SAS® software (Version 9.2 or higher).

Baseline characteristics, efficacy and safety data will be summarized using the appropriate descriptive statistics.

For the efficacy variables, descriptive statistics (including n, SD, mean, minimum, maximum, and 95% CI) for the changes from Baseline during the 6-week treatment period will be presented.

Continuous variables will be summarized by descriptive statistics (sample size [n], mean, SD, median, minimum, and maximum). Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Individual subject data will be presented in listings.

All statistical tests of treatment effects will be performed at a 2-sided significance level of 0.05, unless otherwise stated.

Additional details concerning statistical methods are presented in the SAP.

All references to study medication refer only to the double-blind treatment period.

8.4.1 Analysis Populations

Four analysis sets will be used in analyzing the data obtained from this protocol:

Intent-to-Treat (ITT): includes all consented and randomized subjects. Regardless of any protocol deviations, analyses performed on the ITT set will be based on the randomized treatment assignment and all available data.

Full Analysis Set (FAS): includes all consented and randomized subjects who have had at least 1 patch of double-blind study medication applied and who have a Baseline PANSS total score and at least 1 post-Baseline assessment of the primary efficacy measure (PANSS total score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.

Safety Analysis Set (SAF): includes all subjects who have had at least 1 patch of double-blind study medication applied and who have at least 1 post-dose safety measurement during the double-blind treatment period. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the SAF will be based on treatment actually received. The SAF will be used for the analysis of dermal evaluations and safety endpoints.

Pharmacokinetic Analysis Set (PAS): includes all subjects who have received at least 1 dose of study medication during the double blind treatment period and have at least 1 blood sample for PK assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may

influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model based approach. Excluded cases will be documented together with the reason for exclusion.

8.4.2 Primary Efficacy Analysis

The primary efficacy analysis (the analysis of the primary variable) will be performed on the Full Analysis Set (FAS).

The primary efficacy variable, change from Baseline to Week 6 in the PANSS total score for each of the 3 treatment arms, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in PANSS total score as the repeated dependent variable, with country, treatment (HP-3070-9.0 [9.0 mg], HP-3070-18.0 [18.0 mg], and placebo), visit, treatment by visit interaction, and the Baseline PANSS total score as covariates. An unstructured covariance matrix will be assumed. In the event the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order (from least to most restrictive): heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive (1) (ARH[1]), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0[q], with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive (1) (AR[1]), and compound symmetry (CS). If either ARH(1) or AR(1) structure is used, a random subject intercept will also be included in the model.

The MMRM model may be repeated on additional analysis sets as a sensitivity analysis.

If the normality assumption is violated, ANCOVA analysis on rank-transformed data will be used as a supportive analysis.

8.4.3 Key Secondary Efficacy Analysis

Change from Baseline to Week 6 in the CGI-S scores will be assessed using the same MMRM model used for the change in PANSS scores.

Each study drug dose will be compared with placebo and model-based point estimates for the treatment effects, 95% confidence intervals (CIs), and p-values will be calculated. The analysis set will be the FAS.

In order to control the family-wise Type I error rate, the Hochberg-based matched parallel gatekeeping procedure will be used to account for multiple doses and multiple primary and key secondary endpoints.

The primary and key secondary efficacy hypotheses will be grouped into 2 hierarchical families. Family 1 is the HP-3070-9.0 versus placebo (Hypothesis 1) and HP-3070-18.0 versus placebo (Hypothesis 2), based on the primary endpoint of change from baseline in PANSS total score at Week 6. Family 2 is HP-3070-9.0 versus placebo (Hypothesis 3) and HP3070-18 versus placebo (Hypothesis 4), based on the key secondary endpoint of change from Baseline in CGI-S at Week 6.

The matched parallel gatekeeping procedure performs multiplicity adjustments as follows:

1. The comparisons for the primary endpoint (Hypotheses 1 and 2) are performed using a truncated Hochberg procedure (gamma = 0.9).
2. The comparisons for CGI-S (Hypotheses 3 and 4) corresponding to the doses that were significant in Step 1 are performed, using a regular Hochberg procedure.

Further details are provided in the SAP.

8.4.4 Other Secondary Efficacy Analyses

The same statistical model will be used for the analysis for the change from Baseline in the PANSS subscales, CDSS, CGI-S, and the scores for CGI-I, and MSQ at each assessment.

The differences in proportions of CGI-I, and PANSS responders will be analyzed using the Cochran-Mantel-Haenszel Test.

Details are provided in the SAP.

8.4.5 Subgroup Analyses

Details of subgroup analyses for primary and key secondary objectives are described in the SAP.

8.4.6 Safety Analyses

Safety analyses will be performed on the Safety Analysis Set (SAF).

Scores for C-SSRS, SAS, BARS, and AIMS will be summarized for each treatment arm using descriptive statistics at each visit for raw numbers and change from baseline values.

Adverse events will be coded using MedDRA. The collection of AEs will begin after the subject has signed the ICF. The TEAEs during the double-blind treatment period are defined as AEs with onset date on or after the start of study medication through the 30 day follow-up period, or AEs with onset prior to the first dose of study medication and with an increase in severity after the start of study medication through the 30 days follow-up period. The same rule applies for Run-in Period.

For each study treatment, numbers of events and incidence rates will be tabulated by preferred term and system organ class. Adverse events will be summarized separately for the Screening/Run-in Period and Double-blind Treatment Period. Adverse events will be summarized by severity and relationship to drug. If the subject has the same AE on multiple occasions, the summary will reflect the maximum severity or closest relationship reported.

The SAEs, including death as an outcome, and AEs leading to withdrawal of subjects will be tabulated for each treatment arm. Commonly occurring AEs, i.e., those which occur in 5% or more of the subjects in any treatment arm will be summarized using descriptive statistics.

All laboratory test results, vital signs measurements, ECG results, weight, and body mass index will be summarized for each treatment arm using descriptive statistics at each visit for raw numbers and change from baseline values.

Patch adhesion and adhesive residue assessment results will be summarized at each visit by treatment arm, and by treatment arm overall.

The results of the PK analyses will be presented in a stand-alone report.

8.4.7 Data to be Analyzed

Data handling will be the responsibility of Quintiles. The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the SAP prepared by Quintiles and approved by the Sponsor before database lock.

The statistical analysis will be performed by Quintiles. After database lock, the final SAS data sets in SDTM and ADaMs formats will be transferred to Noven with SAS programs and all supportive documentation.

8.4.8 Missing Data

MMRM is the best method to control Type I error rate and minimize bias in the presence of missing data, although this does not fully overcome the issues and assumptions are still required to be made regarding the missing data mechanisms. Nevertheless, in the presence of a high dropout rate performance of sensitivity analysis is critical. The purpose of sensitivity analysis is to explore whether different analyses under different sets of missingness assumptions provide robust efficacy results. The sensitivity analysis will be performed on primary endpoints. The extent to which efficacy results are stable across such an analysis provides confidence in the statistical conclusions.

- Missing data can be considered to be missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR) according to the National Academy of Sciences (2010). Details are provided in the SAP.

8.5 Subject Disposition and Characteristics

The disposition summary will include all enrolled subjects. Subject characteristics will be obtained at Screening and will be summarized for all subjects. Summaries will include descriptive statistics for continuous variables (sample size, mean, and SD, median, minimum, and maximum) and for categorical variables (sample size, frequency and percent). Subject characteristics may include, but are not limited to: age, gender, race/ethnicity, height, weight, and body mass index.

8.6 Safety

Safety variables will be summarized based on the SAF.

8.6.1 Adverse Events

The TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of the study drug. Adverse event summaries will include incidence of TEAEs by MedDRA preferred term and system organ class, SAEs (including deaths), AEs that led to study drug discontinuation, AEs by severity, and AEs by relationship to study drug.

8.6.2 Clinical Laboratory Evaluations

Laboratory assessments will be presented as mean changes from Baseline and incidence of abnormal values. Shift tables will be presented for selected parameters. Of special interest are prolactin levels, fasting glucose, and lipids.

8.6.3 Vital Signs Measurements, Physical Findings and Other Safety Evaluations

Descriptive statistics for the change from Baseline will be summarized at each visit for C-SSRS, SAS, BARS, and AIMS.

Mean changes from Baseline and incidence of treatment-emergent abnormal vital signs, weight, and ECG results will be summarized. The number and proportion of subjects with orthostatic hypotension will also be summarized.

8.6.4 Dermal Evaluations

Data for patch adhesion and adhesive residue assessment will be presented and summarized at each visit by treatment arm, and by treatment arm overall. Data for skin irritation and discomfort will be presented as TEAEs.

8.7 Pharmacokinetic Analyses

Plasma asenapine and desmethyl asenapine concentrations will be analyzed and listed.

A model-based approach will be used to assess the impact of covariates on asenapine exposure and to explore the exposure-response relationship of relevant endpoints. Details on the methodology of population PK model development, exposure-response analysis and model-based simulations will be included in a standalone PK report.

8.8 Interim Analyses

No interim analysis for efficacy is planned.

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or Quintiles with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to the Sponsor/designee before enrollment of any subject into the study.

Sponsor/designee should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor or Quintiles of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the Ethics Committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (48th General Assembly, Somerset West, Republic of South Africa, October 2008 [or current version]), the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety, and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated consent form.

9.4 Study Administration

9.5 Administrative Structure

Central organizations used for the conduct, monitoring, and/or evaluation of this trial are provided on the Contact List.

A Medical Advisor will be made available to every Investigator as designated by the Sponsor. The central and regional Medical Advisors will consult with sites on general eligibility questions, subject safety, protocol conduct, compliance, as well as additional tasks specified in the protocol. The Medical Advisor will also work closely with the local clinical and safety teams designated by the Sponsor. The administrative structure is presented in Table 10.

Table 10 Administrative Structure

Data Management Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703	**Biostatistics** Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703
Medical Writing Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703	**Clinical Manager** Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703
Medical Advisor Elena Vlad, MD, Psych, PhD Medical Director, Medical and Scientific Services Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703	**Clinical Safety** Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703
Electronic Data Capture Oracle Health Sciences Global Business Unit 77 Fourth Avenue Waltham, MA 02451 ERT (eResearch Technology) 1818 Market Street, Suite 1000 Philadelphia, PA 19103	**Clinical Research Organization** Quintiles, Inc. 4820 Emperor Drive Durham, NC 27703
Scale Management and Training ProPhase, LLC. 3 Park Avenue, 28th & 37th Floor New York, NY 10016 ERT (eResearch Technology) 1818 Market Street, Suite 1000 Philadelphia, PA 19103	**Central ECG reading** Quintiles Data processing Centre (India) Pvt. Ltd. 502-A, Leela Business Park, M.V.Road, Andheri-(East), Mumbai-400059 India Quintiles Data processing Centre (India) Pvt. Ltd. Third Floor, Etamin Block, Prestige Technology Park II, Bellandur, Sarjapur-Marathahalli outer Ring road, Banglore-560103, Karnataka India
IVRS/IWRS Cenduit, LLC 4825 Creekstone Drive Suite 400 Durham, NC 27703	**Central Laboratory** Q^2 Solutions 27027 Tourney RoadSuite 2E Valencia, CA 91355
Model Based Analysis Metrum Research Group, LLC 2 Tunxis Rd., Suite 112, Tariffville, CT 06081	**Bioanalytic Lab** Q^2 Solutions 19 Brown Rd Ithaca, NY 14850

9.6 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents

until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor.
The Investigator must contact Sponsor prior to disposing of any study records.

9.7 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, Quintiles, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

9.8 Investigator Information

9.8.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997; the US CFR Title 21 parts 50, 56, and 312; and European Legislation); and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

9.8.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

9.8.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

9.9 Financing and Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. The terms of the insurance will be kept in the study files.

10.0 REFERENCES

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HP-3070-GL-04
HP-3070

11.0 APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia

PROTOCOL NO: HP-3070-GL-04

This protocol is a confidential communication of Noven. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Noven Pharmaceuticals, Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Quintiles, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Noven Pharmaceuticals, Inc.
HP-3070-GL-04
HP-3070

12.0 APPENDIX 2: POSITIVE AND NEGATIVE SYNDROME SCALE (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? _____

SCI–PANSS BOOKLET

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.

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? _____

SCI–PANSS BOOKLET

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.

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? _____

SCI–PANSS BOOKLET

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? _____

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? _____

SCI–PANSS BOOKLET

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. _____

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.

SCI–PANSS BOOKLET

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.)? _____

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:

_____

_____

_____

_____

SCI–PANSS BOOKLET

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 _____

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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PANSS

Positive and Negative Syndrome Scale

Stanley R. Kay, Ph.D.
Lewis A. Opler, M.D., Ph.D.
Abraham Fiszbein, M.D.

Rating Criteria

MHS

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Positive Scale (P)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

Negative Scale (N)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

General Psychopathology Scale (G)

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

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

Supplementary Items for the Aggression Risk Profile

S1. Anger. Subjective state of displeasure and irritation directed at others. *Basis for rating:* verbal report of angry feelings during the course of the interview and, thereupon, corresponding hostile behaviors observed during the interview or noted from reports by primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Expresses some irritation or ill feelings toward others but, otherwise, shows no emotional or behavioral signs of anger.
4	Moderate	Presents an overtly angry exterior, but temper remains under control.
5	Moderate Severe	Patient appears highly irritable, and anger is vented through frequently raised voice, occasional verbal abuse, or thinly veiled threats.
6	Severe	Patient appears highly irritable, and anger is vented through repeated verbal abuse, overt threats, or destructiveness.
7	Extreme	An explosive level of anger is evidenced by physical abuse directed or attempted at others.

Supplementary Items for the Aggression Risk Profile

S2. Difficulty in delaying gratification. Demanding, insistent that needs be satisfied immediately, and noticeably upset when fulfillment of needs or desires is delayed. *Basis for rating:* observation of behavior during the course of the interview as well as reports from primary care workers or family.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Patient is occasionally demanding and impatient but settles down quickly when spoken to.
4	Moderate	Demanding behavior occurs more than just occasionally or else has an insistent quality that makes the patient a "nuisance." No outbursts of hostility, however, typically follow, and the patient ordinarily can be managed without difficulty.
5	Moderate Severe	Demanding behavior is both frequent and persistent, resulting in occasional confrontations with other patients, staff, or family. As a rule, however, the patient regains control without serious incident.
6	Severe	Patient gets seriously upset whenever needs or demands are not met immediately. Explosive or violent behavior may once or twice ensue, and loss of control is an ever-present possibility.
7	Extreme	The failure to instantly cater to the patient's needs or demands tends to provoke explosive, violent, or impulsive behavior. Close supervision is typically required.

Supplementary Items for the Aggression Risk Profile

S3. Affective lability. Emotional expressions are unstable, fluctuating, inappropriate, and/or poorly controlled.
Basis for rating: affective state observed during the course of the interview.

	Rating	Criteria
1	Absent	Definition does not apply.
2	Minimal	Questionable pathology; may be at the upper extreme of normal limits.
3	Mild	Some incongruous affective responses are observed or a few unexplained shifts in emotional tone may occur.
4	Moderate	Affect is frequently incongruent with thoughts (e.g., inappropriate silliness, anger, or worry), or there are several radical changes in emotional tone during the course of the interview.
5	Moderate Severe	Emotional expressions are highly unstable and occasionally seem beyond the patient's control. The affective picture may show sudden shifts to the extremes, with generally poor modulation.
6	Severe	Emotions appear to be uncontrolled during most of the interview and may be dominated by autistic or irrelevant stimuli. The affective state takes on a fleeting quality, with peculiar or kaleidoscopic changes. Primitive emotional discharge, e.g., displays of ecstasy or rage, may be seen.
7	Extreme	Patient seems to lack any control over his or her emotional state, which fluctuates freely in response to inappropriate external or internal events. Extreme emotional states, such as excitement or fury, at times dominate.

Patient Name or ID: _____ Rater: _____ Date: ___ / ___ / ___

PANSS QuikScore™ Form

- P1. Delusions
- P2. Conceptual disorganization
- P3. Hallucinatory behavior
- P4. Excitement
- P5. Grandiosity
- P6. Suspiciousness/persecution
- P7. Hostility
- N1. Blunted affect
- N2. Emotional withdrawal
- N3. Poor rapport
- N4. Passive/apathetic social withdrawal
- N5. Difficulty in abstract thinking
- N6. Lack of spontaneity and flow of conversation
- N7. Stereotyped thinking
- G1. Somatic concerns
- G2. Anxiety
- G3. Guilt feelings
- G4. Tension
- G5. Mannerisms and posturing
- G6. Depression
- G7. Motor retardation
- G8. Uncooperativeness
- G9. Unusual thought content
- G10. Disorientation
- G11. Poor attention
- G12. Lack of judgment and insight
- G13. Disturbance of volition
- G14. Poor impulse control
- G15. Preoccupation
- G16. Active social avoidance
- S1. Anger
- S2. Difficulty in delaying gratification
- S3. Affective lability

Use this scale for all items:

1 = Absent
2 = Minimal
3 = Mild
4 = Moderate
5 = Moderate/ Severe
6 = Severe
7 = Extreme

MHS

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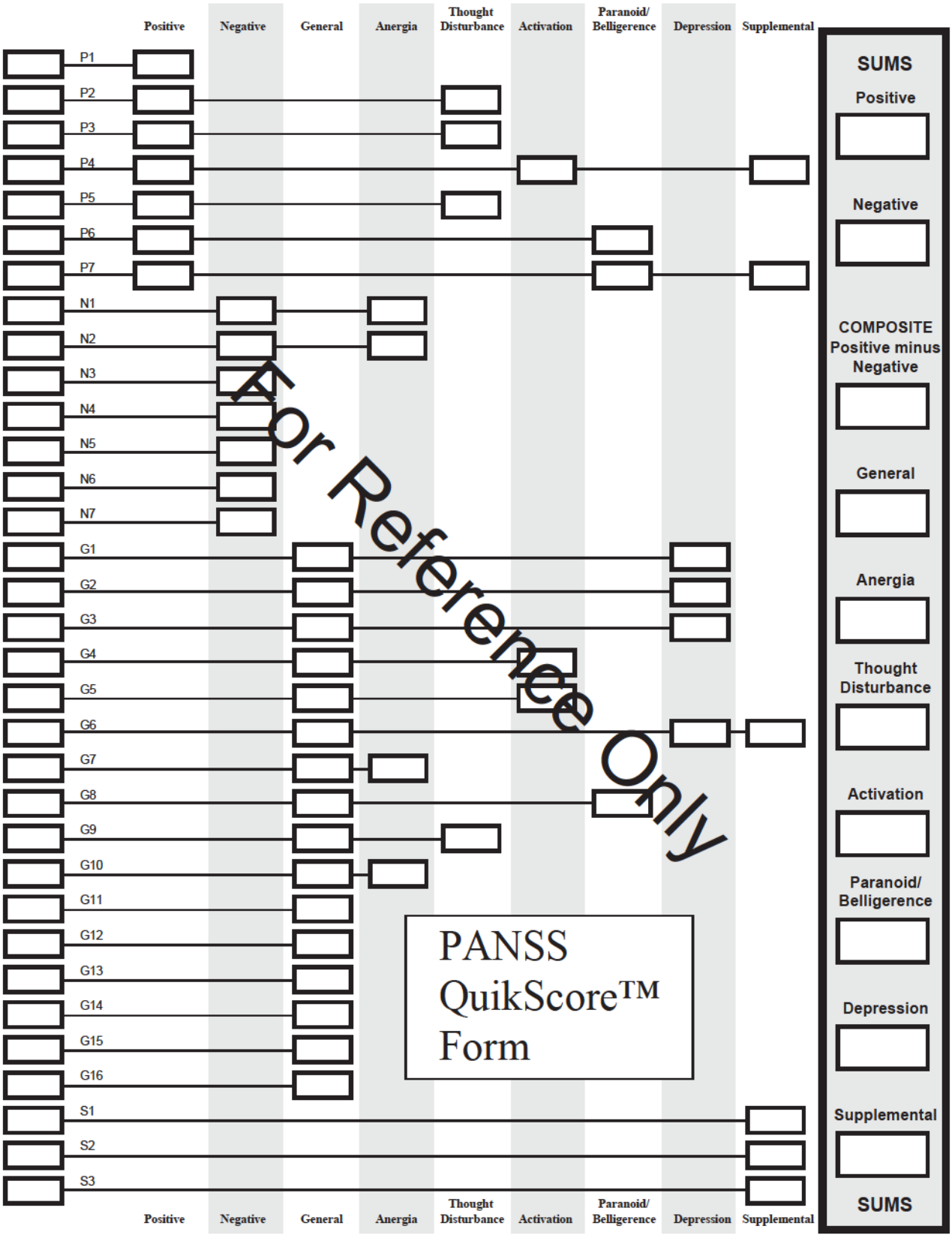
In Canada, 3770 Victoria Park Avenue, Toronto, ON M2H 3M6, (800) 268-6011.
Internationally, +1-416-492-2627.
Fax, +1-416-492-3343 or (888) 540-4484.

Patient Name or ID: _____ Rater: _____ Date: ___ / ___ / ___



Positive and Negative Syndrome Scale (PANSS) Profile Form

Patient Name or ID: _____ Rater: _____ Date: ___ / ___ / ___

%ile	T	Positive	Negative	Composite	General Psychopath.	Anergia	Thought Disturbance	Activation	Paranoid/ Belligerence	Depression	T	%ile
99	100+			37+	87+	27+		20+		27+	100+	99
99	99			36	86						99	99
99	98			35	85	26		19		26	98	99
99	97				84						97	99
99	96	49		34	83				21		96	99
99	95	48		33	82	25				25	95	99
99	94		49	32	81			18			94	99
99	93	47			80				20		93	99
99	92	46	48	31		24				24	92	99
99	91		47	30	79						91	99
99	90	45		29	78			17			90	99
99	89	44	46	28	77	23			19	23	89	99
99	88				76						88	99
99	87	43	45	27	75			16		22	87	99
99	86		44	26	74	22			18		86	99
99	85	42		25	73						85	99
99	84	41	43		72		28			21	84	99
99	83		42	24	71	21		15	17		83	99
99	82	40		23	70		27				82	99
99	81	39	41	22	69					20	81	99
99	80			21	68	20	26				80	99
99	79	38	40		67			14	16		79	99
99	78		39	20	66					19	78	99
99	77	37		19	65	19	25				77	99
99	76	36	38	18	64				15		76	99
99	75		37		63		24	13		18	75	99
99	74	35		17	62	18					74	99
99	73	34	36	16			23				73	99
99	72			15	60				14	17	72	99
99	71	33	35	14	60	17	22	12			71	99
98	70		34		59						70	98
97	69	32		13	58		21		13	16	69	97
96	68	31	33	12	57						68	96
96	67		32	11	56		20	11		15	67	96
95	66	30			55				12		66	95
93	65	29	31	10	54	15					65	93
92	64			9	53		9			14	64	92
90	63	28	30	8	52			10			63	90
89	62		29		51	14	8		11		62	89
86	61	27		7	50					13	61	86
84	60	26	28	6	49		17	9			60	84
82	59			5	48	13			10		59	82
79	58	25	27	4	47		16			12	58	79
76	57	24	26		46						57	76
73	56			3	45	12	15	8			56	73
69	55	23	25	2	44				9	11	55	69
66	54		24	1	43		14				54	66
62	53	22				11					53	62
58	52	21	23	0	42			7	8	10	52	58
54	51			-1	41		13				51	54
50	50	20	22	-2	40	10					50	50
46	49	19	21	-3	39		12		7	9	49	46
42	48				38			6			48	42
38	47	18	20	-4	37	9	11				47	38
35	46		19	-5	36					8	46	35
31	45	17		-6	35		10		6		45	31
27	44	16	18		34	8		5		7	44	27
24	43			-7	33		9				43	24
21	42	15	17	-8	32				5		42	21
18	41	14	16	-9	31	7	8			6	41	18
16	40			-10	30			4			40	16
14	39	13	15		29				4		39	14
12	38		14	-11	28	6	7			5	38	12
10	37	12		-12	27			3			37	10
8	36	11	13	-13	26		6				36	8
7	35				25	5			3	4	35	7
6	34	10	12	-14			5				34	6
5	33	9	11	-15	24						33	5
4	32			-16	ô23	4	4				32	4
3	31	ô8	ô10								31	3
2	30			ô-17							30	2

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13.0 APPENDIX 3: CLINICAL GLOBAL IMPRESSION - SEVERITY OF ILLNESS SCALE (CGI-S)

Clinical Global Impression- Severity of Illness Scale

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

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

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14.0 APPENDIX 4: CLINICAL GLOBAL IMPRESSION - IMPROVEMENT SCALE (CGI-I)

Clinical Global Impression - Improvement Scale

Rate total improvement whether or not in your judgment it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has patient changed?

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

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

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15.0 APPENDIX 5: CALGARY DEPRESSION SCALE FOR SCHIZOPHRENIA (CDSS)

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last two weeks unless stipulated. **N.B.** The last item, #9, is based on observations of the entire interview.

1. DEPRESSION: How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?

0. Absent	
1. Mild	Expresses some sadness or discouragement on questioning.
2. Moderate	Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.
3. Severe	Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

2. HOPELESSNESS: How do you see the future for yourself? Can you see any future? - or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0. Absent	
1. Mild	Has at times felt hopeless over the last two weeks but still has some degree of hope for the future.
2. Moderate	Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
3. Severe	Persisting and distressing sense of hopelessness.

3. SELF DEPRECIATION: What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as others? Do you feel inferior or even worthless?

0. Absent	
1. Mild	Some inferiority; not amounting to feeling of worthlessness.
2. Moderate	Subject feels worthless, but less than 50% of the time.
3. Severe	Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

4. GUILTY IDEAS OF REFERENCE: Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0. Absent	
1. Mild	Subject feels blamed but not accused less than 50% of the time.
2. Moderate	Persisting sense of being blamed, and/or occasional sense of being accused.
3. Severe	Persistent sense of being accused. When challenged, acknowledges that it is not so.

5. PATHOLOGICAL GUILT: Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?

0. Absent	
1. Mild	Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2. Moderate	Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
3. Severe	Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

6. MORNING DEPRESSION: When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

0. Absent	No depression.
1. Mild	Depression present but no diurnal variation.
2. Moderate	Depression spontaneously mentioned to be worse in a.m.
3. Severe	Depression markedly worse in a.m., with impaired functioning which improves in p.m.

7. EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

0. Absent	No early wakening.
1. Mild	Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. Moderate	Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. Severe	Daily wakes 1 hour or more before normal time.

8. SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0. Absent	
1. Mild	Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. Moderate	Deliberately considered suicide with a plan, but made no attempt.
3. Severe	Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

9. OBSERVED DEPRESSION: Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.

0. Absent	
1. Mild	Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2. Moderate	Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3. Severe	Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

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16.0 APPENDIX 6: MEDICATION SATISFACTION QUESTIONNAIRE (MSQ)

MEDICATION SATISFACTION QUESTIONNAIRE

Overall, how satisfied are you with your current medication?

Extremely dissatisfied	Very dissatisfied	Somewhat dissatisfied	Neither dissatisfied nor satisfied	Somewhat satisfied	Very satisfied	Extremely satisfied
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

"Spanish Medication Satisfaction Questionnaire", translated from English to Spanish by Edith Grandiccelli de Talamo, on September 3, 2007 from "Medication Satisfaction Questionnaire", .

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17.0 APPENDIX 7: SIMPSON ANGUS SCALE (SAS)

SIMPSON-ANGUS SCALE

(SAS)

SAS - United States/English - Mapi.
ID7808 / SAS_AU1.0_eng-USori.doc

SIMPSON-ANGUS SCALE (SAS)

1. GAIT: The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:	
0 = Normal	☐
1 = Diminution in swing while the patient is walking	☐
2 = Marked diminution in swing with obvious rigidity in the arm	☐
3 = Stiff gait with arms held rigidly before the abdomen	☐
4 = Stooped shuffling gait with propulsion and retropulsion	☐

2. ARM DROPPING: The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome the arms fall very slowly:	
0 = Normal, free fall with loud slap and rebound	☐
1 = Fall slowed slightly with less audible contact and little rebound	☐
2 = Fall slowed, no rebound	☐
3 = Marked slowing, no slap at all	☐
4 = Arms fall as though against resistance; as though through glue	☐

2

SAS - United States/English - Mapi.
ID7808 / SAS_AU1.0_eng-USori.doc

SIMPSON-ANGUS SCALE (SAS)

3. SHOULDER SHAKING: The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐

4. ELBOW RIGIDITY: The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐

3

SAS - United States/English - Mapi.
ID7808 / SAS_AU1.0_eng-USori.doc

SIMPSON-ANGUS SCALE (SAS)

5. FIXATION OF POSITION or Wrist Rigidity: The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and both ulner and radial deviation:	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐

6. LEG PENDULOUSNESS: The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the scoring on this item:	
0 = The legs swing freely	☐
1 = Slight diminution in the swing of the legs	☐
2 = Moderate resistance to swing	☐
3 = Marked resistance and damping of swing	☐
4 = Complete absence of swing	☐

4

SAS - United States/English - Mapi.
ID7808 / SAS_AU1.0_eng-USori.doc

SIMPSON-ANGUS SCALE (SAS)

7. HEAD DROPPING: The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:	
0 = The head falls completely with a good thump as it hits the table	☐
1 = Slight slowing in fall, mainly noted by lack of slap as head meets the tab	☐
2 = Moderate slowing in the fall quite noticeable to the eye	☐
3 = Head falls stiffly and slowly	☐
4 = Head does not reach the examining table	☐

8. GLABELLA TAP: Subject is told to open his eyes wid and ne to link. The glabella region is tapped at a steady, rapid speed. The number of times pati t blink s in suc sion is noted:	
0 = 0 - 5 blinks	☐
1 = 6 – 10 blinks	☐
2 = 11 – 5 blin	☐
3 = 16 20 blin	☐
4 = 2 nd more blinks	☐

SAS - United States/English - Mapi.
ID7808 / SAS_AU1.0_eng-USori.doc

SIMPSON-ANGUS SCALE (SAS)

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

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

SAS - United States/English - Mapi.
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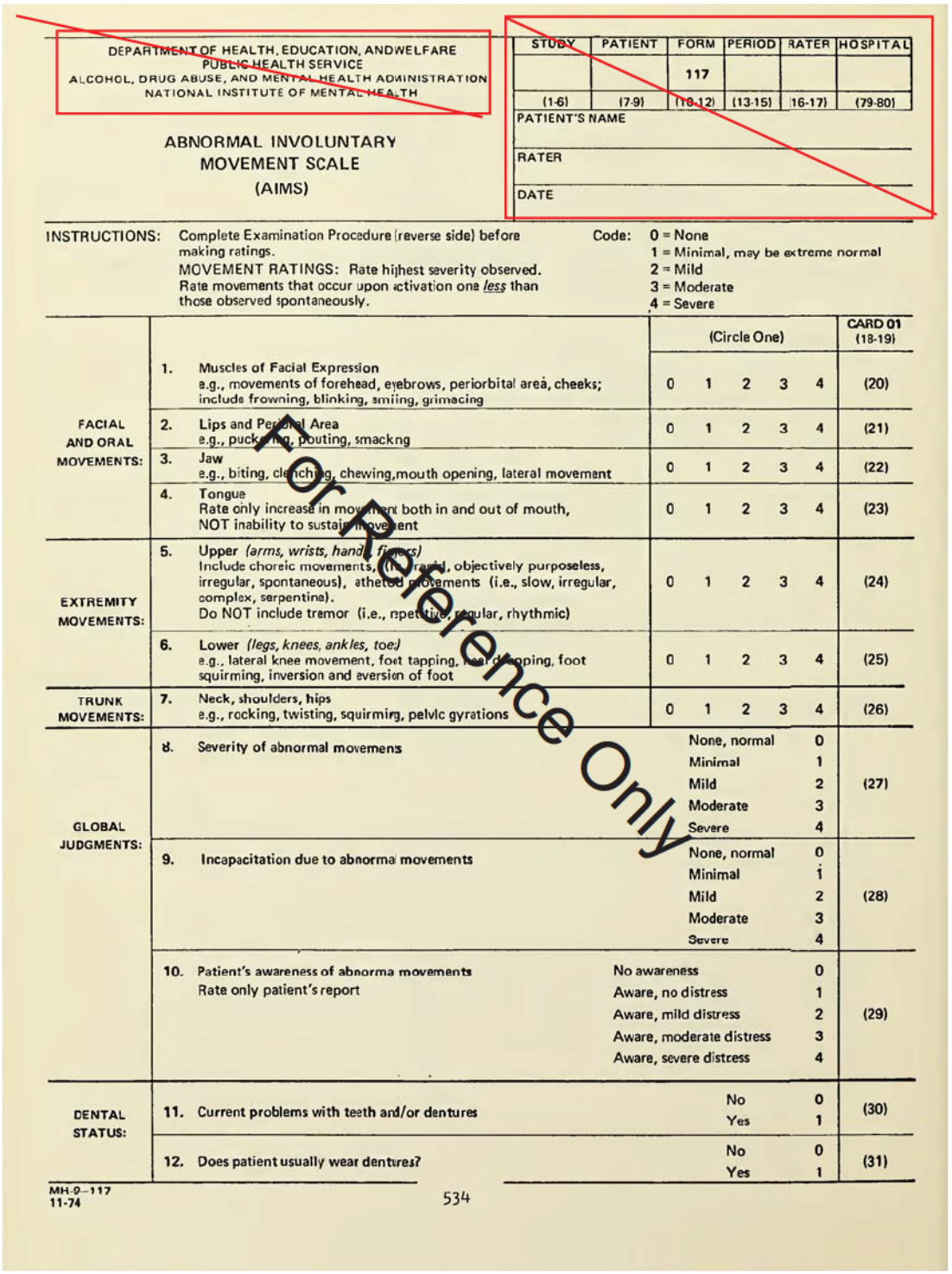
18.0 APPENDIX 8: ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH

STUDY	PATIENT	FORM	PERIOD	RATER	HOSPITAL
		117			
(1-6)	(7-9)	(10-12)	(13-15)	16-17)	(79-80)

PATIENT'S NAME

RATER

DATE

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

INSTRUCTIONS: Complete Examination Procedure (reverse side) before making ratings.
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one *less* than those observed spontaneously.

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

			(Circle One)	CARD 01 (18-19)
FACIAL AND ORAL MOVEMENTS:	1.	Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	0 1 2 3 4	(20)
	2.	Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	(21)
	3.	Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	(22)
	4.	Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0 1 2 3 4	(23)
EXTREMITY MOVEMENTS:	5.	Upper *(arms, wrists, hands, fingers)* Include choreic movements, i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	(24)
	6.	Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	(25)
TRUNK MOVEMENTS:	7.	Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	(26)
GLOBAL JUDGMENTS:	8.	Severity of abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4	(27)
	9.	Incapacitation due to abnormal movements	None, normal 0 Minimal 1 Mild 2 Moderate 3 Severe 4	(28)
	10.	Patient's awareness of abnormal movements Rate only patient's report	No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	(29)
DENTAL STATUS:	11.	Current problems with teeth and/or dentures	No 0 Yes 1	(30)
	12.	Does patient usually wear dentures?	No 0 Yes 1	(31)

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11-74

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EXAMINATION PROCEDURE

Either before or after completing the Examination Procedure observe the patient unobtrusively, at rest (e.g., inwaiting room).

The chair to be used in this examination should be a hard, firm one without arms.

---

1. Ask patient whether there is anything in his/her mouth (i.e., gum, candy, etc.) and if there is, to remove it.

2. Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?

3. Ask patient whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities

4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position).

5. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)

6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.

■ 8. Ask patient to tap thumb with each finger, as rapidly as possible for 10–15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)

9. Flex and extend patient's left and right arms (one at a time.) (Note any rigidity and rate on DOTES.)

10. Ask patient to stand up. Observe in profile. Observe all body areas again, hips included.)

■ 11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)

■ 12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.

■ Activated movements

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11-74

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The AIMS is a 12-item scale designed to record in detail the occurrence of dyskinetic movements. In the development of this scale, the Psychopharmacology Research Branch has had the benefit of consulting with many of the scientists who have previously revised rating scales for dyskinetic movements and the continuing advice of a formal consultant neurologist (Dr. Roger Duvoisin). One of the units in a PRB collaborative study (St. Paul Ramsey Hospital) had separately undertaken the development of a rating scale and had actively carried out studies with patients showing dyskinetic movements utilizing video-recording techniques. Preliminary versions of the AIMS were used to rate video recordings of patients with dyskinetic movements and although no formal interrater reliability studies have been conducted there was relatively good consensus among the group doing the ratings. Because of the great need for an assessment instrument in this field, the scale is being made available to the larger scientific community through the ECDEU Battery despite the fact that it has not been validated using psychometric procedures.

APPLICABILITY	Patients receiving neuroleptic drugs.
UTILIZATION	Once at pretreatment; at least one post-treatment rating. Additional ratings are at the discretion of the investigator.
TIME SPAN RATED	Period of the examination only.
ENCODING FORMAT	Available in non-opscan format, the AIMS can also be transcribed to the General Scoring Sheet should the investigator desire BLIPS processing. A 12 x 5 matrix is required; i.e., 12 rows and 5 columns, as follows:

Item					
1	0	1	2	3	4
2	0	1	2	3	4
3	0	1	2	3	4
4	0	1	2	3	4
5	0	1	2	3	4
6	0	1	2	3	4
7	0	1	2	3	4
8	0	1	2	3	4
9	0	1	2	3	4
10	0	1	2	3	4
11	0	1			
12	0	1			

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CARD FORMAT = (19x, I2I, I2)

Item	Column	Item	Column
1	20	7	26
2	21	8	27
3	22	9	28
4	23	10	29
5	24	11	30
6	25	12	31
		Total	32-33

Total Score = Sum of the items. Total Score Range = 0 - 42.

DOCUMENTATION:

a. Raw score printout
b. Means and standard deviations
c. Variance analyses

537

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19.0 APPENDIX 9: BARNES AKATHISIA RATING SCALE (BARS)

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

Patient name:
Patient research no.:
Hospital No.:
Ward:
Rater:

Instructions

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

Objective

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

Subjective

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

Distress related to restlessness

0 No distress
1 Mild
2 Moderate
3 Severe

Global clinical assessment of akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable.* Non-specific inner tension and fidgety movements

2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

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

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20.0 APPENDIX 10: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

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

____

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* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

	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	____	____

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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21.0 APPENDIX 11: M.I.N.I. INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW FOR **SCHIZOPHRENIA** AND **PSYCHOTIC DISORDERS** STUDIES

English Version 6.0.0

DSM-IV

USA: **D. Sheehan[1], J. Janavs, K. Harnett-Sheehan, M. Sheehan, C. Gray.**
[1]University of South Florida College of Medicine- Tampa, USA

EU: **Y. Lecrubier[2], E. Weiller, T. Hergueta, C. Klingelander, N. Kadri, D. Baldwin, C. Even.**
[2]Centre Hospitalier Sainte-Anne – Paris, France

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.

M.I.N.I. 6.0 for Psychotic Disorders (October 10, 2010) (10/10/10)

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	DSM-IV-TR	ICD-10	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	❒			
		Past	❒			
		Recurrent	❒			
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	❒	296.20-296.26 Single	F32.x	❒
		Past	❒	296.20-296.26 Single	F32.x	❒
		Recurrent	❒	296.30-296.36 Recurrent	F33.x	❒
B	SUICIDALITY	Current (Past Month) ❒ Low ❒ Moderate ❒ High	❒			
C	MANIC EPISODE	Current	❒			
		Past	❒			
	HYPOMANIC EPISODE	Current	❒			
		Past	❒	❒ Not Explored		
	BIPOLAR I DISORDER	Current	❒	296.0x-296.6x	F30.x- F31.9	❒
		Past	❒	296.0x-296.6x	F30.x- F31.9	❒
	BIPOLAR II DISORDER	Current	❒	296.89	F31.8	❒
		Past	❒	296.89	F31.8	❒
	BIPOLAR DISORDER NOS	Current	❒	296.80	F31.9	❒
		Past	❒	296.80	F31.9	❒
D	PANIC DISORDER	Current (Past Month)	❒	300.01/300.21	F40.01-F41.0	❒
		Lifetime	❒	300.01/300.21	F40.01-F41.0	❒
E	AGORAPHOBIA	Current	❒	300.22	F40.00	❒
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)				
		Generalized	❒	300.23	F40.1	❒
		Non-Generalized	❒	300.23	F40.1	❒
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	❒	300.3	F42.8	❒
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	❒	309.81	F43.1	❒
I	ALCOHOL DEPENDENCE	Past 12 Months	❒	303.9	F10.2x	❒
	ALCOHOL ABUSE	Past 12 Months	❒	305.00	F10.1	❒
J	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.2X-F19.2X	❒
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	❒	304.00-.90/305.20-.90	F11.1-F19.1	❒
K	PSYCHOTIC DISORDERS	Lifetime	❒	295.10-295.90/297.1/	F20.xx-F29	❒
		Current	❒	297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29	❒
	SCHIZOPHRENIA	Current	❒	295.10-295.60	F20.xx	❒
		Lifetime	❒	295.10-295.60	F20.xx	❒
	SCHIZOAFFECTIVE DISORDER	Current	❒	295.70	F25.x	❒
		Lifetime	❒	295.70	F25.x	❒
	SCHIZOPHRENIFORM DISORDER	Current	❒	295.40	F20.8	❒
		Lifetime	❒	295.40	F20.8	❒
	BRIEF PSYCHOTIC DISORDER	Current	❒	298.8	F23.80-F23.81	❒
		Lifetime	❒	298.8	F23.80-F23.81	❒

	DELUSIONAL DISORDER	Current	❒	297.1	F22.0	❒
		Lifetime	❒	297.1	F22.0	❒
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current	❒	293.xx	F06.0-F06.2	❒
		Lifetime	❒	293.xx	F06.0-F06.2	❒
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current	❒	291.5-292.12	none	❒
		Lifetime	❒	291.5-292.12	none	❒
	PSYCHOTIC DISORDER NOS	Current	❒	298.9	F29	❒
		Lifetime	❒	298.9 296.24	F29	❒
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.24/296.04-296.94	F30.2/F31.2/F31.5/ F31.65/F32.3/F33.3	❒
		Lifetime	❒	296.24/296.04-296.94	F30.2/F31.2/F31.5/ F31.65/F32.3/F33.3	❒
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.24/296.34	F32.3/F33.3	❒
		Past	❒	296.24/296.34	F32.3/F33.3	❒
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	❒	296.04-296.64	F30.2/F31.2/F31.5/F31.65	❒
		Past	❒	296.04-296.64	F30.2/F31.2/F31.5/F31.65	❒
	MOOD DISORDER NOS	Lifetime	❒	296.90	F39	❒
L	ANOREXIA NERVOSA	Current (Past 3 Months)	❒	307.1	F50.0	❒
M	BULIMIA NERVOSA	Current (Past 3 Months)	❒	307.51	F50.2	❒
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	❒	307.1	F50.0	❒
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	❒	300.02	F41.1	❒
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT		❒ No	❒ Yes	❒ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	❒	301.7	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?)

The translation from DSM-IV-TR to ICD-10 coding is not always exact. For more information on this topic see Schulte-Markwort. Crosswalks ICD-10/DSM-IV-TR. Hogrefe & Huber Publishers 2006.

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV 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. It can be used by clinicians, 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(es) 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, question G6).

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. Plus 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 BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, 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, 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:

		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?	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. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ❒ No ❒ Yes; Past Episode ❒ No ❒ Yes				
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead? Did you attempt suicide or plan a suicide? IF YES TO EITHER, CODE YES.	NO	YES	NO	YES
A4	Did these symptoms cause significant problems at home, at work, socially, at school or in some other important way?	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? NO YES

ARE **5** OR MORE ANSWERS **(A1-A3)** CODED **YES** AND IS **A4** CODED YES FOR THAT TIME FRAME?

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.

B. SUICIDALITY

				Points
	In the past month did you:			
B1	Have any accident? This includes taking too much of your medication accidentally. IF NO TO B1, SKIP TO B2; IF YES, ASK B1a:	NO	YES	0
B1a	Plan or intend to hurt yourself in any accident either actively or passively (e.g. by not avoiding a risk)? IF NO TO B1a, SKIP TO B2: IF YES, ASK B1b:	NO	YES	0
B1b	Intend to die as a result of any accident?	NO	YES	0
B2	Feel hopeless?	NO	YES	1
B3	Think that you would be better off dead or wish you were dead?	NO	YES	1
B4	Think about hurting or injuring yourself or have mental images of harming yourself, with at least some intent or awareness that you might die as a result?	NO	YES	4
B5	Think about suicide (killing yourself)?	NO	YES	6
	IF NO TO B5, SKIP TO B7. OTHERWISE ASK:			
	Frequency / Intensity Occasionally ❒ Mild ❒ Often ❒ Moderate ❒ Very often ❒ Severe ❒			
B6	Have difficulty restraining yourself from acting on these impulses?	NO	YES	8
B7	Have a suicide method in mind (e.g. how)?	NO	YES	8
B8	Have a suicide plan in mind (e.g. when or where)?	NO	YES	8
B9	Intend to act on thoughts of killing yourself?	NO	YES	8
B10	Intend to die as a result of a suicidal act?	NO	YES	8
B11	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die? This includes times when you were going to kill yourself, but were interrupted or stopped yourself, before harming yourself. IF NO TO B11, SKIP TO B12.	NO	YES	9
B11a	Take active steps to prepare to kill yourself, but you did not start the suicide attempt?	NO	YES	
B11b	Start a suicide attempt, but then **you stopped yourself** before harming yourself (aborted attempt)?	NO	YES	
B11c	Start a suicide attempt, but then **someone or something stopped you** before harming yourself (interrupted attempt)?	NO	YES	
B12	Injure yourself on purpose without intending to kill yourself?	NO	YES	4
B13	Attempt suicide (to kill yourself)?	NO	YES	10
	A suicide attempt means you did something where you could possibly be injured, with at least a slight intent to die.			

IF NO, SKIP TO B14:

Hope to be rescued / survive ❒
Expected / intended to die ❒

In your lifetime:

B14 Did you ever make a suicide attempt (try to kill yourself)? NO YES 4

"A suicide attempt is any self injurious behavior, with at least some intent (> 0) to die as a result or if intent can be inferred, e.g. if it is clearly not an accident or the individual thinks the act could be lethal, even though denying intent." (C-CASA definition). Posner K et al. Am J Psychiatry 164:7, July 2007.

IS AT LEAST **1** OF THE ABOVE (EXCEPT B1) CODED **YES**?

IF YES, ADD THE TOTAL POINTS FOR THE ANSWERS (B1-B14) CHECKED 'YES' AND SPECIFY THE SUICIDALITY SCORE AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURENT AND NEAR FUTURE SUICIDALITY IN THE SPACE BELOW:

NO	YES

SUICIDALITY CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

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' or so 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.) 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; 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:	NO	YES
	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? IF NO, CODE NO TO **C2b**: IF **YES** ASK:	NO	YES
	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** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **C1b** AND **C2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or 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
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES

		Current Episode		Past Episode	
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?	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: IF C1b IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1b IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?	NO	YES	NO	YES
	WHEN RATING PAST EPISODE: IF C1a IS NO, ARE 4 OR MORE C3 ANSWERS CODED YES? IF C1a IS YES, ARE 3 OR MORE C3 ANSWERS CODED YES?				
	CODE YES ONLY IF THE ABOVE 3 OR 4 SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.				
	RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE C3 SYMPTOMS, WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE C3 SYMPTOMS.				
C4	What is the longest time these symptoms lasted?				
	a) 3 days or less		❐		❐
	b) 4 to 6 days		❐		❐
	c) 7 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 with others, at school or in some other important way?	NO	YES	NO	YES

ARE **C3** SUMMARY AND **C5** AND **C6** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4c** AND **C6** CODED **YES** AND IS **C5** CODED **NO**?

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 IS EITHER **C4B** OR **C4C** CODED **YES**?

OR

ARE **C3** SUMMARY AND **C4B** AND **C6** CODED **YES** AND IS **C5** 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**

C7 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 just 4 to 6 days (**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 : CIRCLE NO IN D5, D6 AND D7 AND SKIP TO E1)

D1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, 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 a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms)?	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?	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 faint?	NO	YES
	i	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
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
D5		ARE BOTH **D3,** AND **4** OR MORE **D4** ANSWERS, CODED **YES**? IF YES TO D5, SKIP TO D7.	NO	YES *PANIC DISORDER LIFETIME*
D6		IF **D5** = **NO,** ARE ANY D4 ANSWERS CODED **YES**? THEN SKIP TO **E1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*

D7	In the past month, did you have such attacks repeatedly (2 or more), and 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*

E. AGORAPHOBIA

E1	Do you feel anxious or uneasy in places or situations where help might not be available or escape might be difficult, like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, or traveling in a bus, train or car or where you might have a panic attack or the panic-like symptoms we just spoke about?	NO	YES
	IF **E1** = **NO**, CIRCLE **NO** IN **E2**		
E2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO	YES *AGORAPHOBIA CURRENT*

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **D7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **E2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **D5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

F. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ 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? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
F2	Is this social fear excessive or unreasonable and does it almost always make you anxious?	➡ NO	YES
F3	Do you fear these social situations so much that you avoid them or suffer through them most of the time?	➡ NO	YES
F4	Do these social fears disrupt your normal work, school or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

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,
- URINATING IN A PUBLIC WASHROOM, ETC.

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

NO YES

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❐

NON-GENERALIZED ❐

G. OBSESSIVE-COMPULSIVE DISORDER

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

G1	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** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO 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 **G4**
G2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **G4**
G3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES obsessions
G4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES compulsions
	IS **G3** OR **G4** CODED **YES**?	➡ NO YES
G5	At any point, did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
G6	In the past month, did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

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 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	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
H3	During the past month, have you re-experienced the event in a distressing way (such as in dreams, intense recollections, flashbacks or physical reactions) or did you have intense distress when you were reminded about the event or exposed to a similar event?	➡ NO	YES
H4	**In the past month:**		
a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	ARE **3** OR MORE **H4** ANSWERS CODED **YES**?	➡ NO	YES
H5	**In the past month:**		
a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	ARE **2** OR MORE **H5** ANSWERS CODED **YES**?	➡ NO	YES
H6	During the past month, have these problems significantly interfered with your work, school or social activities, or caused significant distress?		

NO	YES
	POSTTRAUMATIC STRESS DISORDER CURRENT

I. ALCOHOL DEPENDENCE / ABUSE

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

		➡	
I1	**In the past 12 months**, have you had 3 or more alcoholic drinks, - within a 3 hour period, - on 3 or more occasions?	NO	YES

I2 **In the past 12 months**:

a	Did you need to drink a lot more in order to get the same effect that you got when you first started drinking or did you get much less effect with continued use of the same amount?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms (for example, "the shakes", sweating or agitation) or to avoid being hungover? IF YES TO ANY, CODE YES.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	If your drinking caused you health or mental problems, did you still keep on drinking?	NO	YES

ARE **3** OR MORE **I2** ANSWERS CODED **YES**?

NO	YES*

* IF YES, SKIP I3 QUESTIONS AND GO TO NEXT MODULE. "DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

ALCOHOL DEPENDENCE
CURRENT

I3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	If your drinking caused problems with your family or other people, did you still keep on drinking?	NO	YES

ARE **1** OR MORE **I3** ANSWERS CODED **YES**?

NO	YES
	ALCOHOL ABUSE **CURRENT**

J. SUBSTANCE DEPENDENCE / ABUSE (NON-ALCOHOL)

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

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
J1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel elated, to get "a buzz" or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA.

Phencyclidine: PCP ("Angel Dust", "Peace Pill", "Tranq", "Hog"), or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Cannabis: marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Cough Medicine? Any others?

SPECIFY THE MOST USED DRUG(S): _____

WHICH DRUG(S) CAUSE THE BIGGEST PROBLEMS?: _____

FIRST EXPLORE THE DRUG CAUSING THE BIGGEST PROBLEMS AND MOST LIKELY TO MEET DEPENDENCE / ABUSE CRITERIA.

IF MEETS CRITERIA FOR ABUSE OR DEPENDENCE, SKIP TO THE NEXT MODULE. OTHERWISE, EXPLORE THE NEXT MOST PROBLEMATIC DRUG.

J2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use much more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or recovering from the drug, or thinking about the drug?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?	NO	YES

g If (NAME OF DRUG / DRUG CLASS SELECTED) caused you health or mental problems, did you still keep on using it? NO YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

* IF YES, SKIP J3 QUESTIONS, MOVE TO NEXT DISORDER.
"DEPENDENCE PREEMPTS ABUSE" IN DSM IV TR.

NO **YES ***

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:

J3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d If (NAME OF DRUG / DRUG CLASS SELECTED) caused problems with your family or other people, did you still keep on using it? NO YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **YES**

SUBSTANCE ABUSE
CURRENT

K. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES - Part 1

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. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

ALL OF THE PATIENT'S RESPONSES TO THE QUESTIONS SHOULD BE CODED IN COLUMN A. USE THE CLINICIAN JUDGMENT COLUMN (COLUMN B) ONLY IF THE CLINICIAN KNOWS FROM OTHER OUTSIDE EVIDENCE (FOR EXAMPLE, FAMILY INPUT) THAT THE SYMPTOM IS PRESENT BUT IS BEING DENIED BY THE PATIENT.

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

			COLUMN A Patient Response			COLUMN B Clinician Judgment (if necessary)	
					BIZARRE		BIZARRE
K1	a	Have you ever believed that people were spying on you, or that someone was plotting against you or trying to hurt you?	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things? **NOTE**: ASK FOR EXAMPLES, TO RULE OUT ACTUAL STALKING.	NO	YES	YES →K6	YES	YES →K6
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	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →K6	YES	YES →K6
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	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →K6	YES	YES →K6
K4	a	Have you ever believed that you were being sent special messages through the TV, radio, internet, newspaper, books, or magazines or that a person you did not personally know was particularly interested in you?	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do you currently believe these things?	NO	YES	YES →K6	YES	YES →K6

					BIZARRE		BIZARRE
K5	a	Have your relatives or friends ever considered any of your beliefs odd or unusual? **INTERVIEWER:** ASK FOR EXAMPLES. CODE **YES** ONLY IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS (FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION OR OTHERS NOT EXPLORED IN **K1** TO **K4**).	NO	YES	YES	YES	YES
	b	IF **YES / YES BIZARRE**: Do they currently consider your beliefs strange?	NO	YES	YES	YES	YES
K6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:	NO	YES		YES	
		IF **YES:** Did you hear a voice commenting on your thoughts or behavior, or did you hear two or more voices talking to each other?	NO		YES		YES
	b	IF **YES**: Have you heard these things in the past month? SCORE AS "YES BIZARRE" IF PATIENT HEARD A VOICE COMMENTING ON THEIR THOUGHTS OR BEHAVIOR OR HEARD TWO OR MORE VOICES TALKING TO EACH OTHER.	NO	YES	YES ↳**K8b**	YES	YES ↳**K8b**
K7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES		YES	
	b	IF **YES**: Have you seen these things in the past month?	NO	YES		YES	

CLINICIAN'S JUDGMENT

K8	b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	NO	YES
K9	b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	NO	YES
K10	b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, FOR EXAMPLE, SIGNIFICANT 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	IS THERE AT LEAST ONE "**YES**" FROM **K1** TO **K10b**?	NO	YES

K11 b

ARE THE ONLY SYMPTOMS PRESENT THOSE IDENTIFIED BY THE CLINICIAN FROM **K1** TO **K7** (COLUMN B) AND FROM **K8b** OR **K9b** OR **K10b**?

IF **YES**, SPECIFY IF THE LAST EPISODE IS CURRENT (AT LEAST ONE "b" QUESTION IS CODED "**YES**" FROM **K1b** TO **K10b**) AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **K1a** TO **K10b**) AND PASS TO THE NEXT DIAGNOSTIC MODULE.

IF **NO**, CONTINUE.

WARNING: IF AT LEAST ONE "b" QUESTION IS CODED **YES**, CODE **K11c** AND **K11d**.
IF ALL "b" QUESTIONS ARE CODED NO, CODE ONLY **K11d**.

NO **YES**

PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED*

Current ❒
Lifetime ❒

***Provisional diagnosis due to insufficient information available at this time.**

K11c

FROM **K1b** TO **K6b**: ARE ONE OR MORE "b" ITEMS CODED "**YES BIZARRE**"?

OR

ARE TWO OR MORE "b" ITEMS FROM **K1b TO K10b** CODED "**YES**" BUT NOT "**YES BIZARRE**"?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO

Then Criterion "A" of Schizophrenia is not currently met

YES
Then Criterion "A" of Schizophrenia is currently met

K11d FROM **K1a** TO **K6a**: ARE ONE OR MORE "a" ITEMS CODED "**YES BIZARRE**"

OR

ARE TWO OR MORE "a" ITEMS CODED FROM **K1a** TO **K7a** "**YES**" BUT NOT "**YES BIZARRE**"?

(CHECK THAT AT LEAST 2 ITEMS OCCURRED DURING THE SAME 1 MONTH PERIOD.)

NO
Then Criterion "A" of Schizophrenia is not met Lifetime

OR IS **K11c** CODED "**YES**"

YES
Then Criterion "A" of Schizophrenia is met Lifetime

Just before these symptoms began:

K12 a Were you taking any drugs or medicines? ❒ No ❒ Yes ❒ Uncertain

b Did you have any medical illness? ❒ No ❒ Yes ❒ Uncertain

c IN THE CLINICIAN'S JUDGMENT:
ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS. ❒ No ❒ Yes ❒ Uncertain

K12d **SUMMARY:** HAS AN ORGANIC CAUSE BEEN RULED OUT? ❒ No ❒ Yes ❒ Uncertain

IF **K12d** = **NO**: SCORE **K13 (a and b)** AND GO TO THE NEXT MODULE
IF **K12d** = **YES**: CODE **NO** IN **K13 (a and b)** AND GO TO **K14**
IF **K12d** = **UNCERTAIN**: CODE **UNCERTAIN** IN **K13 (a and b)** AND GO TO **K14**

K13a IS **K12d** CODED **NO** BECAUSE OF A GENERAL MEDICAL CONDITION?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE "b" QUESTION IS CODED **YES** FROM **K1b** TO **K10b**)
AND/OR LIFETIME ("a" OR "b" QUESTION IS CODED **YES** FROM **K1a** TO **K10b**).

IF YES TO **K13a** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS

NO	YES
PSYCHOTIC DISORDER **Due to a General Medical Condition**	
Current ❒	
Lifetime ❒	
Uncertain, code later ❒	

K13 b IS **K12d** CODED **NO** BECAUSE OF A DRUG?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE QUESTION "b" IS CODED **YES** FROM **K1b** TO **K10b**)
AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **K1a** TO **K10b**).
IF YES TO **K13b** CURRENT, GO TO MODULE **L** AND SKIP REMAINING **K** QUESTIONS

NO	YES
Substance Induced ***PSYCHOTIC DISORDER***	
Current ❒	
Lifetime ❒	
Uncertain, code later ❒	

K14 Did your ability to function at work, at school, socially and with your family return completely to how you were before these experiences (CLINICIAN: PROVIDE EXAMPLES OF EXISTING HALLUCINATIONS, DELUSIONS OR DISORGANIZED SPEECH OR BEHAVIOR)? NO YES

K15 a During or after a period when you had these beliefs or experiences, did you have difficulty working, or difficulty in your relationships with others, or in taking care of yourself? NO YES

b IF **YES**, how long did these difficulties last? _____
IF ≥6 MONTHS, GO TO **K16.**

c Have you been treated with medications or were you hospitalized because of these beliefs or experiences, or the difficulties caused by these problems? NO YES

d IF **YES**, what was the longest time you were treated with medication or were hospitalized for these problems? _____

K16 a THE PATIENT REPORTED DISABILITY (**K15a CODED YES**) OR WAS TREATED OR HOSPITALIZED FOR PSYCHOSIS (**K15c = YES**). NO YES

b CLINICIAN'S JUDGMENT: CONSIDERING YOUR EXPERIENCE, RATE THE PATIENT'S **LIFETIME** DISABILITY CAUSED BY THE PSYCHOSIS.

absent	❒	1
mild	❒	2
moderate	❒	3
severe	❒	4

K17 How long was the longest period during which you had those beliefs or experiences? _____

WHAT WAS THE TOTAL DURATION OF THE PSYCHOSIS, TAKE INTO ACCOUNT THE ACTIVE PHASE **(K17)** AND THE ASSOCIATED DIFFICULTIES **(K15b)** AND PSYCHIATRIC TREATMENT **(K15d)** IN CHOOSING THE TIME FRAME.

1 ❒ ≥1 day to <1 month
2 ❒ ≥1 month to <6 months
3 ❒ ≥6 months
4 ❒ < 1 day

CHRONOLOGY

K18 a How old were you when you first began having these unusual beliefs or experiences? ☐ age

b Since the first onset how many distinct times did you have significant episodes of these unusual beliefs or experiences? ☐

PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES - PART 2

DIFFERENTIAL DIAGNOSIS BETWEEN PSYCHOTIC AND MOOD DISORDERS

CODE THE QUESTIONS **K19** TO **K23** ONLY IF THE PATIENT DESCRIBED AT LEAST 1 PSYCHOTIC SYMPTOM **(K11a = YES AND K11b = NO)**, NOT EXPLAINED BY AN ORGANIC CAUSE **(K12d = YES OR UNCERTAIN)**.

K19 a DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MAJOR DEPRESSIVE EPISODE (QUESTIONS **A3 SUMMARY** OR **A4b** CODED **YES**)? NO YES

b IF **YES:** IS **A1** (DEPRESSED MOOD) CODED **YES**? NO YES

c DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MANIC EPISODE **(MODULE C)**? NO YES

d IS **K19a** OR **K19c** CODED **YES**? NO YES

↓
STOP.
Skip to K24

NOTE: VERIFY THAT THE RESPONSES TO THE QUESTIONS **K20** TO **K23** REFER TO THE PSYCHOTIC, DEPRESSIVE **(A3 SUMMARY OR A4b)** AND MANIC EPISODES **(MODULE C)**, ALREADY IDENTIFIED IN **K11c** AND **K11d, A3 SUMMARY OR A4b AND MODULE C**. IN CASE OF DISCREPANCIES, RE-EXPLORE THE SEQUENCE OF DISORDERS, TAKING INTO ACCOUNT IMPORTANT LIFE ANCHOR POINTS/MILESTONES AND CODE **K20** TO **K23** ACCORDINGLY.

K20 When you were having the beliefs and experiences you just described (GIVE EXAMPLES TO PATIENT), were you also feeling depressed/high/irritable at the same time? NO YES

↓
STOP.
Skip to K24

K21 Were the beliefs or experiences you just described (GIVE EXAMPLES TO PATIENT) restricted exclusively to times you were feeling depressed/high/irritable? NO YES

K22 Have you ever had a period of two weeks or more of having these beliefs or experiences when you were not feeling depressed/high/irritable? NO YES

↓
STOP.
Skip to K24

K23 a) Which lasted longer: these beliefs or experiences or the periods of feeling depressed/high/irritable?

1 ❒ mood
2 ❒ beliefs, experiences
3 ❒ same

IF THE RESPONSE TO K23a) WAS 2, ASK K23b) AND K23c):

b) Did the beliefs or experiences you just described (GIVE EXAMPLES OF DELUSIONS OR HALLUCINATIONS TO PATIENT) occur for at least 2 weeks without your also feeling depressed/high/irritable? NO YES

c) Did the depressed/high/irritable feelings last more than 50% of the total time that you had these beliefs and experiences? (GIVE EXAMPLES TO PATIENT) NO YES

K24 AT THE END OF THE INTERVIEW, GO TO THE DIAGNOSTIC ALGORITHMS FOR PSYCHOTIC DISORDERS.

CONSULT ITEMS **K11a** AND**K11b**:

IF THE CRITERION "A" OF SCHIZOPHRENIA IS MET (**K11c** AND/OR **K11d** = **YES**) GO TO DIAGNOSTIC ALGORITHM I

IF THE CRITERION "A" OF SCHIZOPHRENIA IS NOT MET (**K11c** AND/OR **K11d** = **NO**) GO TO DIAGNOSTIC ALGORITHM II

FOR MOOD DISORDERS GO TO THE DIAGNOSTIC ALGORITHM III.

L. ANOREXIA NERVOSA

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

L1	a	How tall are you?	❑❑ft ❑❑in. ❑❑❑cm	
	b.	What was your lowest weight in the past 3 months?	❑❑❑lb ❑❑❑kg	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	NO	YES
		In the past 3 months:		
L2		In spite of this low weight, have you tried not to gain weight?	NO	YES
L3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	NO	YES
L4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
L5		ARE 1 OR MORE ITEMS FROM **L4** CODED **YES**?	NO	YES
L6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	NO	YES

FOR WOMEN: ARE **L5 AND L6** CODED **YES**?

FOR MEN: IS **L5** CODED **YES**?

NO	YES
	ANOREXIA NERVOSA **CURRENT**

HEIGHT / WEIGHT TABLE CORRESPONDING TO A **BMI THRESHOLD** OF **17.5** KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lb	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kg	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lb	125	129	132	136	140
cm	180	183	185	188	191
kg	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

M. BULIMIA NERVOSA

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

M1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
M2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
M3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
M4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
M5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
M6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	YES ↓ Skip to M8
M7	Do these binges occur only when you are under (____lb/kg)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

M8 IS **M5** CODED **YES** AND IS EITHER **M6** OR **M7** CODED NO?

NO	YES
	BULIMIA NERVOSA **CURRENT**

IS **M7** CODED **YES**?

NO	YES
	ANOREXIA NERVOSA *Binge Eating/Purging Type* **CURRENT**

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 "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 disrupt your normal work, school or social functioning or cause you significant distress?	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 ASK:

Just before these symptoms began:

O1a	Were you taking any drugs or medicines?	❒ No	❒ Yes	❒ Uncertain
O1b	Did you have any medical illness?	❒ No	❒ Yes	❒ Uncertain

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DISORDER?
IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

O2	**SUMMARY**: HAS AN ORGANIC CAUSE BEEN RULED OUT?	❒ No	❒ Yes	❒ Uncertain

P. ANTISOCIAL PERSONALITY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
		➡	
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
	ANTISOCIAL PERSONALITY DISORDER **LIFETIME**

THIS CONCLUDES THE INTERVIEW

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Telugu		Organon
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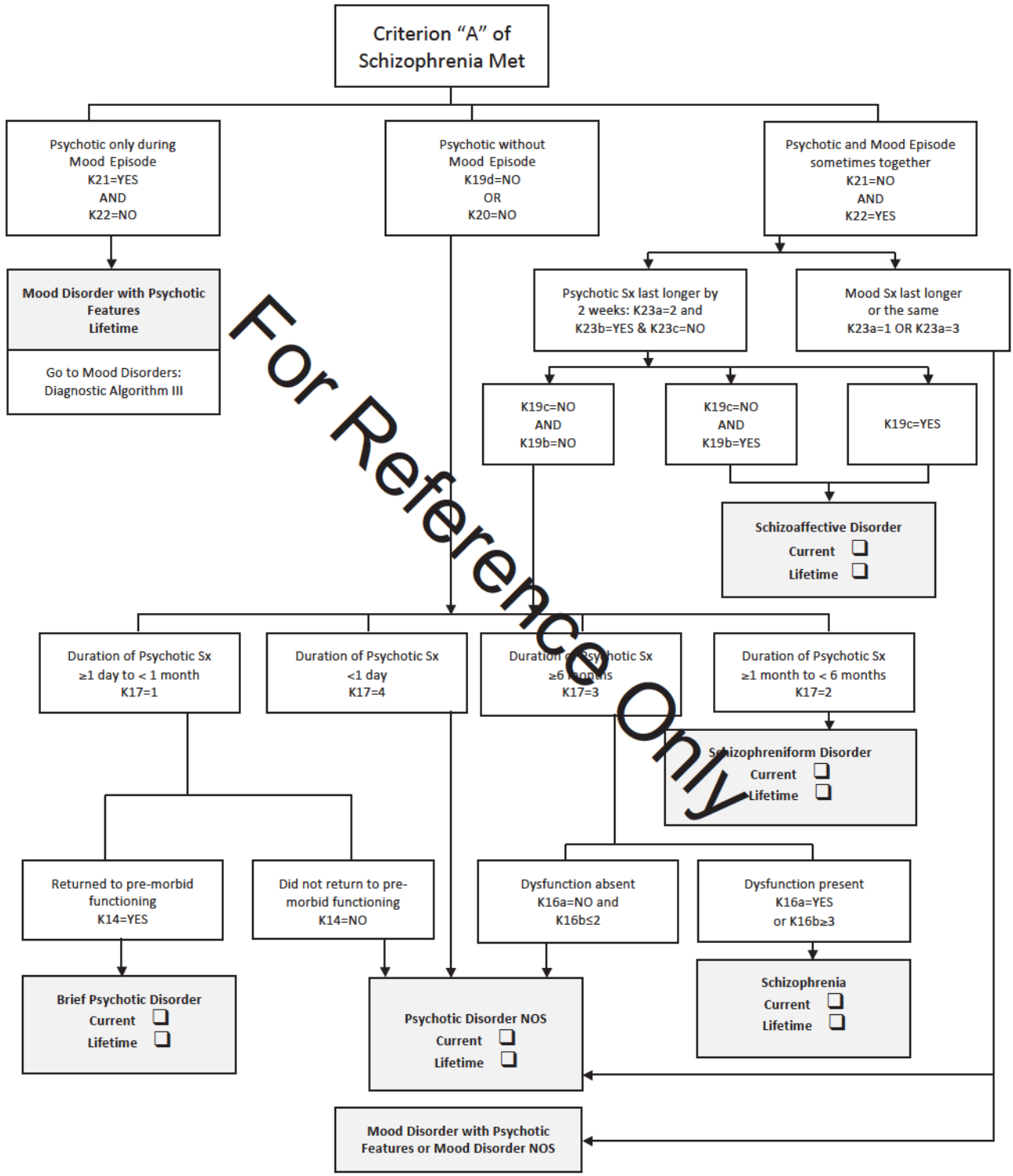
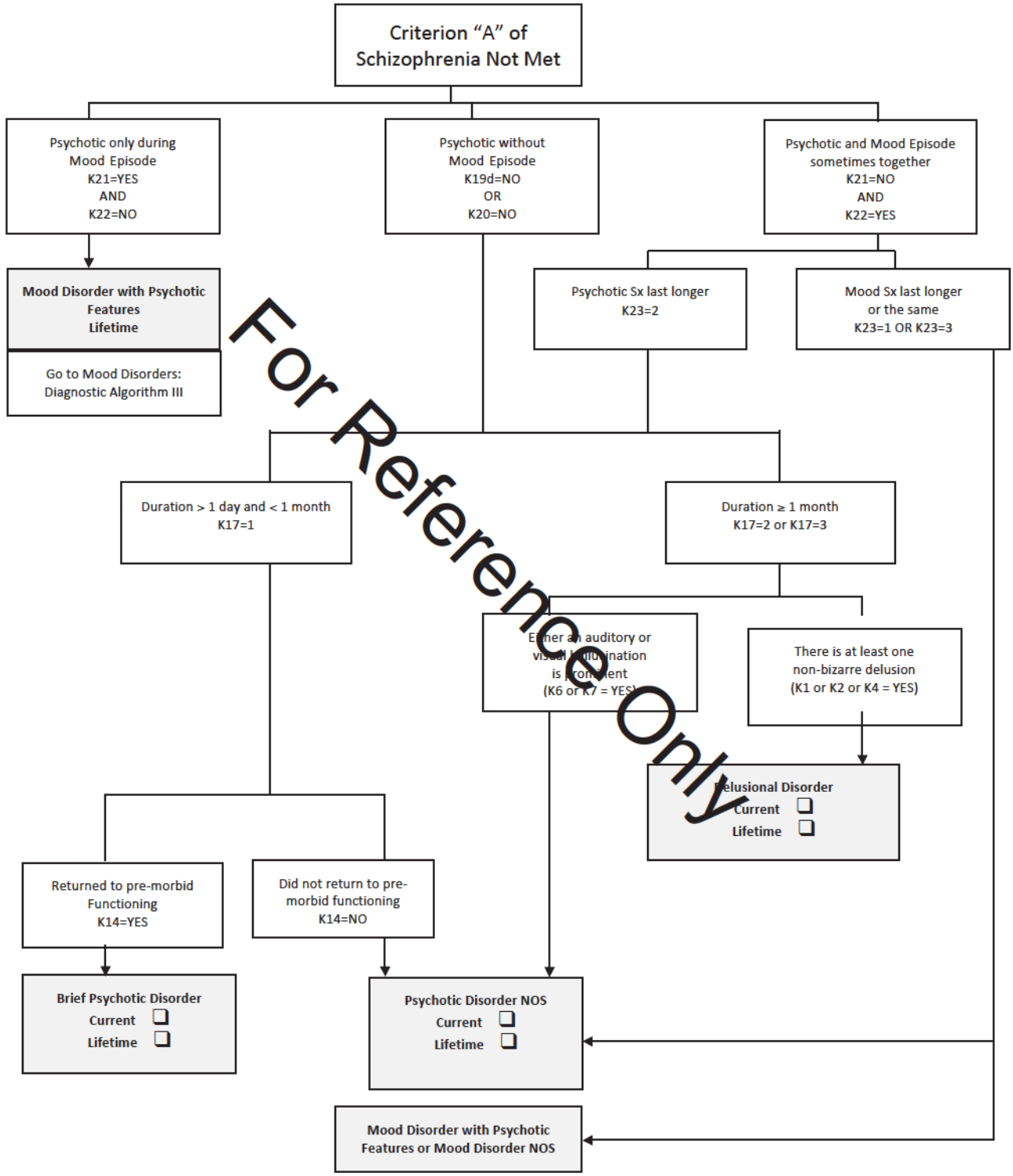
PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM I

For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is not currently met, but is present lifetime, current and lifetime diagnoses may be different.



PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHM II

For both current and lifetime diagnoses, circle the appropriate diagnostic box (separately if necessary). One positive diagnosis excludes the others for that time frame. If criterion A of schizophrenia is present lifetime, current and lifetime diagnoses may be different.



MOOD DISORDERS: DIAGNOSTIC ALGORITHM III

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

MODULE K:

1a	IS **K21** CODED YES?	NO	YES
1b	IS **K19d** CODED YES?	NO	YES

MODULES A and C:		Current	Past
2 a	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **A3e**	YES	YES
b	CIRCLE YES IF A DELUSIONAL IDEA IS IDENTIFIED IN **C3a**	YES	YES

c Is a 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 "Hypomanic Symptoms" coded NO (current and past)?

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 a Manic Episode coded YES (current or past)?

Specify:
- If the Bipolar I Disorder is **current** or **past** or both
- With **Single Manic Episode**: If Manic episode (current or past) = YES
  and MDE (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, mixed or hypomanic or unspecified (all mutually exclusive)
- **Unspecified** if the Past Manic Episode is coded YES AND
  Current (C3 Summary AND C4a AND C6 AND O2) are coded YES

BIPOLAR I DISORDER

	current	past
Bipolar I Disorder	❑	❑
Single Manic Episode	❑	❑

With Psychotic Features

Current	❑
Past	❑

Most Recent Episode

Manic	❑
Depressed	❑
Mixed	❑
Hypomanic	❑
Unspecified	❑

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)?

Specify:

- If the Bipolar Disorder is **current** or **past** or both
- If the most recent mood episode is **hypomanic** or **depressed** (mutually exclusive)

BIPOLAR II DISORDER

	current	past
Bipolar II Disorder	❑	❑

Most Recent Episode

Hypomanic	❑
Depressed	❑

f Is MDE 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 C7b 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 C7c coded YES?

Specify if the Bipolar Disorder NOS is **current** or **past** or both.

BIPOLAR DISORDER NOS

	current	past
Bipolar Disorder NOS	❑	❑

M.I.N.I. PLUS

The shaded modules below are additional modules available in the MINI PLUS beyond what is available in the standard MINI.
The un-shaded modules below are in the standard MINI.

These MINI PLUS modules can be inserted into or used in place of the standard MINI modules, as dictated by the specific needs of any study.

	MODULES	TIME FRAME
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)
	MDE WITH CATATONIC FEATURES	Current (2 weeks)
	MDE WITH ATYPICAL FEATURES	Current (2 weeks)
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MINOR DEPRESSIVE DISORDER (DEPRESSIVE DISORDER NOS)	Current (2 weeks) Past Recurrent
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MOOD DISORDER	Current (2 weeks) Past
AY	DYSTHYMIA	Current
B	SUICIDALITY	Current (Past Month) ❒ Low ❒ Moderate ❒ High
C	MANIC EPISODE	Current Past
	HYPOMANIC EPISODE	Current Past
	BIPOLAR I DISORDER	Current Past
	BIPOLAR II DISORDER	Current Past
	BIPOLAR DISORDER NOS	Current Past
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current (2 weeks) Past
	SUBSTANCE INDUCED MANIC EPISODE	Current (2 weeks) Past

	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current (2 weeks) Past
	MOOD DISORDER NOS	Lifetime
D	PANIC DISORDER	Current (Past Month) Lifetime
	ANXIETY DISORDER WIITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current
E	AGORAPHOBIA	Current
F	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month) Generalized Non-Generalized
FA	SPECIFIC PHOBIA	Current
G	OBSESSIVE-COMPULSIVE DISORDER (OCD)	Current (Past Month)
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED OCD	Current
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)
HL	POSTTRAUMATIC STRESS DISORDER	Lifetime
I	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months
IL	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Lifetime Lifetime
J	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months
JL	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Lifetime Lifetime
K	PSYCHOTIC DISORDERS	Lifetime Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime
	SCHIZOPHRENIA	Current Lifetime
	SCHIZOAFFECTIVE DISORDER	Current Lifetime
	SCHIZOPHRENIFORM DISORDER	Current Lifetime
	BRIEF PSYCHOTIC DISORDER	Current Lifetime
	DELUSIONAL DISORDER	Current Lifetime
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current Lifetime

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	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current Lifetime
	PSYCHOTIC DISORDER NOS	Current Lifetime
L	ANOREXIA NERVOSA	Current (Past 3 Months)
M	BULIMIA NERVOSA	Current (Past 3 Months)
	BULMIA NERVOSA, PURGING TYPE	Current
	BULMIA NERVOSA, NON-PURGING TYPE	Current
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current
N	GENERALIZED ANXIETY DISORDER (GAD)	Current (Past 6 Months)
	GAD DUE TO A GENERAL MEDICAL CONDITION	Current
	SUBSTANCE INDUCED GAD	Current
O	SOMATIZATION DISORDER	Current Lifetime
P	HYPOCHONDRIASIS	Current
Q	BODY DYSMORPHIC DISORDER	Current
R	PAIN DISORDER	Current
S	CONDUCT DISORDER	Current (past 12 months)
T	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) Children /Adolescents)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
TA	ATTENTION DEFICIT/ HYPERACTIVITY DISORDER	Current (Past 6 months) (Adults)
	ADHD COMBINED	
	ADHD INATTENTIVE	
	ADHD HYPERACTIVE / IMPULSIVE	
U	PREMENSTRUAL DYSPHORIC DISORDER	Current
V	MIXED ANXIETY DEPRESSIVE DISORDER	Current
W	ADJUSTMENT DISORDERS	Current
X	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT	
Y	ANTISOCIAL PERSONALITY DISORDER	Lifetime

SHORT-FORM PATIENT SATISFACTION QUESTIONNAIRE (PSQ-18)

These next questions are about how you feel about the medical care you receive.

On the following pages are some things people say about medical care. Please read each one carefully, keeping in mind the medical care you are receiving now. (If you have not received care recently, think about what you would expect if you needed care today.) We are interested in your feelings, good and bad, about the medical care you have received.

How strongly do you AGREE or DISAGREE with each of the following statements?

(Circle One Number on Each Line)

	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
1. Doctors are good about explaining the reason for medical tests	1	2	3	4	5
2. I think my doctor's office has everything needed to provide complete medical care	1	2	3	4	5
3. The medical care I have been receiving is just about perfect	1	2	3	4	5
4. Sometimes doctors make me wonder if their diagnosis is correct	1	2	3	4	5
5. I feel confident that I can get the medical care I need without being set back financially	1	2	3	4	5
6. When I go for medical care, they are careful to check everything when treating and examining me	1	2	3	4	5
7. I have to pay for more of my medical care than I can afford	1	2	3	4	5
8. I have easy access to the medical specialists I need	1	2	3	4	5

Patient Satisfaction Questionnaire
21

How strongly do you AGREE or DISAGREE with each of the following statements?

(Circle One Number on Each Line)

	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
9. Where I get medical care, people have to wait too long for emergency treatment	1	2	3	4	5
10. Doctors act too businesslike and impersonal toward me	1	2	3	4	5
11. My doctors treat me in a very friendly and courteous manner	1	2	3	4	5
12. Those who provide my medical care sometimes hurry too much when they treat me	1	2	3	4	5
13. Doctors sometimes ignore what I tell them	1	2	3	4	5
14. I have some doubts about the ability of the doctors who treat me	1	2	3	4	5
15. Doctors usually spend plenty of time with me	1	2	3	4	5
16. I find it hard to get an appointment for medical care right away	1	2	3	4	5
17. I am dissatisfied with some things about the medical care I receive	1	2	3	4	5
18. I am able to get medical care whenever I need it	1	2	3	4	5